

## Aagenaes Syndrome

► Cholestasis, Progressive Familial Intrahepatic

## Aberfeld Syndrome

► Schwartz-Jampel Syndrome

## Abetalipoproteinemia

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### Synonyms

Microsomal triglyceride transfer protein deficiency; Apo B deficiency; ABL; MTP deficiency

### Definition and Characteristics

Abetalipoproteinemia (ABL) is an autosomal recessive disorder characterized by the virtual absence of apolipoprotein B containing lipoproteins from plasma. Clinical manifestations are chronic fat malabsorption, deficiency of fat-soluble vitamins, retinopathy, acanthocytosis, steatorrhea and variable neurological manifestations.

### Prevalence

Rare.

### Genes

MTP gene localized on chromosome 4q22 coding for the microsomal triglyceride transfer protein [1,2].

### Molecular and Systemic Pathophysiology

The microsomal triglyceride transfer protein (MTP) is required for the assembly and secretion of apoB containing lipoproteins in the liver and intestine [3]. The role of MTP is to translocate apoB across the endoplasmic reticulum (ER) membrane and to catalyze the assembly of apoB with triglycerides, cholesteryl ester and phospholipids. MTP is a heterodimer consisting of protein disulfide isomerase and a 97-kDa M subunit essential for the lipid transfer activity. The MTP complex is found in the lumen of the endoplasmic reticulum of liver and intestinal cells.

Approximately 20 frameshift, missense and splice site mutations in the MTP gene have been reported. These mutations result in truncated or structurally modified proteins devoid of function [4]. In patients with ABL the intestinal fat absorption is defective, serum concentration of cholesterol and triglycerides are very low and apo B containing lipoproteins (chylomicrons, VLDL, IDL, and LDL) are virtually absent.

### Diagnostic Principles

Very low concentrations of serum total cholesterol and triglycerides and the absence of detectable apo B points to ABL. Detection of mutations in the MTP gene confirms the diagnosis.

### Therapeutic Principles

The intake of triglycerides containing long-chain fatty acids should be restricted. Long-chain fatty acids should be substituted by medium-chain fatty acids. Fat-soluble vitamins may be given to prevent neurological deficits.

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## ABL

- Abetalipoproteinemia

## Abnormalities of the Fibrinolytic System

- Fibrinolytic Disorders

## Absence of the Spleen

- Asplenia

## Absorptive Hypercalciuria

- Hypercalciuria

## AB-Variant of GM2-Gangliosidoses

- GM2 Activator Protein Deficiency

## Acanthocytosis

- Bassen-Kornzweig Syndrome

## Acanthosis Nigricans

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### Synonyms

Pseudoacanthosis nigricans; Acanthosis nigricans (AN) maligna

### Definition and Characteristics

A mostly symmetric eruption characterized by hyperpigmented, velvety cutaneous thickening typically involving the axillae, neck, groin, antecubital, popliteal and umbilical areas. Histologically, there is epidermal papillomatosis, acanthosis, occasionally with increased melanization of the epidermis and presence of melanophages in the upper corium.

### Prevalence

The prevalence is highly associated with obesity: Up to 66% of adolescents and up to 74% of adults with obesity have AN. AN maligna is exceedingly rare with only 2 out of 12,000 cancer patients [1].

### Genes

INSR (MIM#147670), PPAR- $\gamma$  (MIM#601487), AGPAT2 (MIM#603100), BSCL (MIM#606158), LMNA (MIM#150330), ALMS1 (MIM#606844), FGFR2 (MIM#176943), FGFR3 (MIM#134934) [2].

### Molecular and Systemic Pathophysiology

The molecular causes underlying AN are heterogeneous and depend on the clinical subtype [1]. All pathogenetic events lead to increased epidermal proliferation and suppressed differentiation in the affected areas. Insulin resistance is most often implicated as the molecular cause of obesity-associated AN and of several forms of syndromic AN including type A syndrome (hyperandrogenemia, insulin resistance, acanthosis nigricans, HAIR-AN syndrome), type B syndrome, Leprachaunism or Rabson-Mendenhall syndrome. In obesity-associated AN reduction in the number of insulin receptors and/or postreceptor alterations were suggested. In type A syndrome, Leprachaunism and Rabson-Mendenhall syndrome mutations involving the insulin receptor have been reported while in other conditions insulin receptor antibodies have been detected. The resulting hyperinsulinemia leads to interaction of insulin with insulin-like receptors such as

the insulin-like growth factor-1 receptor mediating enhanced epidermal proliferation. In other rare syndromic AN subtypes, e.g. cutis gyrata syndrome, Crouzon syndrome, thanatophoric dysplasia and SAD-DAN syndrome, the development of AN is linked to mutations of fibroblast growth factor receptor 2 and 3, two receptor tyrosine kinases mediating also proliferative activities on epidermal cells. In addition, an epidermal nevus-like form of AN has been described [3]. In AN maligna elevated levels of distinct circulating growth factors such as  $\alpha$ -melanocyte-stimulating hormone and transforming growth factor- $\alpha$  have been described. An altered expression of the epidermal growth factor receptor and increased activation of the extracellular signal-regulated kinase have been shown in lesional skin of patients with AN maligna [4].

### Diagnostic Principles

Benign and syndromic types of AN must be distinguished from AN maligna. Sudden onset and rapid spread are suggestive for AN maligna. Any underlying neoplasm (especially a gastrointestinal cancer) must be ruled out. In contrast, benign AN and AN associated with obesity are usually mild and easy to diagnose in light of a positive family history, or apparent obesity, respectively.

### Therapeutic Principles

Treatment depends on the underlying condition. In obesity-associated AN weight reduction reduces AN. In patients with AN maligna complete removal of the underlying tumor is curative while in syndromes with insulin resistance treatment of hyperinsulinemia will improve AN. Drugs known to induce AN (systemic corticosteroids, nicotinic acid, estrogens, oral contraceptives, methyltestosterone, and topical fucidinic acid) should be replaced or reduced in their dosage when possible. Symptomatic treatment has been described in anecdotal reports and includes topical keratolytics, podophyllin, retinoids, calcipotriol as well as systemic cyproheptadine and dietary fish oil supplement in some cases [1].

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## Acanthosis Nigricans Maligna

### ► Acanthosis Nigricans

## Accelerated Idioventricular Rhythm

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### Synonyms

Slow ventricular tachycardia; AIVR

### Definition and Characteristics

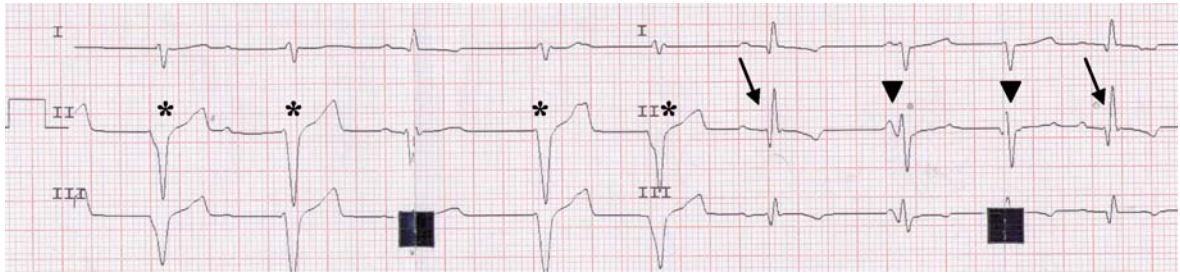
Accelerated idioventricular rhythm (AIVR) is an ectopic rhythm with three or more consecutive ventricular premature beats with a faster rate than the normal ventricular intrinsic escape rate (30–40 beats/min) but slower than ventricular tachycardia.

### Prevalence

Clinically, AIVR can occur in conjunction with any heart disorder (e.g., coronary artery disease, rheumatic heart disease, dilated cardiomyopathy, acute myocarditis, hypertensive heart disease and digitalis intoxication) or in absence of apparent heart disease both in adults and in children. No age and sex predilection have been described.

### Molecular and Systemic Pathophysiology

Accelerated idioventricular rhythm is generated by abnormalities in the ventricular myocardium that set up the mechanisms for generating an ectopic rhythm (reentry, abnormal automaticity and triggered activity) but abnormal automaticity is likely the electrophysiological mechanism behind the genesis of AIVR. In particular, enhanced phase-4 depolarization of the ventricular muscle fibers is the underlying mechanism in many cases. Several conditions, including myocardial ischemia (especially inferior wall ischemia or infarction), digoxin toxicity, electrolyte imbalance (e.g., hypokalemia) and hypoxemia may accentuate the phase-4 depolarization in the subordinate pacemaker tissues of the atrioventricular (AV) junction or His-Purkinje system, thus increasing the rate of impulse generation. Accelerated idioventricular rhythm occurs when the rate of an ectopic ventricular focus exceeds the sinus rate because of sinus slowing or when the ventricular focus accelerates sufficiently to overtake



**Accelerated Idioventricular Rhythm. Figure 1** Three leads (I, II, and III) ECG showing an accelerated idioventricular rhythm. The QRS complexes (asterisk) are wide and bizarre and have large negative amplitudes and an overall uniform appearance with T waves of opposite polarity. Note the capture complexes (arrows) and the fusion beats (head arrows) inserted into run of accelerated idioventricular rhythm. Paper speed = 50 mm/sec; 5 mm = 1 mV.

the sinus rate. Because the ventricular ectopic rate and the sinus rate are similar, both compete for the dominance of the cardiac rhythm.

### Diagnostic Principles

The electrocardiographic features of AIVR are following (Fig. 1)

- Three or more consecutive ventricular premature beats with a faster rate than the normal ventricular intrinsic escape rate (30–40 beats/min) but slower than ventricular tachycardia;
- Gradual onset when the rate of ectopic ventricular focus exceeds the sinus rate because of sinus slowing or when the ventricular focus accelerates sufficiently to overtake the sinus rate;
- Gradual termination when the sinus rhythm accelerates and/or the ectopic ventricular rhythm decelerates;
- Presence of fusion beats when the two pacemaker sites compete for the control of ventricular depolarization;
- Presence of capture beats because of the slow rate of the ectopic ventricular focus;
- Usually one regular ventricular focus, rarely multiform irregular ventricular foci.

### Therapeutic Principles

Accelerated idioventricular rhythm associated with an absence of a paroxysmal onset of the arrhythmia, a slow rate of the ventricular ectopic focus and intermittence of the ventricular runs is usually hemodynamically well tolerated with benign prognosis. Therefore, administration of specific antiarrhythmic drugs is not required but any underlying heart disorder must be cared.

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## Accessory Atrioventricular Pathways

### ► Atrioventricular Conduction Disturbances

## Accessory Nipple(s)

### ► Polythelia

## Accidental Hypothermia

### ► Hypothermia

## ACD

### ► Contact Dermatitis, Allergic

## ACEi

► Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced

## Acetazolamide-responsive Episodic Ataxia

► Episodic Ataxia Type 1 and Type 2

## Achalasia

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### Synonyms

Cardiospasm; Aperistalsis; Megaesophagus; Esophageal dystonia; Dolichoesophagus

### Definition and Characteristics

The defining characteristics of achalasia are failure of the esophago-gastric-junction (EGJ) high-pressure zone to relax adequately with swallowing and aperistalsis in the smooth muscle esophagus as measured by manometry. The lower esophageal resting pressure (LES) is elevated in 60% [1]. The functional significance is of poor bolus transit as evident by fluoroscopy, scintigraphy or impedance measurement. Dysphagia is a fundamental symptom of achalasia and is perceived as a relative obstruction to the passage of food or liquid from the oral cavity to the stomach. However, other symptoms such as regurgitation, chest pain, heart burn, and weight lost may predominate. Achalasia has been divided into classic and vigorous forms, the latter defining a subset of patients with higher mean simultaneous esophageal contraction amplitudes. However, the cutoff values for higher esophageal contractions has been arbitrarily (>50–70 mmHg) and much overlap with classic achalasia (esophageal dilation,

tortuosity, tertiary contractions, chest pain, response to pneumatic dilation) may be detected. Achalasia may be primary (idiopathic) or secondary. Secondary achalasia can be caused by infiltration of the LES (carcinoma, lymphoma, amyloidosis), as a result of a paraneoplastic syndrome (pseudoachalasia), by protozoal infection with *Trypanosoma cruzi* (Chaga disease) or surgery (fundoplication, gastric banding, vagal injury).

### Prevalence

Achalasia is a relatively rare condition. Prevalence appears to be less than 10/100,000. Incidence ranges from 0.03 to 1 case per 100,000 people per year. The incidence increases with age and peaks in the seventh decade. Additionally, a small incidence peak occurs in the 20–40 years age group. Hereditary components are not proven yet and there is only one single twin study. However, familial occurrence of achalasia may be detected [2]. Allgrove's, or 4 Å' syndrome may be a rare cause of achalasia.

### Molecular and Systemic Pathophysiology

Achalasia is the most recognized motor disorder of the esophagus and the only primary motility disorder with an established pathology. The complex physiology of esophageal motility provides several potential pathological defects that may lead to achalasia. Potential targets include extrinsic and intrinsic innervation, interstitial cells of Cajal (ICC), and smooth muscle. Among the most consistent described abnormalities is the loss of myenteric nerve fibres in the LES and esophageal body. Substantial decrease or complete lack of NOS positive innervation in the myenteric plexus of the LES as well as possibly also in the gastric fundus have been reported in human. The neuronal loss is not selective for nitrergic nerves and eventually also affects other neurons including cholinergic neurons. Immunohistochemical techniques have demonstrated the presence of a lymphocytic infiltrate and collagen deposition within the myenteric plexus. There is little evidence to suggest a defect in smooth muscle, but together with loss of myenteric neurons, secondary loss of ICC may occur. It has been suggested that an immune mediated process accounts for the loss of myenteric neurons and that loss of nitrergic neurons may be early in the development of achalasia (e.g. vigorous achalasia) with generalized neuronal loss later in the disease process. The findings of circulating antineuronal nuclear autoantibody type 1 (anti-Hu) in secondary achalasia caused by paraneoplastic syndromes and antineuronal antibodies in serum of primary achalasia patients labeling myenteric and submucosal neurons suggest an autoimmune etiology. The concept that circulating mediators may contribute to the development of



achalasia is also supported by the finding that serum from achalasia patients alters neurochemical coding in the myenteric plexus and NO-mediated motor response in normal human fundus [3].

### Diagnostic Principles

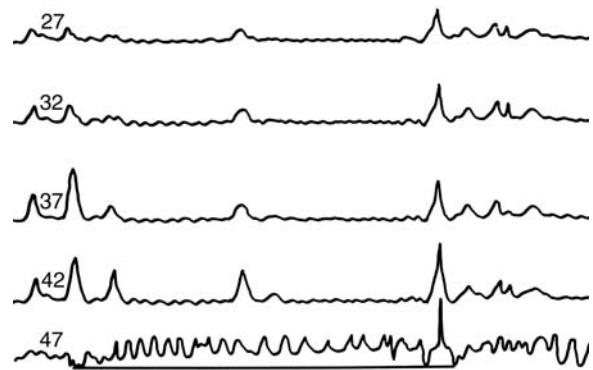
The diagnosis of achalasia should be suspected in anyone with dysphagia for solids and liquids with regurgitation of food and saliva. Patients usually learn to live with their dysphagia by using various manoeuvres, including lifting the neck or drinking carbonated beverages to help empty the esophagus. Regurgitation becomes a problem with progression of the disease, especially when the esophagus begins to dilate. Heartburn is a frequent complaint and chest pain occurs in some patients. Most patients with achalasia have some slight degree of weight loss. Patients with achalasia often develop dysphagia for solids and fluids simultaneously, whereas patients with esophageal peptic or tumor stenosis complain about dysphagia only for solids at the beginning and develop dysphagia for fluids later on disease progress with increasing stenosis. However, in any case, esophageal cancer has to be ruled out by upper GI endoscopy. In achalasia, the endoscope can be easily pushed through the LES into the stomach whereas rigidity is always suspicious of malignoma. Endoscopy together with endoscopic ultrasonography and computed tomography may also be helpful to make the diagnosis of pseudoachalasia. In addition, it has been suggested that patients with achalasia more likely develop esophageal carcinoma. When achalasia is suspected, a barium swallow with fluoroscopy should be obtained. Early in the disease, the esophagus is normal in diameter, but with a loss of normal peristalsis replaced by to-and-fro movement in the supine position. As the disease progresses, the esophagus becomes more dilated and tortuous, does not empty, and retained food and saliva produce a heterogeneous air-fluid level at the top of the barium collum. The distal esophagus is characterized by a smooth tapering leading to the closed LES, resembling bird's beak (Fig. 1).

Esophageal manometry is the gold standard by which to establish the diagnosis of achalasia. However, it does not rule out pseudoachalasia. Characteristic is aperistalsis of the smooth muscle part of the tubular esophagus, meaning that all wet or dry swallows are followed by simultaneous contractions that are identical to each other (isobaric or mirror images) (Fig. 2).

In addition, abnormal LES function is seen in all patients with achalasia, incomplete or absent LES relaxation in 70–80% and shortened and functionally inadequate LES relaxation (<6 sec) in 20–30% of patients. The sphincter pressure is usually raised, but can be normal in 20–40% of patients.



**Achalasia. Figure 1** Achalasia of the esophagus showing elongated and tortuous esophagus following barium swallow.



**Achalasia. Figure 2** Esophageal manometry illustrates characteristic aperistalsis of the tubular esophagus (manometry ports at 27, 32, and 37 cm inc.) with simultaneous contractions of low amplitude. The LES (47 cm inc.) fails to relax upon swallowing.

### Therapeutic Principles

Esophageal aperistalsis and impaired LES relaxation is usually not reversed by any mode of therapy. Therefore, every treatment option for achalasia is limited to

reducing the pressure gradient across the LES, thus facilitating esophageal emptying by gravity and preventing development of megaesophagus [4,5]. This can be achieved most effectively by pneumatic dilation, surgical myotomy, or, less effectively by pharmacological agents injected endoscopically into the LES (e.g. botulinum toxin) or taken orally (e.g. calcium-channel blockers or nitrates). Dilation and myotomy both provide definitive therapy for the majority of patients, whereas smooth-muscle relaxants provide only minor relief with decreasing effectiveness with time. Therefore, pneumatic dilation of the LES is usually the first treatment choice. The clinical response upon dilation improves proportionally with increasing balloon diameter. About 30–40% of patients might require subsequent dilations. This can be performed several times, however, the success rate may decrease with subsequent dilations. The main adverse event with pneumatic dilation is esophageal perforation, which occurs at a cumulative rate of 2%. For unknown reasons, dilation is less effective in children. Surgical myotomy for achalasia involves carrying out an anterior myotomy across the LES (Heller's myotomy). Myotomies are usually done laparoscopically through the abdomen and may be combined with an antireflux procedure (loose Nissen fundoplication, incomplete Toupet, Dor fundoplication). Endoscopic injection of botulinum toxin type A into the LES inhibits the release of acetylcholine from nerve terminals, thereby countering the effect of the selective loss of inhibitory neurotransmitters. It is initially effective in 80–90% of patients, however, symptoms may recur in more than 50% of these patients within 6 months, possibly because of regeneration of the affected receptors. It has been suggested that older patients (>60 years) and those with vigorous achalasia are more likely to have a sustained responses to botulinum toxin. However, injection of botulinum toxin should be reserved to those patients who are not candidates for pneumatic dilation or surgical myotomy.

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## Achondrodoplasia

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## Synonyms

Dwarfism for achondroplasia group; Ach

## Definition and Characteristics

For Ach group, autosomal dominant FGFR3 mutations with complete penetrance leading to dwarfism and other defects, some of which are neonatal lethal. FGFR2 mutations are associated with craniosynostosis and syndactyly. SHOX haploinsufficiency, including in Turner's syndrome, is associated with short stature and other skeletal defects.

## Prevalence

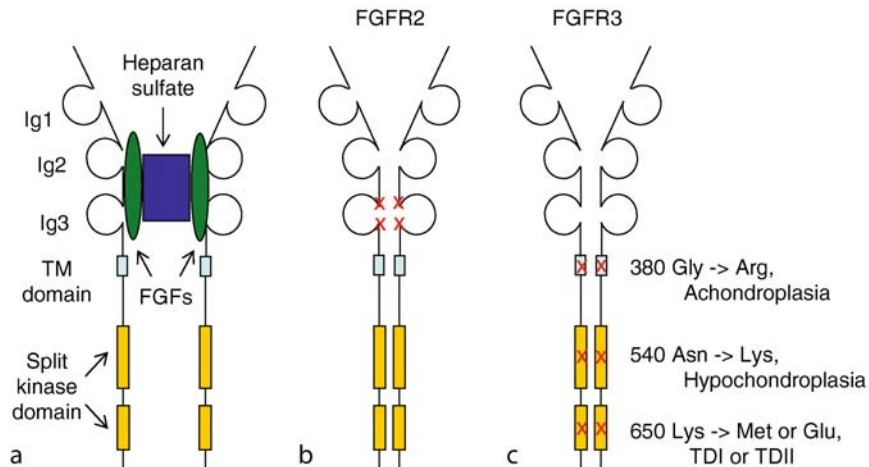
For Ach group, prevalence varies from 1/10,000 to 1/40,000, with 7/8 of mutations being sporadic. SHOX is mutated in 2% of children with short stature.

## Genes

FGFR3 on chromosome 4p16.3, FGFR2 on chromosome 10q25.3–q26. SHOX is on chromosome Xpter-p22.32, in pseudoautosomal region 1 (so not inactivated with X inactivation).

## Molecular and Systemic Pathophysiology

Fibroblast growth factor receptors (FGFRs) are receptor tyrosine kinases with an extracellular ligand binding domain consisting of three Ig domains, a transmembrane domain, and a cytoplasmic kinase domain (Fig. 1). These receptors are activated by fibroblast growth factors (FGFs) in conjunction with heparan sulfate. After activation, the receptors dimerize and autophosphorylate, leading to signal transduction through various pathways. The FGFR mutations are gain-of-function, activating through stabilizing dimers or leading to constitutively active kinases. As FGFR3 is important for growth regulation of long bones, activating mutations result in short-limbed dwarfism and mid-face hypoplasia. Disease severity varies with the degree of FGFR3 activation, such that the more benign forms of hypochondroplasia, exhibiting mild short stature, and achondroplasia (Ach),



**Achondrodoplasia. Figure 1** (a) Depicted is a general schematic of fibroblast growth factor receptors (FGFRs), which exist as dimers when activated. In the monomer, the extracellular ligand binding domain is made up of three Ig domains (Ig1, Ig2, Ig3) which bind fibroblast growth factors (FGFs) in conjunction with heparan sulfate. Shown is one possible configuration of two FGF molecules, heparan sulfate and an FGFR dimer. FGFRs also have a single pass transmembrane (TM) domain and a split kinase domain. (b) In Apert, Crouzon and Pfeiffer syndromes, FGFR2 is activated by mutations (depicted by x) which disrupt the intrachain disulfide bonds of Ig3, allowing unpaired cysteines to form interchain disulfide bonds, resulting in dimerization. (c) Activating FGFR3 mutations (depicted by x) result in various dwarfism syndromes, ranging from achondroplasia (380 Gly → Arg) and hypochondroplasia (540 Asn → Lys) to the more severe neonatal lethal thanatophoric dysplasias, TDI (650 Lys → Met) and TDII (650 Lys → Glu).

exhibiting short limbed dwarfism, are associated with mildly activating mutations, 540 Asn → Lys and 380 Gly → Arg respectively. Mutations in the kinase loop which result in greater activation, such as 650 Lys → Met and 650 Lys → Glu are associated with the neonatal lethal thanatophoric dysplasia (TD) syndromes TDI and TDII respectively. As FGFR2 is important for skull bone fusion, FGFR2 mutant syndromes Apert and Crouzon and Pfeiffer exhibit craniosynostosis and syndactyly. FGFR2 mutations disrupt the intrachain disulfide bonds that form the Ig domains of the extracellular domain. The unpaired cysteines can then form interchain disulfide bonds, resulting in dimerization and activation of the mutant FGFR2.

SHOX (short stature HOmeoboX containing gene), also known as PHOG (pseudoautosomal homeobox containing osteogenic gene), haploinsufficiency is associated with idiopathic short stature, as well as short stature in various syndromes, such as Turner's (XO), Leri-Weill dyschondrosteosis (LWD), and Langer. As loss of SHOX is associated with premature growth plate fusion, SHOX appears to repress growth plate fusion and skeletal maturation in distal limbs. Loss of SHOX appears to account for some of the skeletal defects associated with Turner's syndrome (in which one copy of the SHOX gene is deleted), including the Madelung deformity (which is bilateral shortening and bowing of the radius with a dorsal subluxation

of the distal ulna), short fourth metacarpals, cubitus valgus, and sensorineural deafness.

### Diagnostic Principles

The neonatal lethal syndromes TDI and TDII can be diagnosed before birth, by ultrasound, or at birth, by presentation of very short limbs and large heads with midfacial hypoplasia. TDII patients have long straight femurs, while TDI patients have short curved femurs. Patients with Ach present with short limb dwarfism and large heads with midfacial hypoplasia. Diagnosis is confirmed by X-rays, as achondroplasia patients exhibit large calvarial and small facial bones, as well as other abnormalities.

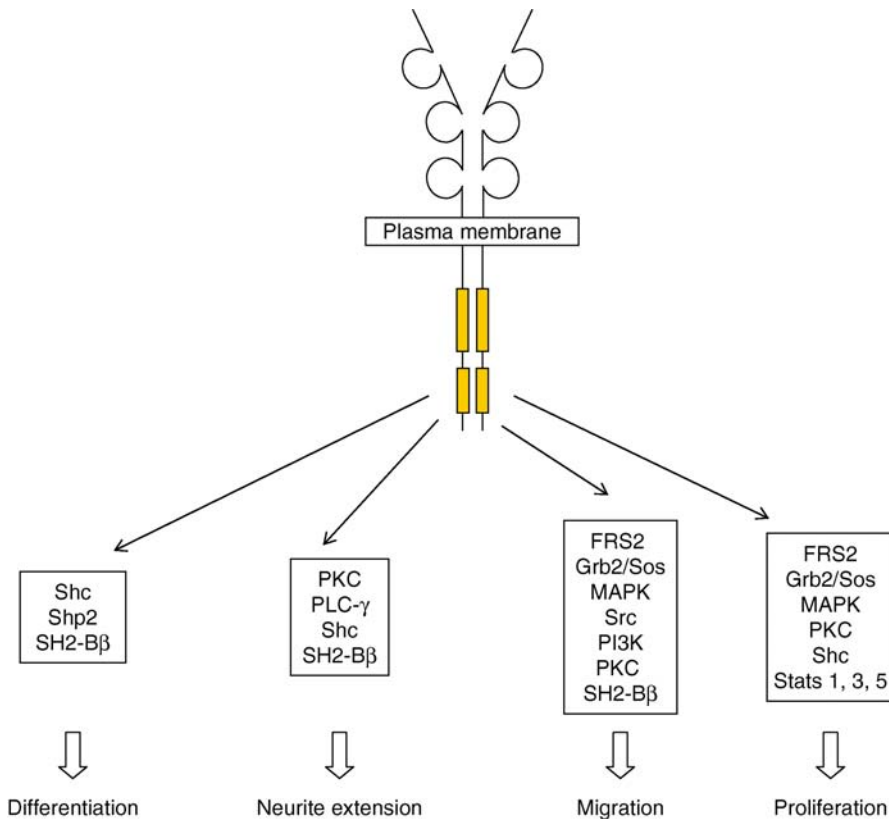
SHOX haploinsufficiency should be considered in children with otherwise unexplained short stature, and especially in patients with any X chromosome abnormalities, such as those with Turner's syndrome.

### Therapeutic Principles

Growth hormone, GnRH analog or antiestrogen for SHOX haploinsufficiency. Ach-surgery for stenotic spinal cords and tibial bowing.

### ►Physeal Dysplasia





**Achondroplasia. Figure 2** Once activated by ligand or mutation, fibroblast growth factor receptors (FGFRs) dimerize and autophosphorylate, leading to signal transduction through various pathways. These pathways, some of which are depicted here, activate different cellular processes, such as differentiation, neurite extension, migration and proliferation.

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## Achromatopsia

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### Synonyms

Rod monochromatism; Rod monochromacy; Total colorblindness; Pingelapese blindness

### Definition and Characteristics

Achromatopsia is a rare autosomal recessively inherited disorder of the retina, characterized by nonprogressive low vision from early infancy, pendular nystagmus, photophobia, loss of color discrimination, absent photopic, but normal scotopic electroretinographic (ERG) responses.

Most individuals have complete achromatopsia with total lack of function of all three types of cone photoreceptors. Rarely, individuals have incomplete achromatopsia, in which symptoms are less severe.

### Prevalence

Estimated prevalence is less than 1:30,000 [1]. On the island of Pingelap in Micronesia, the prevalence of achromatopsia or ‘Pingelapese blindness’ is between 1:25 and 1:100 [2], secondary to gene drift and the founder mutation S435F in the CNGB3 gene.

### Genes

CNGA3 (ACHM2 locus; OMIM \*600053, #216900) on Chr. 2q11.2 encodes the alpha-subunit of the cyclic nucleotide-gated channel 3 and consists of 8 exons distributed over 53 kb of genomic sequence. The 3.8 kb mRNA transcript generates a 749 amino acid polypeptide. In the retina it is cone-specific.

Mutations in CNGA3 account for 20–25% of all patients and have been described in autosomal recessive complete and incomplete achromatopsia, and also cone dystrophy [3]. Most CNGA3 mutant alleles are missense mutations that spread over the whole gene and protein.

CNGB3 (ACHM3 locus; OMIM \*605080, #262300) on Chr. 8q21–q22 consists of 18 exons encompassing over 200 kb of genomic sequence and encodes the 809 amino acid long beta-subunit of the cyclic nucleotide-gated channel 3. Northern blot analysis revealed a major transcript of 4.4 kb, specifically expressed in cones.

The vast majority of CNGB3 mutations give rise to truncated polypeptides and several recurrent mutations have been found: the most common mutation c.1148delC accounts for 75% of all CNGB3 mutant alleles. CNGB3 mutations are found in 45–50% of all achromats, rendering the ACHM3 locus the major locus for autosomal recessive achromatopsia [4].

GNAT2 (ACHM4 locus, OMIM + 139340) on Chr. 1p13 encodes the guanine nucleotide-binding protein, alpha-transducing activity polypeptide 2 (syn.: cone transducin). Eight exons form a transcriptional unit of 9967 bp and code for a 354 amino acid polypeptide. Northern blot analysis revealed a cone-specific major transcript of 1.7 kb.

Mutations in GNAT2 play only a minor role in autosomal recessive achromatopsia, accounting for less than 2% of all patients with complete and incomplete achromatopsia, and also a very mild phenotype of oligo-cone trichromacy [5].

### Molecular and Systemic Pathophysiology

CNGA3 and CNGB3 encode the alpha- and beta-subunit of the cone photoreceptor cGMP-gated channel

(CNG channel), while GNAT2 encodes the cone-specific alpha-subunit of transducin, the G-protein that couples to the cone visual pigment (Fig. 1). Transducin thus mediates one of the first steps of the phototransduction cascade, while the CNG channels represent the final component.

An animal model may help to clarify the underlying pathogenic mechanisms. The analysis of the CNGA3 knockout mouse model shows complete absence of physiologically measurable cone function, a decrease in the number of cones in the retina, and morphologic abnormalities of the remaining cones. CNGA3(–/–) cones fail to transport opsin into the outer segment and down-regulate various proteins of the phototransduction cascade. Apoptotic cell death is induced.

Autosomal recessive canine cone degeneration (cd) in the Alaskan malamute and the German shorthaired pointer breeds is due to mutations in the canine CNGB3 gene. Cd pups develop dayblindness and photophobia, but remain ophthalmoscopically normal throughout life. Cone function is detectable in electroretinograms in very young cd-pups, but begins to fail at a few weeks of age and is undetectable in mature cd-affected dogs. Adult cd-retinae lack all cones.

In addition, heterologous *in vitro* expression of mutant CNG channels have shown that the mutations observed in human achromats can disrupt channel function, including defects in protein production, trafficking and processing, and altered single channel properties.

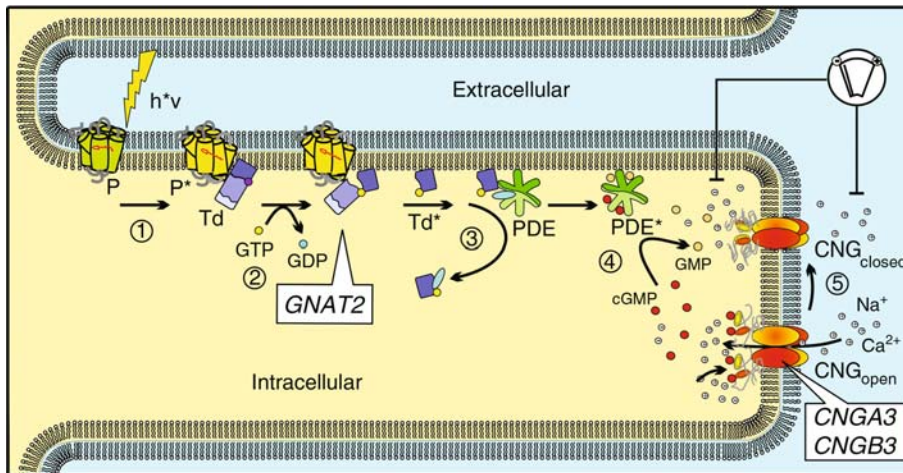
Cpf13 (cone photoreceptor function loss) mice are a model for GNAT2 associated achromatopsia and have poor cone-mediated responses on electroretinograms at 3 weeks of age that become undetectable by 9 months. Rod function is initially normal, but declines with age. Microscopy of retinae reveal progressive vacuolization of photoreceptor outer segments. Immunocytochemistry with cone-specific markers show progressive loss of labelling for alpha-transducin, but cone outer segments remain intact throughout life.

### Diagnostic Principles

Diagnosis of achromatopsia is based on color vision tests (Farnsworth Munsell 100-Hue test; saturated/desaturated Panel D-15 test, Rayleigh anomaloscope equation), electrophysiology (single-flash/30-Hz flicker electroretinogram), fundus appearance, and visual fields.

### Therapeutic Principles

In the absence of causal therapy, the treatment of achromatopsia includes dark or special filter glasses, red-tinted contact lenses to reduce photophobia and improve visual acuity, low vision aids, and occupational aids. Surveillance includes regular ophthalmologic examination. To avoid additional light damage to the



**Achromatopsia. Figure 1** Schematic drawing of the phototransduction cascade in the cone outer segment. Components known to be associated with autosomal recessive achromatopsia are highlighted. The visual pigment (P) of the photoreceptor cell consists of the transmembrane-spanning protein opsin and the chromophore 11-*cis*-retinal. Following the absorption of a photon ( $h\nu$ ) [1], the light-activated  $P^*$  repeatedly contacts the G-protein transducin Td catalyzing the exchange of GDP for GTP at the guanine binding site of the transducin  $\alpha$ -subunit (GNAT2) and its subsequent release from the inhibitory  $\beta/\gamma$ -subunits [2]. The activated GTP\*transducin  $Td^*$  then binds the inhibitory  $\gamma$ -subunit of the phosphodiesterase (PDE) thereby activating the catalytic  $\alpha'$ -subunits of the membrane-associated PDE [3]. The heterotetrameric cGMP-gated cation channels (CNG), consisting of two  $\alpha$ - (CNGA3) and two  $\beta$ -subunits (CNGB3), are directly gated by cGMP and control the influx of cations across the photoreceptor plasma membrane in the dark. The hydrolysis of cGMP by the activated  $PDE^*$  [4] results in a decrease of the intracellular cGMP level and in channel closure [5]. This decreases the conductance of the plasma membrane to the cation influx, and results in the hyperpolarization of the plasma membrane, inhibition of neurotransmitter release at the synaptic ends, and signalling of the light stimulus to adjacent neurons.

retina, appropriate protective (dark) glasses in bright light are recommended.

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## Achromatous Pityriasis Faciei

### ► Pityriasis Alba

## Acid $\alpha$ -Glucosidase Deficiency

### ► Glycogen Storage Disease Type II

## Acid $\beta$ -Glucosidase Deficiency

### ► Gaucher Disease

## Acid Ceramidase Deficiency

- Farber's Disease

## Acid Cholesterol Ester Hydrolase Deficiency

- Cholesterol Ester Storage Disease/Wolman Disease

## Acid Maltase Deficiency

- Glycogen Storage Disease Type II
- Glycogenosis Type II

## Acid Sphingomyelinase Deficient Niemann-Pick Disease

- Niemann-Pick Disease Types A and B

## Acidemia

- Acidosis, Metabolic

## Acidosis, Metabolic

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### Synonyms

Acidemia

### Definition and Characteristics

*Acidemia* is defined by a reduced blood pH, which reflects increased hydrogen ion concentration  $[H^+]$ , whereas *acidosis* is used to describe the processes leading to acidemia either of metabolic or respiratory origin. Normally, blood  $[H^+]$  is  $\approx 40$  nmols/L, corresponding to an arterial blood pH of 7.35–7.45. Blood arterial  $pCO_2$  is maintained between 36 and 40 mmHg and blood  $[HCO_3^-]$  between 24 and 26 mEq/L.

*Metabolic acidosis* (MA) is an acid/base disorder caused by a primary decrease in plasma  $[HCO_3^-]$ . Both types of acidosis lead to acidemia despite compensatory responses which attenuate it. Compensatory responses for MA include: (i) extracellular and intracellular buffering, (ii) increased ventilation (blood  $pCO_2$  decreases by  $\approx 1.2$  mmHg per each 1.0 mEq decrease in plasma  $[HCO_3^-]$  to a nadir of 12–15 mmHg in 12–24 h), and (iii) increased renal acid excretion [1].

### Prevalence

It is very common, particularly among acutely unwell/critical care patients. There are no reliable figures for its overall incidence or prevalence in the population at large.

### Genes

The renal response to metabolic acidosis is mediated, in part, by increased expression of the genes encoding key enzymes of glutamine catabolism and various ion transporters that contribute to the increased synthesis and excretion of ammonium ions and the net production and release of bicarbonate ions (Table 1). Changes in the intracellular pH may affect protein folding in the ER of the renal proximal convoluted tubule and initiate an ER-stress response. This stress response leads to an increased expression of specific genes and cytosolic stress granules. This response generally leads to selective stabilization of the mRNAs that encode the responsive proteins such as  $\zeta$ -crystallin ( $\zeta$ -cryst), AU-factor 1 (AUF1), and HuR [2].

### Molecular and Systemic Pathophysiology

During normal acid-base balance, the kidneys extract and metabolize very little of the plasma glutamine. During chronic acidosis, plasma glutamine increases and, moreover,  $>33\%$  of plasma glutamine is extracted in a single pass through the nephron, exceeding its filtered fraction, and suggesting tubular contribution to the glutamine uptake. Within the mitochondria, glutamine is deaminated by a phosphate-activated glutaminase (GA) and then oxidatively deaminated by glutamate dehydrogenase (GDH) to yield two ammonium ions and  $\alpha$ -ketoglutarate. This pathway generates two  $H^+$  and two  $HCO_3^-$  ions per mole of  $\alpha$ -ketoglutarate. During chronic metabolic acidosis

**Acidosis, Metabolic. Table 1** Specific transporters involved in the renal response to metabolic acidosis

Transporter	Location	Renal response
NHE3 <sup>1</sup>	apical border, proximal convoluted tubular cell	Acidification of the fluid in the tubular lumen and thus facilitation of bicarbonate reabsorption. Active transport of ammonium ions via $\text{NH}_4^+$ - $\text{Na}^+$ exchange
NBC1 <sup>2</sup>	basolateral border, proximal convoluted tubular cell	Facilitates the translocation of reabsorbed $\text{HCO}_3^-$ ions from the basolateral membrane into the renal venous blood.
SN1,24 <sup>3</sup>	proximal convoluted tubule	Na-dependent uptake of glutamine coupled to the efflux of a $\text{H}^+$
BSC1/ NKCC2 <sup>4</sup>	thick ascending loop of Henle	Increased ammonium reabsorption by basolateral uptake
RhBG <sup>5</sup>	collecting duct	Increased luminal trapping of ammonium ions

<sup>1</sup>NHE3 = Sodium hydrogen exchanger 3, <sup>2</sup>NBC1= Sodium bicarbonate cotransporter1 ( $\text{Na}^+/\text{HCO}_3^-$  cotransporter), <sup>3</sup>SN1 = System N transporter, <sup>4</sup>BSC1/NKCC2 = Sodium potassium chloride cotransporter, <sup>5</sup>RhBG= Human Rhesus B glycoprotein

ammonium excretion increases three to ten fold. The adaptation occurs throughout the nephron particularly in the proximal tubule and the collecting tubule [3].

Chronic MA results in alterations in nitrogen balance, protein synthesis, and muscle proteolysis. In the kidney, MA increases sodium and potassium excretion. Mineral balance effects of MA are hypercalciuria as a result of (i) enhanced bone resorption, (ii) reduced tubular calcium reabsorption and (iii) parathyroid hormone (PTH) resistance. Citrate excretion is reduced. MA may alter  $[1,25(\text{OH})_2\text{D}]$ s and PTH levels. In children, reversible growth failure is a dramatic consequence of chronic MA. Cardiovascular effects include negative inotropism, reduced fibrillation threshold, peripheral vasodilatation, and central vasoconstriction.

MA is caused by three general mechanisms (i) organic acid overproduction (e.g. lactic acidosis) or overdosing with toxins (e.g. methanol) that accumulate  $\text{H}^+$  and consume bicarbonate; (ii) inability of the kidneys to excrete acid as in chronic kidney insufficiency; and (iii) gastrointestinal or renal bicarbonate loss. It is convenient to divide the causes of MA on the basis of plasma anion gap:

1. High AG acidosis:  
Lactic acidosis, ketoacidosis (diabetic, starvation, alcohol, inborn errors of metabolism), toxins (salicylates, methanol, ethylene-glycol) and renal failure.
2. Normal AG acidosis:  
Bicarbonate loss (diarrhea, ureteral-gastrointestinal diversions), renal tubular acidosis, chronic kidney disease, drugs (triamterene, amiloride, spironolactone), acid loads (ammonium chloride, parenteral nutrition) [4].

### Diagnostic Principles

**Plasma anion gap (AG):** The plasma AG helps differentiate hyperchloremic metabolic acidosis (normal AG) from high AG metabolic acidosis. In the former

there is an increase in plasma chloride equivalent to the fall in plasma bicarbonate whereas in the latter the fall in plasma bicarbonate is matched by an increase in an unmeasured anion such as lactate. The concept of the plasma AG is based on the principle of electro neutrality: The sum of all anions must equal all the cations:  $[\text{Na}^+ + \text{K}^+ + \text{unmeasured cations (calcium, magnesium, others)}] = [\text{Cl}^- + \text{HCO}_3^- + \text{unmeasured anions (albumin, phosphate, sulfate and organic acids)}]$ . Potassium can be omitted because of its small magnitude.

$\text{AG} = \text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-] = \text{normally } 10\text{--}12 \text{ mEq/L}$

To account for hypoalbuminemia, the following correction should be made:

Albumin-corrected  $\text{AG} = \text{AG} + 2.5 \times (4.4 - \text{albumin in g/dl})$  [5].

### Therapeutic Principles

Treatment is based on removing the underlying cause. When MA is acute the focus should be the correction of the blood pH. If acidosis is severe, blood pH less than 7.20, then the administration of bicarbonate is usually required. Blood  $\text{pCO}_2$  should be appropriately low either by spontaneous compensation or by ventilatory support. The treatment of chronic MA should focus on the correction of the bicarbonate deficit to prevent the cumulative long term complications of acidosis mainly on bone disease, growth and skeletal muscle.

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## Acidosis, Renal Tubular

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### Synonyms

Renal acidosis; Hyperchloremic metabolic acidosis; RTA

### Definition and Characteristics

Renal tubular acidosis (RTA) is a syndrome characterized by hyperchloremic metabolic acidosis secondary to defective renal acidification caused by either impaired tubular reabsorption of filtered bicarbonate, defective renal H<sup>+</sup> excretion or both, in the absence of markedly decreased glomerular filtration rate. The resulting decrease in the rate of net acid excretion is insufficient to maintain the normal acid load generated from diet and a metabolic acidosis ensues [1].

RTA was initially separated into three types: distal RTA (DRTA) (type 1), from a direct inability to secrete acid in distal nephron, proximal RTA (type 2) caused by defective proximal bicarbonate reabsorption, and a combined proximal and distal RTA (or type 3), which represents a transient phenomenon consequence of proximal immaturity in infants with DRTA or due to carbonic anhydrase (CA) deficiency. Type 1 and type 2 are usually associated with hypokalemia. Type 4 RTA designates a hyperkalemic form associated with aldosterone deficiency. An additional type of hyperkalemic distal RTA referred to as voltage dependent DRTA was later described where there is secretory failure for both hydrogen ions and potassium possibly related to impaired sodium reabsorption in the distal nephron. It was first described in patients with chronic

obstructive uropathy, and resembles the distal RTA caused by the administration of amiloride and other epithelial sodium channel (ENaC) antagonists such as triamterene and pentamidine. Incomplete DRTA is defined as impaired ability to maximally decrease urinary pH after acid loading but absence of spontaneous metabolic acidosis (Table 1).

### Prevalence

The acquired forms of distal RTA are common in patients with chronic interstitial nephropathies such as obstructive uropathy, but the precise prevalence is unknown. Isolated hereditary proximal RTA is an extremely rare disorder, but proximal RTA as part of the Fanconi syndrome is more common. Similarly, hereditary DRTA is relatively rare.

### Genes

Inactivating mutations in SLC4A4, the gene coding for the Na<sup>+</sup>/HCO<sub>3</sub><sup>−</sup> symporter (OMIM 604278), cause permanent isolated proximal RTA with various ocular abnormalities such as band keratopathy, glaucoma, and cataracts, as it is abundantly expressed in ocular tissues. Recessive mixed proximal-distal RTA accompanied by osteopetrosis and mental retardation is caused by inactivating mutations in the cytoplasmic carbonic anhydrase II gene (OMIM 259730) [1].

Hereditary DRTA is a genetically heterogeneous disorder with mutations identified in the genes encoding the anion exchanger (AE1), cytosolic carbonic anhydrase enzyme (CA II), and H<sup>+</sup>-ATPase (B1 and A4 subunits) (Table 2) [1–3]. AE1 gene mutations are often responsible for the autosomal-dominant type of DRTA (OMIM 179800) or autosomal-recessive (OMIM 109270). ATP6V1B1 mutations are associated with autosomal-recessive DRTA and severe deafness in childhood (OMIM 267300), whereas ATP6V0A4 mutations (OMIM 602722) are associated with mild hearing loss that develops later, in early adulthood. Deficiency of CA II is also the primary defect underlying the autosomal-recessive syndromes of osteopetrosis, renal tubular acidosis, and cerebral calcification [1].

### Molecular and Systemic Pathophysiology

An average western diet generates ~60–80 mEq of acid per day (~1 mEq/Kg body weight). The kidney eliminates 1/3 of acid excess as phosphate and other weak acids collectively referred to as titratable acidity (TA), and about 2/3 as ammonium (NH<sub>4</sub><sup>+</sup>). Freely filtered bicarbonate (~4,320 mEq daily) is largely reabsorbed at the proximal tubule (PT). The process involves luminal secretion of H<sup>+</sup> by a specific Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE-3), and basolateral absorption of HCO<sub>3</sub><sup>−</sup> via a specific 1Na<sup>+</sup>/3HCO<sub>3</sub><sup>−</sup> co-transporter (NBC-1). Simultaneously, the actively secreted H<sup>+</sup>

**Acidosis, Renal Tubular. Table 1** Classification of proximal and distal RTA

Proximal RTA
• Primary isolated proximal RTA
• Inherited
Autosomal dominant
Autosomal recessive with mental delay and ocular abnormalities
• Sporadic (transient in infants)
• Secondary proximal RTA
• Fanconi syndrome (►primary or secondary: cystinosis, ►galactosemia, ►fructose intolerance, ►tyrosinemia, ►Wilson disease, ►Lowe syndrome, ►metachromatic leukodystrophy, ►pyruvate carboxylase deficiency, multiple myeloma, light chain disease)
• Drugs: acetazolamide, outdated tetracycline, iphosphamide, streptozotocin, valproate, 6-mercaptopurine, lead, cadmium, mercury, foscarnet
• Associated with other disorders: ►vitamin D deficiency, ►hyper-parathyroidism, chronic hypocapnia, ►Leigh syndrome, cyanotic congenital heart disease, ►medullary cystic disease, ►nephrotic syndrome, renal transplant, ►amyloidosis; paroxysmal nocturnal hemoglobinuria
Distal RTA
• Primary DRTA
• Inherited
Autosomal dominant
Autosomal recessive
Autosomal recessive with deafness
Autosomal recessive with osteopetrosis
• Transient (in infancy)
• Secondary DRTA
• ►Hypercalciuria and nephrocalcinosis: ►primary hyperparathyroidism, ►hyperthyroidism, ►vitamin D excess, nephrocalcinosis, ►Fabry disease, ►X-linked hypophosphatemia
• Congenital renal diseases such as ►sickle cell disease, hereditary ovalocytosis, ►Ehlers-Danlos syndrome, oxalosis, Wilson disease, ►congenital adrenal hyperplasia, ►hyperoxaluria
• Autoimmune diseases: ►systemic lupus erythematosus, ►Sjögren syndrome, ►chronic active hepatitis, ►primary biliary cirrhosis, ►thyroiditis; fibrosing alveolitis, ►rheumatoid arthritis, human immunodeficiency virus-associated nephropathy, polyarteritis nodosa
• Dysproteinemic syndromes: ►hypergammaglobulinemia, cryoglobulinemia, amyloidosis
• Acquired chronic interstitial diseases: kidney transplant rejection, ►medullary sponge kidney, ►obstructive nephropathy, and reflux nephropathy, analgesic nephropathy, leprosy
• Drugs and toxins: amphotericin B, lithium, toluene, analgesic abuse, amiloride, trimethoprim, pentamidine, vanadium

reacts with  $\text{HCO}_3^-$  to form  $\text{H}_2\text{O}$  and  $\text{CO}_2$  by CA type IV at the luminal membrane. The net result is the removal of a filtered  $\text{HCO}_3^-$  and a transfer of one  $\text{HCO}_3^-$  to the blood compartment (Fig. 1).

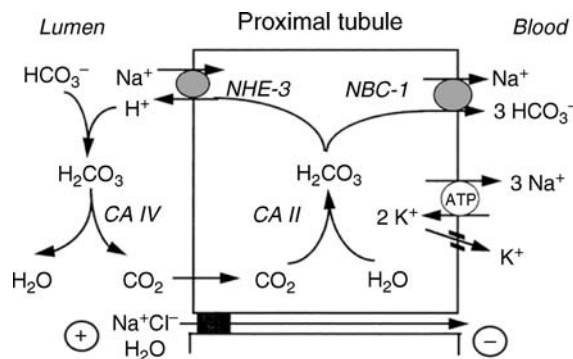
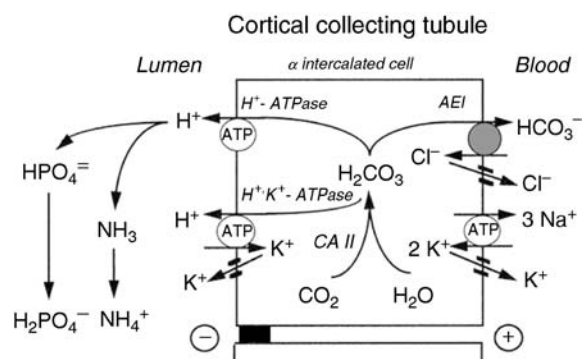
In the  $\alpha$ -type intercalated cell of the cortical collecting duct (CCD),  $\text{H}^+$  secretion is tightly regulated by  $\text{H}^+$  pumps on the apical surface that actively secrete acid to the lumen. The net urinary elimination of  $\text{H}^+$  depends on its buffering and excretion as TA and  $\text{NH}_4^+$ . Availability of phosphate as a buffer depends on the amount filtered, whereas  $\text{NH}_4^+$  is stimulated by acidosis via increased production of  $\text{NH}_3$  in the proximal tubule

followed by a complex process of  $\text{NH}_4^+$  transport in the thick ascending limb and final transfer to the collecting tubule as  $\text{NH}_3$ , which reacts with secreted  $\text{H}^+$ .  $\text{NH}_4^+$  excretion leads to the new addition of  $\text{HCO}_3^-$  to the blood via  $\text{Cl}^-/\text{HCO}_3^-$  exchange, through an anion exchanger (AEI), at the basolateral cellular surface. Cytoplasmic CA type II is also involved in this process (Fig. 2).

Urinary Anion Gap (UAG) can be used as a tool to roughly estimate urinary ammonium. The major anions in the urine include  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ , sulfate, phosphate, and organic anions. The main cations are  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{NH}_4^+$ ,

**Acidosis, Renal Tubular. Table 2** Genes and molecular mechanisms in primary renal tubular acidosis (modified from [4])

Syndrome	Chromosome	Locus	Gene product
<b>Proximal RTA (type 2)</b>			
Autosomal dominant	?	?	?
Autosomal recessive with ocular involvement	4q21	SLC4A4	NBC-1
Sporadic in infancy			NHE-3 immaturity?
<b>Distal RTA (type 1)</b>			
Autosomal dominant	17q21–22	SLC4A1	AE1
Autosomal recessive with deafness	2p13	ATP6V1B1	B1 subunit of H <sup>+</sup> ATPase
Autosomal recessive without deafness	7q33–34	ATP6V0A4	A4 subunit of H <sup>+</sup> ATPase
Distal RTA with osteopetrosis (autosomal recessive)	8q22	CA2	CAII
<b>Hyperkalemic Distal RTA (type 4)</b>			
Pseudohypoaldosteronism I Autosomal dominant	4q31.1	MLR	Mineralocorticoid receptor (MR)
Autosomal recessive	16p12 12p13	SNCC1B/SCNNIG SNCCIA	β and γ ENAC α ENAC
Early-childhood hyperkalemia			MR immaturity?
Pseudohypoaldosteronism II (Gordon's syndrome)	12p13.3 17p11-q21	WNK1 WNK4	WKN1 kinase WKN4 kinase

**Acidosis, Renal Tubular. Figure 1** Schematic model of bicarbonate reabsorption in proximal convoluted tubule (modified from [4]).**Acidosis, Renal Tubular. Figure 2** Schematic model of H<sup>+</sup> secretion in cortical collecting tubule (modified from [4]).

Ca<sup>++</sup>, and Mg<sup>++</sup>. Since only urinary Cl<sup>-</sup>, Na<sup>+</sup>, and K<sup>+</sup> are routinely measured, it follows that Cl<sup>-</sup> + UA = Na<sup>+</sup> + K<sup>+</sup> + UC. UAG = UA - UC = (Na<sup>+</sup> + K<sup>+</sup>) - Cl<sup>-</sup>. NH<sup>+</sup> is an abundant cation in the urine particularly when acidosis is present and thus changes in its concentration will affect the UAG [4]. Therefore, UAG is most helpful in differentiating patients with distal RTA in whom the UAG is increased (i.e. positive), from other causes of hyperchloremic acidosis such as diarrhea with an enhanced NH<sub>4</sub><sup>+</sup> excretion resulting in a decreased UAG (i.e. negative). Urinary sodium availability affects the ability to lower pH, and in salt-retaining states distal H<sup>+</sup> secretion may be impaired.

### **Diagnostic Principles**

The clinical phenotype of patients with RTA, particularly in the hereditary forms, often suggests the diagnosis in the context of a non-anion gap metabolic acidosis. Primary proximal RTA is characterized by vomiting and growth retardation early in infancy, eventually with psychomotor delay and sometimes ocular abnormalities. In secondary forms, patients' symptoms are those of Fanconi syndrome and underlying disorders. Prominent clinical features in patients with primary DRTA include growth retardation, polyuria, hypercalciuria, and nephrocalcinosis-lithiasis. Hypokalemia is a feature of both proximal and distal RTA. In

some cases of hereditary DRTA, severe hypokalemia causing muscle paralysis is the form of presentation [5]. Neurosensory deafness is a clue to the presence of DRTA caused by ATP6V1B1 mutations. In secondary forms, the primary disease may be responsible for the main symptoms. The hyperkalemic forms are usually asymptomatic and diagnosed based on hyperkalemic metabolic acidosis.

During acidosis, patients with proximal RTA can lower the urine pH <5.5. Ammonium excretion is only slightly reduced or even normal. During correction of the acidosis, with alkali loading, urine pH is high and fractional bicarbonate excretion is higher than normal (5–15%).

Type I DRTA is characterized by low plasma potassium and reduced net acid excretion. Ammonium excretion is low and this can be inferred by the finding of a positive UAG. The urine pH is >5.5 regardless of the degree of the acidosis.  $K^+$  and  $Ca^{++}$  are wasted in urine whereas citrate excretion is very low. After an alkali loading, fractional bicarbonate excretion remains <5%, and the urine-blood  $pCO_2$  gradient is less than 20 mmHg, reflecting impaired distal  $H^+$  secretion.

## Therapeutic Principles

Proximal RTA is treated with high doses of oral bicarbonate or citrate (10–20 mEq/Kg/d), sometimes combined with thiazides to enhance proximal reabsorption of bicarbonate, and the specific treatment of the underlying disease. Primary DRTA requires treatment often throughout life with oral supplements of mixed sodium and potassium bicarbonate, or potassium bicarbonate alone. Infants require as much as 5–8 mEq per Kg of citrate or  $HCO_3^-$  per Kg body weight, whereas adults require only about 0.5–1 mEq per Kg body weight. Citrate salts partially correct the hypocitraturia, and prevent nephrolithiasis. Correction of the metabolic acidosis allows normal growth if initiated early in life. In type 4 RTA fludrocortisone combined with loop diuretics and sometimes bicarbonate may be useful.

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## Acidosis, Respiratory

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## Synonyms

Hypercapnia

## Definition and Characteristics

Respiratory acidosis (RA) is an acid-base disorder characterized by a primary elevation of arterial carbon dioxide tension ( $PaCO_2$ ). Compensation for RA involves an increase in plasma  $HCO_3^-$  that occurs in two phases: (i) a rapid response from titration of non-bicarbonate buffers which has a modest effect, and (ii) a slower kidney response that leads to suppression of net acid excretion and reduced bicarbonate reabsorption. As a result of these compensations [ $HCO_3^-$ ] rises by about 0.4 mEq/L per each 1.0 mm/Hg increase in blood  $pCO_2$  elevation.

## Prevalence

The prevalence of RA is not precisely known, but it is recognized as a common acid-base disorder. According to the National Institutes of Health, [chronic obstructive pulmonary disease](#) (COPD) kills over 120,000 people in the United States each year and is the fourth leading cause of death and of the top leading causes of death in the U.S., it is the only one that is rising. RA is frequently seen in hospitalized patients particularly those with respiratory failure. Patients with COPD develop chronic RA and exacerbations leading to superimposed acute RA.

## Genes

Specific genes in humans and mice regulate the breathing pattern at baseline and breathing control during chemical stimulation. Most mammalian cells maintain tight control of intracellular pH using a group of transmembrane proteins that specialize in acid-base transport. Exposure to chronic hypercapnia induces changes in expression of acid-base transporters in alveolar and renal epithelial cells [1]. In response to hypercapnia, several transcription

factors such as c-Jun, kinase Fos and small Maf proteins are involved in the brain adaptation to hypercapnia. At the genomic level, hypercapnic acidosis attenuates the activation of nuclear factor-kappaB, a key regulator of the expression of multiple genes involved in the inflammatory response. Hypercapnic stimulation also activates c-Jun NH<sub>2</sub>-terminal (JNK) cascade via influx of extracellular Ca<sup>2+</sup> through voltage-gated Ca<sup>2+</sup> channels. In addition, several transmembrane proteins including Rhombex-29 (rhombencephalic expression protein-29 kDa) and Past-A (proton-associated sugar transporter-A) have been implicated in the regulation of H<sup>+</sup> sensitivity and brain acidosis-mediated energy metabolism, respectively (Table 1).

### Molecular and Systemic Pathophysiology

Carbon dioxide (CO<sub>2</sub>), also known as the “green gas,” is a by-product of cellular energy utilization and its elimination is effected by alveolar epithelial cells. The effects of the “green gas” on human health are not completely understood. In patients with acute respiratory failure, gas exchange is impaired due to the accumulation of fluid in the lung airspaces. Non-excitabile, alveolar epithelial cells sense and respond to high levels of CO<sub>2</sub>. Increased levels of CO<sub>2</sub> inhibit alveolar fluid reabsorption independently of pH. High CO<sub>2</sub> inhibits Na, K-ATPase function, via activation of protein kinase C  $\zeta$  (PKC), which phosphorylates the Na,K-ATPase, causing it to endocytose from the plasma membrane into intracellular pools [2]. Within a few seconds of high CO<sub>2</sub> there is calcium mobilization and activation of AMP-dependent kinase. Once activated, AMPK up-regulates energy-generating pathways while inhibiting energy-consuming events, thereby promoting cellular adaptation to stressful conditions like high CO<sub>2</sub> concentrations and activating a signaling cascade leading to the inhibition of alveolar function [3]. Renal epithelial cells also respond to changes in CO<sub>2</sub> concentrations via yet unidentified mechanisms,

which seem independent of intracellular pH suggesting the existence of a CO<sub>2</sub> sensor. RA has been reported to impair cellular functions such as host inflammatory response and other deleterious effects including intracranial bleeding, decreased colonic Na<sup>+</sup> transport and changes in pulmonary vascular resistance leading to ventilation/perfusion mismatch.

RA can be *acute* or *chronic*. Acute causes of RA include acute lung injury, aspiration, angioedema, bronchospasm, pulmonary embolism, pneumothorax, severe obstructive sleep-apnea. The most common causes of chronic RA are bronchitis and emphysema leading to chronic obstructive pulmonary disease. Other common causes of chronic RA include central sleep apnea, obesity hypoventilation syndrome, hypothyroidism and severe chronic interstitial lung disease [4].

Most of the important clinical manifestations of hypercapnia result from its effects on the central nervous system (CNS). CNS effects of acute RA include an excitable state, severe breathlessness, disorientation, confusion and coma. Motor effects, which include myoclonic jerks and seizures, occur in both acute and chronic hypercapnia. RA also produces cerebral vasodilation and intracranial hypertension. Cardiovascular effects include depressed myocardial contractility, sympathetic system stimulation, arrhythmias and vascular vasodilatation. In the kidneys, acute RA stimulates antidiuretic hormone release and reduces renal sodium and water excretion. Salt and water retention commonly follow sustained hypercapnia.

### Diagnostic Principles

Arterial blood gases are required to assess RA. Differentiating between acute and chronic RA is made on clinical grounds. Acute RA is associated with normal plasma bicarbonate whereas chronic hypercapnia is associated with increased plasma HCO<sub>3</sub><sup>-</sup> owing to renal compensation. Patient's medical history, physical and radiological exams are useful.

**Acidosis, Respiratory. Table 1** Hypercapnia and changes in the expression of acid-base transporters

Na, K-ATPase (Sodium Potassium ATPase)	High CO <sub>2</sub> level results in decreased activity in a concentration dependent manner by activating protein kinase C $\zeta$ (PKC) in alveolar epithelial cells
Erythroid chloride-bicarbonate exchanger (band 3 protein)	Chronic RA increases basolateral Cl <sup>-</sup> /HCO <sub>3</sub> <sup>-</sup> exchanger mRNA in type $\alpha$ intercalated cells of distal nephron
NHE1 (Sodium hydrogen exchanger 1)	Chronic exposure to CO <sub>2</sub> increases expression of NHE1 protein in cerebral cortex, heart and kidney of neonatal mouse
NBCn1 (Sodium bicarbonate cotransporter)	Chronic exposure to CO <sub>2</sub> increases expression of NBCn1 protein in cerebral cortex, heart and kidney of neonatal mouse
AE3 (Anion exchanger 3)	Hypercapnia decreases expression of AE3 protein in brain of mouse, but increases expression of AE3 in heart of neonatal mouse
Past A (Proton-associated sugar transporter-A; Mammalian sugar transporter)	Hypercapnia increases expression of Past-A in neurons of the ventral medullary surface (VMS)



## Therapeutic Principles

Hypoxemia secondary to carbon dioxide retention is a crucial factor determining morbidity and mortality of patients with acute or chronic RA. Therefore an emphasis should be placed on adequate oxygenation and lowering of CO<sub>2</sub> levels. In addition to oxygen and CO<sub>2</sub> elimination, other goals in treatment should include removal of the underlying cause and airway preservation. When RA is severe, ventilatory support in the form of either noninvasive positive pressure ventilation or mechanical ventilation may be required. The large tidal volumes with excessively high airway pressure associated with mechanical ventilation in patients with acute respiratory failure and in patients with acute exacerbations of COPD often lead to alveolar distension and barotrauma. Therefore, an alternate approach that uses lung-protective ventilation [5] strategy and allows PaCO<sub>2</sub> to rise is called “permissive hypercapnia” (or controlled mechanical hypoventilation). In this form of induced RA, lower tidal volumes (5–7 ml/kg) and peak inspiratory pressures can be used. The degree of permissive hypercapnia is severe, typically between 70 and 80 mmHg, and a bicarbonate drip needs to be used to prevent the development of acidemia. Permissive hypercapnia is sometimes used in the management of acute lung injury, acute respiratory distress syndrome, status asthmaticus, and neonatal respiratory failure but it may have deleterious effects on alveolar epithelial cell function that outweigh its potential benefits.

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## Acne Rosacea

### ► Rosacea

## Acne Vulgaris

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## Definition and Characteristics

Exclusively human disorder of the pilosebaceous unit, mostly affecting the so called “sebaceous follicles” located on the face, chest, shoulders and back (seborrheic areas).

## Prevalence

Initiating with the adrenarche and mostly with puberty it exhibits a peak incidence at 15–18 years of age. Neonatal and infantile acne can occur but are rare. Adolescents are reported to experience acne lesions in 70–87%, whereas acne is clinically relevant in 30%. There is a spontaneous regression after puberty, but acne persists over the age of 25 years in 10% and can last up to the fourth decade of life, and even up to the sixth decade of life in some cases. Two to 7% of the patients with acne experience a severe course associated with considerable scarring. Acne occurs in all races with a more severe course in Caucasians than in pigmented races. Japanese usually present a milder course of acne than other populations.

## Genes

Identical sebum excretion rates but varying distribution and severity of acne were described in homozygotic twins [1]. Among heterozygous twins acne was present in both twins in 54% sets only. An association of frequency and severity of acne in a family with a heavy course in the descendants was described. Nodulocystic infantile acne is often observed in relatives of patients with extensive steatocystoma, adolescent and postadolescent acne [2]. A correlation has been suggested between neonatal acne and familial hyperandrogenism. 50% of postadolescent acne patients have at least one first-degree relative with the condition. Several chromosomal abnormalities, including 46XYY genotype, 46XY+ (4p+; 14q–), and partial trisomy 13

**Acne Vulgaris. Table 1** Gene mutations reported in patients with acne or acneiform disorders [2,4,5]

Gene	Locus	Type of mutation	Clinical picture
FGFR2	10q26	Somatic mutation	Apert syndrome with acne, acneiform naevus [4]
GCCR	5q31	Point mutations, microdeletion	Acne in females with familial glucocorticoid resistance
CYP21A2	6p21.3	Several mutations	Acne in heterogenous or homogenous females with nonclassic congenital adrenal hyperplasia
HSD11B1	Chr. 1		Hypercortisolism with acne
CYP1A1	15q22–q24	Mutation in exon 7 (m1)	Acne vulgaris [5]
MUC1	1q21	Higher frequency of longer repeat length of tandem repeats	Severe acne
PSTPIP1	15q24–q26.1	Missense mutations	PAPA syndrome
RBP4	10q24		Retinol-binding protein deficiency with acne

FGFR2, fibroblast growth factor receptor 2; GCCR, glucocorticoid receptor; CYP, cytochrome P450; HSD, hydroxysteroid dehydrogenase; MUC, polymorphous epithelial mucin; PAPA, pyogenic arthritis, pyoderma gangrenosum, severe cystic acne; RBP, retinol-binding protein

have been reported associated with nodulocystic acne. Recent investigations provided first evidence for a possible association of gene mutations and the development of acne (Table 1).

### Molecular and Systemic Pathophysiology

Several factors contribute to the pathogenesis of acne, among them increased sebaceous gland activity with hyperseborrhea, abnormal follicular differentiation and increased cornification, bacterial hypercolonization as well as inflammation and immunological host reaction are considered to be the major ones [3].

Several clinical observations point to the importance of androgens in acne. Androgens play an essential role in stimulating sebum production; androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne. Moreover, systemic administration of testosterone and dehydroepiandrosterone increases the size and secretion of sebaceous glands. Irregularities of the menstrual cycle, pregnancy etc. have some influence on the acne course in females. Further, nutritional factors, weather, including ultraviolet light, and other environmental factors are accused to modify acne in some patients. Psychological factors and stress have still no proven influence on the pathogenesis of acne but are often involved in its course. Several drugs can induce acne or acneiform lesions.

### Diagnostic Principles

The diagnosis is made from the clinical appearance of the patient (see above).

### Therapeutic Principles

The exact classification of acne is a fundamental requirement for the decision of the therapeutic regimen (Table 2).

Formation of scars requires the administration of systemic treatment. Bacterial hypercolonization is not involved at the onset of acne but it plays a role in the maintenance of the disease. In comedonic acne abnormal keratinization of the infundibulum and the distal part of the sebaceous duct leading to formation of comedones can be directly influenced through cical retinoids and in mild forms through cical azelaic acid or salicylic acid. In papulopustular acne, benzoyl peroxide and topical and systemic antibiotics primarily exhibit antimicrobial but also anti-inflammatory activities. Inflammation leading to formation of papules, pustules, cysts and nodules has been considered as secondary to bacterial hypercolonization till recently and, consequently, it has neither been carefully investigated nor became direct target of treatment. Current research indicates that acne could be an inflammatory disorder, therefore, treatment with anti-inflammatory compounds may be introduced in the future. Nodulocystic (conglobate) acne requires systemic administration of anti-androgens and/or isotretinoin, these compounds classically induce sebosuppression. Special acne forms, such as infantile and prepubertal acne, androgenization signs in female patients with acne tarda, patients with acne fulminans, or those with acneiform diseases, such as acne inversa (hidradenitis suppurativa), may necessitate an alternative treatment. Targeting the androgen receptor or androgen-metabolizing enzymes may become an interesting approach for cical gene therapy in the future.

**Acne Vulgaris. Table 2** Simplified acne classification for the therapeutic decision

Acne form	Comedones	Inflammation	Papules/ pustules	Small nodules, cysts, fistules	Nodules	Scar formation
Comedonic	Few	None	None or few	None	None	None
Mild papulopustular	Numerous	Marked	Few to many	None or few	None	None
Severe papulopustular	Numerous	Strong	Very numerous	Many	None or few	Present
<i>Nodulocystic (conglobate)</i>	Fistule- comedones	Very strong	Very numerous	Many	Few to many, deeply located	Present

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## Acosta's Disease

### ► Mountain Sickness, Acute

## Acoustic Neuroma

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### Definition and Characteristics

Acoustic neuromas (AN) are Schwann cell tumors originating from the vestibular portion of the eighth cranial nerve.

### Prevalence

AN are the most common lesion of the cerebellopontine angle and constitute about 6% of all intracranial tumors.

The incidence in the United States is 1 in 100,000 with 2,500 new cases diagnosed each year (US) [1].

### Molecular and Systemic Pathophysiology

An AN is a slowly growing lesion which arises from Schwann cells surrounding the vestibular portion of the eighth cranial nerve. There are two forms known, sporadic and familial cases (neurofibromatosis 2). The sporadic form constitutes over 90% and is not hereditary. NF2 is the only gene known to be associated with neurofibromatosis 2.

Unilateral hearing loss is the most common presenting symptom. Other possible symptoms are tinnitus, disequilibrium, vertigo, headache and aural fullness. In a later stage, facial numbness, facial weakness, diplopia, neuropathies of cranial nerves III, IV, VI, IX, X and XI and cerebellar and brainstem compression can occur.

### Diagnostic Principles

The gold standard is gadolinium enhanced magnetic resonance imaging.

### Therapeutic Principles

Therapy depends on size and clinic. Asymptomatic lesions can be followed. Symptomatic or extending lesions beyond the inner auditory canal (IAC) should be removed by surgery [2]. The alternative therapy is stereotactic radiation or gamma knife with the drawback of certain complications, including hydrocephalus and cranial nerve neuropathies as well as a lack of elimination of the tumor [3].

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## Acoustic Overexposure

- ▶ Hearing Loss, Noise-induced and Acoustic Trauma

## Acoustic Trauma

- ▶ Hearing Loss, Noise-induced and Acoustic Trauma

## ACPO

- ▶ Ogilvie's Syndrome

## Acquired Afibrinogenemia

- ▶ Disseminated Intravascular Coagulation
- ▶ Fibrinogen: Qualitative Disorders

## Acquired Epidermolysis Bullosa

- ▶ Epidermolysis Bullosa Acquisita

## Acquired Hepatic Porphyria

- ▶ Porphyria Cutanea Tarda

## Acquired Hypogammaglobulinemia

- ▶ Immunodeficiency, Common Variable

## Acquired Idiopathic Sideroblastic Anemia

- ▶ Anemia, Sideroblastic Acquired Idiopathic

## Acquired Immunodeficiency Syndrome

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### Synonyms

AIDS

### Definition and Characteristics

Acquired immunodeficiency syndrome is a result of progressive immune dysfunction due to infection with the human immunodeficiency virus (HIV). The incubation period may be shorter for children who have perinatally acquired HIV infection than for children infected through blood or blood products, and it is usually shorter than for HIV-infected adults. Early clinical signs and symptoms of HIV infection are nonspecific such as failure to thrive and developmental delay. Pulmonary diseases are common and include *Pneumocystis carinii* pneumonia and lymphoid interstitial pneumonitis. Microcephaly, developmental delay, spasticity, gait abnormalities and abnormal reflexes may be present. Hepatomegaly is also commonly seen. HIV cardiomyopathy is not uncommon and may cause congestive cardiac failure. Proteinuria may be caused by HIV nephropathy and may progress to nephrotic syndrome. Chronic diarrhea may result from infections with opportunistic pathogens. Recurrent herpes simplex and varicella-zoster virus infections, severe molluscum contagiosum, chronic fungal infections, atopic dermatitis, and drug-induced eruptions, particularly with cotrimoxazole treatment, are common skin manifestations. Children with AIDS are frequently stunted and severe wasting may be seen in advanced disease.

## Prevalence

In 2006, approximately 10,000 children less than 13 years of age were living with AIDS in the US [1]. The prevalence is higher in developing countries.

## Molecular and Systemic Pathophysiology

Perinatal transmission of HIV in untreated women ranges from 13 to 30% [2]. However, with administration of zidovudine to women during pregnancy and labor and to infants for the first 6 weeks of life has been shown to reduce perinatal HIV transmission by two-thirds [3]. The risk of HIV infection from blood or blood products is very small and is estimated to be 1 in 2 million from a single unit of blood [4]. HIV transmission through sexual contact occurs in children who are sexually abused or in sexually active adolescents. The primary target for HIV is CD4<sup>+</sup> T lymphocyte. HIV also requires a chemokine coreceptor to enter cells and polymorphisms in these receptors are associated with resistance to HIV infection and different rates of disease progression. Infection with HIV leads to a progressive decrease in CD4<sup>+</sup> T lymphocyte number as well as function. Therefore, in addition to T cell dysfunction, humoral immunity can also be significantly impaired in children with AIDS.

## Diagnostic Principles

Detecting HIV DNA or RNA by PCR is the preferred method for diagnosing HIV infection in infants. Almost all of them have a positive HIV PCR by 1 month of age [5]. HIV-exposed infants should be tested by 48 h of age and if negative, repeat PCR testing should be performed at 14 days of age. Infants negative for HIV by PCR at 48 h and at 14 days should be retested at 1–2 months of age, and if negative, again at 3–6 months of age. HIV infection is diagnosed by two positive HIV PCR tests performed on separate blood samples. Similarly, two negative PCR results, one performed at 1–2 months and the other at 4–6 months of age, make the diagnosis of HIV infection extremely unlikely. The HIV antibody test is the appropriate screening test for children older than 18 months of age. Positive ELISA reactions for HIV are confirmed by Western blot analysis. CD4 cell count should be monitored carefully in children with AIDS.

## Therapeutic Principles

Proper care of HIV-infected children requires a multidisciplinary team. The primary care practitioner should rely on HIV care providers for the management of antiretroviral drugs.

Immunizations generally are safe for HIV-infected children, although the immune response may be poor. In children with AIDS, live viral vaccines may result in

infections and diseases resulting from vaccine viruses, although the risk is quite small. It is recommended to withhold measles and varicella vaccines from children with AIDS who have severe immunosuppression, defined as CD4<sup>+</sup> T lymphocytes less than 15%. Pneumocystis carinii pneumonia prophylaxis should be administered to HIV-exposed infants beginning at 6 weeks of age, even if HIV infection is not confirmed and to children with AIDS. The recommended regimen is cotrimoxazole taken orally 3 days a week. Alternative regimens include dapsone or pentamidine. Children with AIDS who have recurrent oral candidiasis may benefit from antifungal prophylaxis with oral nystatin, clotrimazole, or fluconazole. Weekly azithromycin or daily rifabutin is suggested as prophylaxis against Mycobacterium avium-intracellulare infection in children who have CD4<sup>+</sup> T lymphocyte cell counts less than 100 cells per mm. The treatment of HIV infection with antiretroviral drugs is complex and should be supervised by a specialist who has knowledge of the mechanisms of action of antiretroviral agents, their toxicities, drug interactions, and cross-resistance patterns. The choice of antiretroviral regimen for children is based on factors such as the availability of pediatric formulations, drug interactions, and the frequency of drug dosing. Combination antiretroviral therapy consists of a protease inhibitor or nonnucleoside reverse transcriptase inhibitor in combination with two or more nucleoside reverse transcriptase inhibitors. Adherence to complex drug regimens can be difficult and poor compliance to medications is the result of a large number or volume of medications, poor palatability, varied dosing schedules, and different effects of food on drug bioavailability.

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## Acquired Lipodystrophy

### ► Panniculitis



## Acquired Peripheral Neuropathies

### ► Peripheral Neuropathies, Acquired

hypogonadism, testicular atrophy and neuropsychiatric features. Severe AE can be complicated by an immunodeficiency status with secondary infections mostly due to candida albicans.

### Prevalence

Very rare.

## Acrocephalosyndactyly

### ► Apert Syndrome

## Acrocyanosis

### ► Ethylmalonic Encephalopathy and Acrocyanosis

### Molecular and Systemic Pathophysiology

Autosomal recessive disease with chromosomal location at 8q24.3. Mutations in the SLC39A4 gene (SLC, solute carrier family 39, member 4) are the reason for AE. The SLC39A4 gene encodes hZIP4, one member of a human zinc/iron-regulated transporter-like protein (hZIP). In the murine system ZIP4 recently has been identified as a tissue-specific, zinc-regulated zinc transporter and thus shares functional similarities with the three other members of the ZIP family (ZIP1, ZIP2, ZIP3). Acquired zinc deficiency is caused by a too low supplementation of oral zinc. Causes for acquired zinc deficiency include intestinal malabsorption syndromes, Crohn's disease, pancreatic insufficiency, deficient diets, and parenteral nutrition.

### Diagnostic Principles

The eczematous lesions located in the typical areas lead to the diagnosis which is confirmed by the determination of the plasma zinc level. Low levels of alkaline phosphatase, a zinc-dependent metalloenzyme, may indicate zinc deficiency as well.

### Therapeutic Principles

Zinc supplementation is very effective and causes a rapid resolution of the skin manifestations.

### ► Zinc Deficiency and Excess

## Acrodermatitis Enteropathica

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### Definition and Characteristics

Acrodermatitis enteropathica (AE; OMIM 201100) is an autosomal recessive disease that manifests with acral dermatitis and low serum zinc levels.

Erythematous scaly plaques and eczematous or vesiculobullous lesions are mostly located in the groins, in the perioral and periorbital areas and on the acros. Nail changes such as onychodystrophy, onycholysis, and paronychia, and oral and ocular manifestations such as stomatitis, perlèche, blepharitis, conjunctivitis, and photophobia may occur. Other manifestations include loss of appetite, apathy, diarrhea, stomatitis, glossitis, growth retardation, hair loss,

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## Acromegaly

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### Synonyms

Occurrence of GH-producing adenomas prior to epiphyseal closure leads to gigantism

### Definition and Characteristics

Somatotroph adenomas of the anterior pituitary gland leading to elevated levels of growth hormone (GH) and insulin-like growth-factor-1 (IGF-1, somatomedin-C) with thickening of skin and bones and enlargement of most viscera.

### Prevalence

Fifty cases per million. 10–15% of all pituitary adenomas are GH-producing.

By far, the most common cause for acromegaly is pituitary adenomas (>98%). GH-producing pituitary carcinomas are rare. Other rare causes are paraneoplastic GH-producing tumors (breast cancer, lung cancer, pancreatic cancer), hypothalamic and ectopic (lung cancer, pancreatic cancer, carcinoids) GH-RH producing tumors.

### Genes

About 40% of somatotroph tumors exhibit a mutation in the alpha subunit of a stimulatory G-protein (Gs), which is located on chromosome 20.

Acromegaly can be associated with the MEN-I syndrome and the McCune-Albright syndrome.

### Molecular and Systemic Pathophysiology

Pituitary tumors appear to be intrinsic, i.e., they arise from the gland itself and are not the result of a constant hypothalamic stimulation. Pituitary tumors are of monoclonal origin. In about 40% of patients with acromegaly, a mutation in the Gs alpha protein is found. This mutant Gs alpha oncogene is named Gsp (G stimulatory protein). The encoded protein has lost its GTPase-activity, which normally disrupts cAMP stimulation. Thus Gsp leads to continuous cAMP stimulation and excessive GH secretion as well as somatotroph proliferation without GH-RH stimulation.

As a consequence, the mutation correlates with constitutively increased cAMP response element-binding protein (CREB) phosphorylation and activity leading to enhanced GH synthesis.

Human growth hormone is produced by somatotroph cells in the anterior pituitary gland. Secretion of GH is stimulated by growth hormone-releasing hormone (GH-RH) and inhibited by somatostatin.

Binding of GH to its receptors on target tissues causes a dimerization and activation of the two adjacent receptors. Most of the GH effects are mediated by IGF-1, which is predominantly expressed in the liver. However, local IGF-1 appears to be the main cause of growth stimulation in the respective organs.

GH-producing pituitary tumors can cause three groups of symptoms:

1. Symptoms due to local tumor growth within the sella turcica, including decreased vision (e.g., hemianopsia) and headache
2. Symptoms due to loss of function or impaired normal pituitary function
3. Symptoms due to GH excess

Occurrence of GH-producing adenomas prior to epiphyseal closure leads to gigantism. After epiphyseal closure, GH excess causes a variety of symptoms, which are mainly mediated by IGF-1: coarsening facial features are as typical as enlarging hands and feet. Enlargement of viscera, especially cardiomegaly is a severe problem, as it can cause congestive heart failure.

Patients with acromegaly can also present with hypertension, sleep apnea, and impaired glucose tolerance. Furthermore, GH-producing tumors can exhibit a cosecretion of prolactin.

Acromegaly is associated with an increased risk to develop colon cancer.

### Diagnostic Principles

Firstly, one should consider the typical clinical features. Confirmation of the diagnosis is made by elevated serum levels of glucose-suppressed GH concentrations and IGF-1 concentrations followed by radiologic investigations.

Furthermore, screening for MEN-1 should be done once the diagnosis of acromegaly is confirmed.

### Therapeutic Principles

Treatment options include surgery, radiation, or pharmacological suppression of GH release (bromocriptine, long-acting somatostatin analogs).

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## Acromesomelic Chondrodysplasia

► Chondrodysplasia, Acromesomelic, Resembling Grebe-Type

## Acromesomelic Chondrodysplasia Resembling Grebe-Type Chondrodysplasia

► Chondrodysplasia, Acromesomelic  
► Resembling Grebe-Type

## Acropachy

► Clubbing

## Acro-renal-ocular Syndrome

► Okihiro Syndrome

## Actinic Cheilitis

► Actinic Keratosis

## Actinic Keratosis

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### Synonyms

Solar keratosis; Senile keratosis; On the lip: Actinic cheilitis

### Definition and Characteristics

Actinic keratosis (AK) is a common sun-induced pre-cancerous neoplasm of epidermal keratinocytes confined to the epidermis. The AK is the initial manifestation of a continuum of clinical and histologic abnormalities that progresses from AK or Bowen's disease to invasive squamous cell carcinoma (SCC) in 5–10% of the cases.

AK present on sun-exposed regions as skin colored to reddish brown or yellowish black, thin or raised papules or plaques with discrete keratosis (appearing like dry adherent scale), sometimes also with marked or even horn-like keratosis.

### Prevalence

It affects over 50% of elderly fair-skinned people who have been frequently exposed to the sun. The incidence of AK differs in various regions depending on the degree of sun exposure. Together with squamous cell carcinoma (SCC) it is the second most common type of skin cancer (after basal cell carcinoma) and the number of patients with AK and SCC is increasing dramatically (in the Netherlands approx. by 80% until 2015) [1].

### Genes

Inactivating mutations in the p53 tumor suppressor gene are frequent.

### Molecular and Systemic Pathophysiology

The major carcinogenic agent in skin carcinogenesis is cumulative life time exposure to ultraviolet (UV) radiation. Other risk factors include race, age, gender, and DNA repair capacity. Chronic UV radiation causes (i) mutations in cellular DNA, and (ii) relative immunosuppression in the cutaneous immune system (e.g., dendritic cells), thus impairing immunological tumor rejection. The combination of immunosuppressive drugs

with UV radiation (e.g., in patients after organ transplantation) increases the risk for SCC 65- to 250-fold. The UV-A spectrum may also be involved by generating oxidative stress which may participate in chromosomal changes, thus inducing genomic instability, a characteristic finding when AK have developed into SSC [2]. UV-B is absorbed in DNA with the formation of UV-specific dipyrimidine photoproducts, which, if insufficiently repaired and erroneously replicated, lead to characteristic mutations in dipyrimidine sequences (C→T and CC→TT transition mutations).

In AK these mutations are often found in the p53 tumor suppressor gene and may present the initial event in skin carcinogenesis. Upon stress p53 alters expression of genes, leading to cell cycle arrest for repair of DNA damage. Mutations in the p53 gene prevent UVB-induced apoptosis and deletion of DNA-damaged cells, resulting in clonal expansion of mutated cells which become targets to further mutations (for review, see [3]).

Another gene likely to be mutated in SSC by UV-radiation (10–20%) is the ras oncogene [4]. Its exact role in the carcinogenic cascade is not clear yet, but it appears to be important in SSC, especially in xeroderma pigmentosum.

For complete tumorigenic conversion from AK into SSC functional loss of p53, mutations of ras and other genes and certain chromosomal aberrations need to be completed by additional chromosomal aberrations [3]. They can be provoked by an oxidative damage response (induced e.g., by UV-A [2]).

### Diagnostic Principles

Like SCCs, the vast majority of AKs and Bowen's disease lesions are asymptomatic. The diagnosis is usually made clinically, according to the clinical criteria described above. The lesions vary from pinhead size to several centimeters and are often better recognized by palpation than by visualization.

They are usually surrounded by sun-damaged skin (solar elastosis).

Erythema, induration, erosion and increase in size or thickness are indicative of evolution into SCC.

### Therapeutic Principles

AK and suspicious lesions should be treated before they progress to invasive SCC. Surgical excision with histological control are mandatory when clinical diagnosis is not clear or when there is suspicion of invasive SSC (induration, ulcer, or increase in size or thickness). In most cases, however, destructive modalities, such as cryosurgery using liquid nitrogen, electrodesiccation, curettage, laser therapy or photodynamic therapy or topical drugs such as 5-fluorouracil, imiquimod or diclofenac are the mainstays of therapy. An integrated

program of skin cancer awareness, sun protection, and prophylactic approaches is critical.

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## Actinic Keratosis and Squamous Cell Carcinoma

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### Synonyms

SCC

### Definition and Characteristics

SCC is a malignant tumor arising from the keratinocytes which show various degrees of maturation towards keratin formation. Actinic keratosis (AK) is the prestage of SCC, representing a carcinoma in situ. In contrast to SCC, spontaneous regression of AK in the early stage can be observed. The clinical appearance may vary, usually multiple or single standing nodules with hyperkeratotic surface, sometimes ulcerating. Most AK and SCC are located on the chronically UV-exposed skin areas (face, scalp, neck, arms, hands) of elderly people.

### Prevalence

160:100,000 in Australia. Non-melanoma skin cancer is the cancer with the most dramatically increasing frequency of all cancer types in the Western world [1].

### Molecular and Systemic Pathophysiology

Ultraviolet radiation, in particular the UVB range (290–320 nm), is the most important factor inducing AK and SCC. UVB radiation primarily hits the keratinocytes by inducing damage in DNA, including some in the tumor suppressor gene p53. Most of the photolesions are repaired by the nucleotide excision repair (see Xeroderma pigmentosum). If not, upon replication the DNA with the photoproduct is left mostly with a C→T mutation in the p53 gene (“UV signature”). Upon further UV exposure p53 is induced which, if the DNA damage is too severe, induces apoptosis of the keratinocyte (sunburn cell) [2,3]. For cells carrying a p53 mutation a 50% likelihood exists not to undergo apoptosis, but to survive and to divide later. Thereby a small clone of “apoptosis-defective” cells will arise. In the absence of further UV exposure this clone may undergo spontaneous regression via mechanisms not yet understood. Each additional UV exposure, however, will exert a selection pressure supporting the clonal expansion of the cells carrying mutated p53. Subsequent UV exposure will probably mutate the other p53 allele or other oncogenes in some cells of the clone, thereby inducing malignant transformation. At the early stage (actinic keratosis), (pre) malignant cells can be recognized and eliminated by the immune system which, however, is also impaired by UV radiation. Besides UV being by far the most important inducer of AK and SCC other factors include ionizing radiation, human papillomaviruses and chemical carcinogens (e.g. arsenic).

### Diagnostic Principles

The typical clinical features lead to the diagnosis, which is finally confirmed by histopathologic examination.

### Therapeutic Principles

Systemic retinoids and interferons may reduce the frequency of lesions in patients suffering from multiple tumors. Other than that, surgical removal, cautery, kryotherapy, photodynamic therapy, chemical peeling and topical immunomodulators are frequently used therapeutic strategies. UV protection is recommended as a preventive step.

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## Actinopathies

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### Synonyms

Subtype of nemaline myopathies or NEM3 [1]

### Definition and Characteristics

Congenital myopathy marked by clinical floppiness and large aggregates of actin filaments within muscle fibers [2], which may or may not be associated with nemaline bodies or rods [2]. To date, all observed cases of actin myopathy (accumulation of thin myofilaments) where ACTA1 mutation have been identified have dominant mutations [2,3].

### Prevalence

Approximately 70% of patients whose histopathology shows accumulation of thin myofilaments have mutations in the ACTA1 gene. ACTA1 mutations cause approximately 20% of cases of nemaline myopathy.

### Genes

ACTA1 gene, located on chromosome 1q42.1, coding for  $\alpha$ -skeletal actin, the skeletal muscle fiber-specific thin myofilament actin [4].

### Molecular and Systemic Pathophysiology

Actin or thin myofilaments are essential components of I-bands of sarcomeres anchoring bilaterally at the Z disk, extending between the myosin filaments in the A band and essential for contraction upon nerve stimulus. The overwhelming majority of missense mutations, encountered so far, appear as de novo mutations when parental ACTA1 genes had been analyzed [4]. While a complete genotype–morphophenotype correlative spectrum has not yet been established, i.e., correlation of missense mutations in the ACTA1 gene and the presence of large aggregates of actin filaments within muscle fibers, these two components have been identified in several patients with rods/nemaline bodies [2,4,5] and, hence, nemaline myopathy. In addition to



sarcomeric actin, demonstrated by immunohistochemistry and immunoelectron microscopy, only  $\alpha$ -actinin, a major protein of Z bands, rods/nemaline bodies, and  $\alpha$ -B crystallin, the molecular heat-shock or chaperone - protein, had been demonstrated within islands of actin filaments, quite unlike other protein aggregates within muscle fibers such as desmin-related aggregates in desmin-related myopathies or myofibrillar myopathies and tubulofilamentous aggregates in hereditary inclusion body myositis/myopathies. This lack of diverse proteins may indicate a defect in synthesis or assembly of intrasarcomeric thin filaments or incorporation of mutant actin filaments in regular sarcomeres which, however, are also seen in myofibrils with aggregates of actin filaments. Mutations in the ACTA1 gene have also been seen with aggregates of actin filaments, but without rods or nemaline myopathy and have been seen with rods/nemaline bodies in intranuclear location only. Failure to identify aggregates of actin filaments within biopsied muscle specimens, in spite of mutations in the ACTA1 gene in respective patients, may represent missampling or absence of actin filament aggregation. The mutations in ACTA1 that cause actinopathy are largely clustered at or near the nucleotide binding cleft in the actin monomer [3]. This has led to the hypothesis that the mutations in ACTA1 that cause actinopathy probably interfere with nucleotide binding and then in turn with actin polymerization [3].

### Diagnostic Principles

Clinical symptoms of a floppy infant, occasionally rapidly progressing to death or, in mild cases, of a slowly or nonprogressive myopathy, and a muscle biopsy specimen marked by patches of actin filaments identified by immunohistochemistry and/or electron microscopy, with or without nemaline bodies/rods or intranuclear rod bodies require molecular analysis of the ACTA1 gene for confirmation or alternative interpretation.

### Therapeutic Principles

As the pathogenesis of actin filament aggregation is as unclear, as is the morphogenesis of rods in nemaline myopathies, causative treatment concerning prevention or elimination of actin filament aggregates and restoration of normal muscle fibers is not available, but only supportive therapy concerning sequelae of muscle weakness, i.e., prevention of contractures and assistance in respiration is possible.

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## Activated Protein C Resistance

►Thrombosis, Venous Factor V Leiden, Resistance against Activated Protein C

## Acute Alcohol Disorders

►Alcohol Disorders

## Acute Cerebral Artery Occlusion

►Cerebral Artery Occlusion, Acute

## Acute Chorea

►Chorea of Sydenham

## Acute Colonic Pseudo-Obstruction

►Ogilvie's Syndrome

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## Acute Confusional State

- ▶ Delirium

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## Acute Intestinal Pseudo-Obstruction

- ▶ Ogilvie's Syndrome

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## Acute Coronary Syndrome

- ▶ Myocardial Infarction

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## Acute Iron Intoxication

- ▶ Iron Intoxication, Acute

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## Acute Febrile Neutrophilic Dermatositis

- ▶ Febrile Neutrophilic Dermatositis, Acute

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## Acute Liver Dystrophy

- ▶ Liver Failure, Acute

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## Acute Hemolytic Transfusion Reactions

- ▶ Transfusion Reactions

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## Acute Liver Failure

- ▶ Liver Failure, Acute

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## Acute Hepatitis

- ▶ Hepatitis, Acute

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## Acute Mountain Sickness

- ▶ Mountain Sickness, Acute

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## Acute Inflammation of the Oral Cavity

- ▶ Stomatitis

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## Acute Myocardial Infarction

- ▶ Myocardial Infarction, Acute

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## Acute Intermittent Porphyrism

- ▶ Porphyrism, Acute Intermittent

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## Acute Otitis Media

- ▶ Otitis Media, Acute

## Acute Pericarditis

- Pericarditis, Acute

## Acute Rejection

- Rejection, Acute

## Acute Respiratory Syndrome

- Respiratory Syndrome, Severe Acute

## Acute Rheumatic Fever

- Rheumatic Fever, Acute

## Acute Toxic Hepatitis

- Toxic Hepatitis, Acute

## Acute Viral Hepatitis

- Viral Hepatitis, Acute

## Acylcarnitine Transferase Deficiency

- Carnitine Palmitoyltransferase I Deficiency

## Acylcarnitine Translocase Deficiency

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### Synonyms

Carnitine-acylcarnitine translocase (CACT or CAT) deficiency; Carnitine-acylcarnitine carrier (CAC) deficiency

### Definition and Characteristics

An autosomal recessive defect in the CACT protein [1], situated on the inner mitochondrial membrane, responsible for transporting long-chain acylcarnitines into the mitochondria for energy utilization, especially during fasting periods [2–4].

### Prevalence

Extremely rare with approximately 30 reported cases.

### Genes

The gene for CACT, the solute carrier family 25 member 20 (SLC25A20), is assigned to chromosome 3p21.31 [1,2,4].

### Molecular and Systemic Pathophysiology

A defective CACT protein in the brain, heart, skeletal muscle and liver, causes insufficient fatty acid oxidation in these tissues, consequently resulting in neurological disorders, heart beat disorders, skeletal muscle damage and liver dysfunction [4]. A failure to transport long-chain acylcarnitines formed by carnitine palmitoyltransferase I (CPT I), leads to an accumulation of these in addition to long-chain acyl-CoA intermediates and free long-chain fatty acids outside the mitochondrion of cells [3]. This abnormal fatty acid transport and disrupted  $\beta$ -oxidation results in hypoketosis. The surplus fatty acids are oxidised by microsomal  $\omega$ -oxidation yielding dicarboxylic acids [4]. Additionally, short chain acylcarnitines (propionyl-carnitine, butyryl-/isobutyryl-carnitine and isovaleryl-/2-methylbutyryl-carnitine) are excreted in the urine and are present in the plasma of these patients. These are produced in the mitochondrial matrix from branched chain amino acid pathways [3]. Elevated propionyl-CoA and reduced acetyl-CoA, results in a lowered N-acetylglutamate, which in turn causes secondary urea cycle dysfunction and hyperammonaemia [4].

## Diagnostic Principles

Clinically two forms occur: a severe form with a high incidence of sudden childhood death, and a milder form [1–3]. Clinical symptoms or markers include coma, lethargy, cardiomyopathy, liver dysfunction, hypotonia, seizures, microcephaly and sudden death. Routine laboratory analyses show normal to low blood glucose (due to hepatic glycogen depletion and impaired gluconeogenesis), low blood ketones, acidosis, as well as increased lactate, ammonia, liver enzymes, creatine kinase (due to liver and muscle damage) and uric acid. Special laboratory analyses show slightly elevated dicarboxylic acids, normal acylglycines, lowered free carnitine and increased C<sub>16</sub>–C<sub>18</sub> acylcarnitines [2,4].

## Therapeutic Principles

Treatment of these patients during acute episodes entails glucose infusion in order to normalize blood sugar levels [2,5]. Carnitine supplementation is guided by plasma levels [2–3]. Patients should avoid periods of fasting by eating regularly [5]. Long-chain fatty acids should be restricted and be replaced by medium chain triglycerides [3–4].

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## ADA-deficient Severe Combined Immune Deficiency (ADA-SCID)

► Adenosine Deaminase Deficiency

## ADCL

► Cutis Laxa

## ADCME

► Epilepsies, Familial Benign Myoclonic

## ADD

► Attention-Deficit/Hyperactivity Disorder

## Addiction

► Pathological Gambling

## Addison's Disease

► Adrenal Insufficiency

## Additional Marker Chromosome 15

► Inv Dup (15)

## AD-EDMD

► Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

## Adenine Phosphoribosyltransferase Deficiency

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### Synonyms

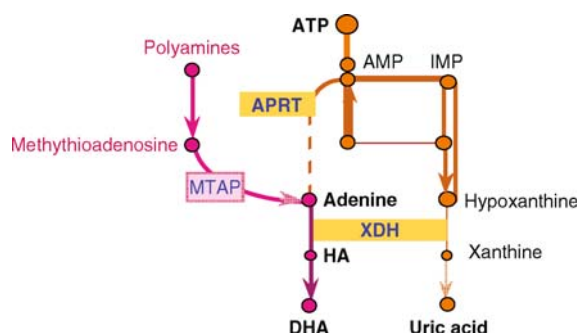
2,8-Dihydroxyadenine urolithiasis; APRT deficiency

### Definition and Characteristics

Autosomal recessive disorder involving adenine phosphoribosyltransferase (APRT), the enzyme that normally metabolizes adenine (a by-product of polyamine synthesis). In APRT deficiency (Fig. 1), adenine is metabolized via xanthine dehydrogenase (XDH) to the extremely insoluble 2,8-dihydroxyadenine (DHA), leading to urolithiasis and, in some cases, chronic renal failure that may require dialysis and/or transplantation [1].

### Prevalence

The prevalence of APRT heterozygotes is around 1%, but the prevalence of APRT-deficient individuals is much lower than expected, possibly due to mis- or under-diagnosis. The disorder is distributed worldwide and is not confined to any particular ethnic group. The prevalence is higher in Japan and Iceland due to founder effects [1,2].



**Adenine Phosphoribosyltransferase Deficiency.** **Figure 1** Role of APRT in removing adenine (a by-product of polyamine synthesis) and its conversion via XDH to DHA in APRT deficiency. HA, 8-hydroxyadenine; MTAP, 5Y-methylthioadenosine phosphorylase.

### Genes

Located on the long arm of chromosome 16 (16q24.3). The gene product is a dimer of identical subunits. The M136T mutation has been found only in Japan and is the most common mutation in that population. Fifteen mutations have been reported in non-Japanese populations, but D65V is the only mutation found in Icelandic patients to date. All mutations lead to enzyme deficiency in vivo, but two (M136T and V150F) show substantial (up to 25%) activity in vitro and thus may be mistaken for carriers of the defect.

### Molecular and Systemic Pathophysiology

APRT, a housekeeping gene expressed in all tissues, normally converts adenine into AMP, but in APRT deficiency adenine is oxidized by XDH in the liver to DHA. DHA is protein bound in vivo, but it can precipitate in the kidney leading to crystalluria and stone formation. Renal stones are not a common cause of renal failure, but chronic (and sometimes acute) renal failure can result due to DHA crystal deposition in the kidney of APRT-deficient patients. Several patients, in whom the disease went unrecognized, developed severe renal failure and have died. Others received dialysis or transplantation, but in some of these the defect was recognized only post-transplant, by the finding of the characteristic DHA crystals at biopsy following a rejection episode [3]. Symptoms may appear at birth or may not become apparent until the seventh decade and up to 50% of patients may be asymptomatic. This may account, at least in part, for the low prevalence of APRT deficiency. Studies in Aprt knockout mice indicate that DHA crystal deposition occurs first within tubular lumens, followed by deposition within epithelial cells and in the interstitium [4].

### Diagnostic Principles

The presence of round, brown crystals in urine deposits examined microscopically [2], or brownish spots on the diaper is suggestive of DHA, but this should be verified by the analysis of urine by HPLC or capillary electrophoresis. Routine stone analysis does not distinguish DHA from uric acid stones, which has led to misdiagnosis in the past. Plasma and urine uric acid are within normal ranges in this defect. APRT deficiency can be confirmed by enzyme assay in erythrocyte lysates, but the results can be misleading if (as in the majority of Japanese cases), the patient bears the M136T mutation that shows significant enzyme activity in vitro, or if the patient recently received a blood transfusion. APRT mutations can be readily detected by PCR and the functional significance of a mutation assessed by the ability of isolated lymphocytes to incorporate radiolabeled adenine into AMP [1].



## Therapeutic Principles

DHA synthesis, and hence stone formation, can be prevented by allopurinol, an inhibitor of XDH (adenine itself has no apparent toxicity *in vivo*). A low purine diet and high fluid intake are also suggested. Unlike uric acid stones, alkali administration is not beneficial, since the solubility of DHA is not altered within the normal physiological pH range. In patients with renal failure, the allopurinol dose must be adjusted to minimize the side effects of oxipurinol (the active metabolite of allopurinol). Invasive treatments have included extracorporeal shockwave lithotripsy and renal transplantation, but urolithiasis (and the ensuing renal damage) may recur if the underlying cause is not recognized [1].

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## Adenomatous Polyposis Coli

### ► Adenomatous Polyposis, Familial

## Adenomatous Polyposis, Familial

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## Synonyms

Adenomatous polyposis coli; Bussey-Gardner polyposis; Gardner syndrome; FAP

## Definition and Characteristics

Familial adenomatous polyposis is an autosomal dominantly inherited disorder characterized by numerous adenomatous polyps predisposing patients to the

development of cancer. The disease is caused by germline mutations in the APC gene located at chromosome 5q21–22. The incidence of FAP is about 1:10,000 and it accounts for ~ 1% of all new colorectal cancer.

In FAP patients adenomas are endoscopically detectable between the age of 10 and 20 years. The progression of one or more adenomas to cancer is thereby a basic feature of FAP. The mean age of manifestations of colonic carcinomas in untreated FAP patients is about 40 years with an almost complete penetrance. However, cancer can arise at an early age and even in children with FAP. The colorectal cancer risk at the age of 20–25 years is 1–6%. Extracolonic manifestations like congenital hypertrophy of the retinal pigment epithelium (CHPRE), desmoid tumours or epidermoid cysts are further FAP characteristics which may serve as diagnostic markers of FAP.

A milder form of FAP, attenuated familial adenomatous polyposis (AFAP), is characterized by the presence of fewer than 100 adenomas, located more proximal and a delayed age of onset (about 15 years later than patients with classical FAP). Patients with AFAP have a cumulative risk of CRC by the age of 80 years of approximately 70%. Family history of polyps or CRC in AFAP patients may often be negative and secondary manifestations can lack. Underlying gene mutations are frequently located in the extreme proximal or distal regions of the APC gene.

## Prevalence

25:1,000,000

## Genes

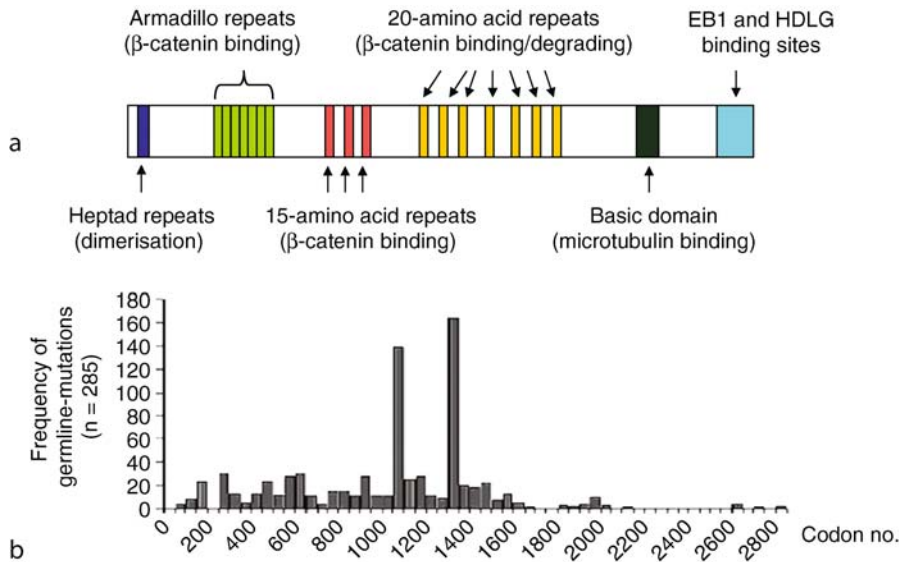
The APC gene (Fig. 1) is located on chromosome 5q21–22 [1,2] and spans over a region of 120 Kb.

Although the APC gene is composed of 15 exons encoding 2843 amino acids there are 21 exons, 7 of which are alternatively expressed [3]. Sixteen different APC transcripts are characterized with distinct 5' regions due to alternative splicing.

Mutations are distributed throughout the gene and the vast majority of these introduce premature stop codons resulting in the production of a truncated APC protein. Germline mutations at the codons 1061 and 1309 are relatively frequent and account for 20% of all identified germline mutations in the APC gene. About 10% of APC mutations are large deletions which can comprise the entire gene. Missense mutations with unknown relevance are relatively rare.

## Molecular and Systemic Pathophysiology

The APC protein contains a couple of functional domains which are required for several biological



**Adenomatous Polyposis, Familial. Figure 1** a) Structure of the APC gene. b) Distribution and frequency of APC germline mutations (data were retrieved from the online APC mutation database at <http://www.perso.curie.fr/Thierry.Soussi/APC.html>).

processes (Fig. 1). Central regions are required for binding and degradation of the  $\beta$ -catenin protein which causes the down regulating of the Wnt signal pathway. A carboxy-terminal located APC region mediates phosphorylation of glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and is required for stabilization of a complex of two proteins [4]. In unstimulated cells GSK3 $\beta$  promotes phosphorylation of conductin/axin which is added to the APC-GSK3 $\beta$  complex. This leads to the recruitment and phosphorylation of  $\beta$ -catenin which is thus targeted for degradation by the ubiquitin/proteasome pathway. If the Wnt pathway is stimulated, GSK3 $\beta$  is unphosphorylated and  $\beta$ -catenin accumulates. In the cytoplasm  $\beta$ -catenin binds to the cell adhesion protein E-cadherin and links E-cadherin to the actin cytoskeleton. Free  $\beta$ -catenin shuttles into the nucleus, binds to transcription factors of the TCF4/LEF family causing altered expression of genes affecting proliferation, migration and apoptosis (c-MYC, cyclinD1, matrilysin, ephrins, caspases). Thus, non-functional APC leads to accumulation of  $\beta$ -catenin and to uncontrolled expression of tumour promoting genes.

### Diagnostic Principles

The classical FAP is clinically defined by the presence of at least 100 colorectal adenomatous polyps [5]. Histological confirmation requires examination of several polyps. In the case of a definite family history the detection of fewer adenomas at an early age is sufficient. Clear diagnosis of FAP is achieved by the

detection of a pathogenic APC gene mutation which can be found in about 95% of FAP patients.

If clinical criteria are suspect and no APC mutation are detectable, FAP diagnosis is supported by the presence of extracolonic diseases like epidermoid cysts, osteomas or desmoid tumours.

Children of affected FAP parents should be examined by flexible sigmoidoscopy from the age of 10 to 12 and years and should be monitored at 1–2 years intervals until the age of 40 years if no adenomas are detectable. Mutation analysis can replace endoscopies in families where a pathogenic mutation has been identified.

### Therapeutic Principles

FAP patients or persons with proven pathogenic APC mutations should generally be treated by (prophylactic) colectomy or proctocolectomy when adenomas become detectable, and before the age of 20–25 years.

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## Adenosine Deaminase Deficiency

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### Synonyms

ADA-deficient severe combined immune deficiency; ADA-SCID

### Definition and Characteristics

Autosomal recessive defect leading to profound depletion of T, B and NK lymphocytes [1]. Typical patients are infants with lymphocytopenia, failure to thrive and life-threatening opportunistic infections (SCID). Fifteen to 20% are less severely affected and present at 1–8 years of age; several adults have been diagnosed at 15–39 years. Some healthy children and adults with very low erythrocyte ADA activity but with significant ADA activity in nucleated cells have been identified by screening and have been designated “partial ADA deficiency.”

### Prevalence

Estimated to occur in 1 per 250,000 to 1 per million live births. ADA deficiency is present in about 15% of all patients with SCID and in about 30% of those with autosomal recessive inheritance.

### Genes

The 12 exon, 32 kb ADA gene is located on chromosome 20q13.11 [2]. A G/C rich “housekeeping” promoter, which lacks TATA and CCAT sequences, allows basal transcription in all cells; an enhancer in the first intron determines high-level ADA expression in thymocytes. The 1.5 kb ADA mRNA is translated into a 363 amino acid, 41.7 kD protein [3].

### Molecular and Systemic Pathophysiology

The highest ADA activity occurs in lymphoid cells. Erythrocytes have about 0.1% of thymocyte activity. Erythrocyte ADA is a soluble protein of 41 kD, but in medullary thymocytes, activated T cells and epithelial cells of kidney, liver and some other tissues ADA also exists in complexes of >200 kD, due to binding of the 41 kD monomer to the cell membrane-associated glycoprotein CD26/dipeptidyl peptidase IV.

ADA catalyzes the deamination of adenosine (Ado) and 2'-deoxyadenosine (dAdo), producing inosine (Ino) and 2'-deoxyinosine (dIno). dAdo arises from DNA breakdown in lymphoid organs, including apoptosis of “negatively selected” immature thymocytes, antigen activation-induced apoptosis of T lymphocytes in lymph nodes and dissolution of the nuclei of erythroid progenitors in marrow.

Red blood cells of ADA-deficient SCID patients show (i) a marked elevation of dATP and total dAdo nucleotides (dAXP) and (ii) reduced activity of S-adenosylhomocysteine (AdoHcy) hydrolase (<5% of normal), due to “suicide-like” inactivation of ADA by dAdo. dAdo is also found in urine.

Toxic effects of dATP and AdoHcy, as well as elevated extracellular Ado acting through G-protein-coupled Ado receptors are thought to impair the viability, differentiation or function of lymphoid cells [1]. Specific pathogenic mechanisms include (i) allosteric inhibition by dATP of ribonucleotide reductase, blocking DNA replication and repair, (ii) induction of apoptosis resulting from the interaction of dATP with cytoplasmic cytochrome c, apoptosis activating factor-1 and procaspase-9 to form the “apoptosome” and (iii) inhibition by AdoHcy of S-adenosylmethionine-dependent transmethylation reactions.

More than 70 different ADA gene mutations, about 60% missense, have been identified. Among 52 phenotypically diverse patients and healthy subjects with “partial deficiency”, whose 43 genotypes were derived from 42 different mutations, the total ADA activity expressed by both alleles of each genotype correlated well with red cell dAXP level and age at diagnosis [4].

### Diagnostic Principles

Erythrocyte ADA activity, measured by spectrophotometric or radiochemical assay, is <1% of normal and dATP (total dAXP) in erythrocytes, measured by HPLC, is elevated 30 to >1,000-fold. In patients transfused prior to testing, ADA deficiency is suggested by an elevation in erythrocyte dATP (dAXP). Although erythrocyte ADA activity is also very low in healthy subjects with “partial ADA deficiency”, dATP (dAXP) is not elevated due to elimination of dAdo by residual ADA activity in non-erythroid tissues.

Because of genetic heterogeneity, ADA genotype analysis is used for diagnosis only if the mutations in a previously affected family member have been determined. Prenatal diagnosis is based on the absence of ADA activity in cultured amniocytes or fibroblasts from a chorionic villus biopsy.

### Therapeutic Principles

SCID is fatal within a year or two. Bone marrow or stem cell transplantation (BMT/SCT), enzyme replacement therapy and experimental gene therapy have all been used to treat ADA. BMT/SCT from an HLA-identical sibling is usually well tolerated and curative. Patients lacking such a donor may receive BMT/SCT from an HLA-haploidentical (usually parental) or HLA-matched unrelated donor, but morbidity is greater and immune reconstitution significantly less.

Enzyme replacement therapy (one or two weekly intramuscular injections of polyethylene glycol-modified bovine ADA (PEG-ADA) is used for patients considered poor candidates for BMT/SCT from an HLA-mis-matched or unrelated donor. PEG-ADA is not curative and in most restoration of immune function is partial. However, it has been well tolerated, with survival comparable to or better than transplantation.

Clinical trials of gene therapy using retroviral vectors have been in progress for over a decade. Gene transfer and expression have been variable and concomitant treatment with PEG-ADA has complicated evaluation of clinical benefit. Greater efficiency of stem cell transduction, resulting in correction of immunodeficiency, has been reported in two patients not receiving PEG-ADA [5]. Gene therapy trials for ADA deficiency are currently on hold, following development of leukemia in 2 of 10 patients with X-linked SCID who had undergone successful stem cell gene therapy using a retroviral vector.

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## Adenylosuccinate Lyase Deficiency

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### Synonyms

ADSL deficiency

### Definition and Characteristics

Autosomal recessive inborn error of purine nucleotide synthesis leading generally to severe psychomotor retardation, frequently accompanied by epilepsy and/or autistic features. Rare patients display only mild mental retardation, isolated muscle hypotonia or autism [1–3].

### Prevalence

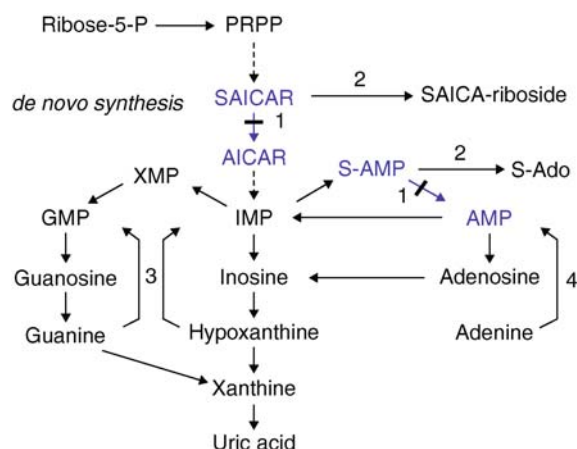
Unknown, but to date about 60 patients have been identified in 14 countries. Most cases have been diagnosed in The Netherlands, Belgium and the Czech Republic.

### Genes

The ADSL gene has been mapped to chromosome 22q13.1-q13.2. The 1452-nucleotide cDNA sequence encodes a 484-amino acid protein. The 4-subunit enzyme has a molecular weight of ~200,000. Thirty seven ADSL gene mutations have been identified. All are missense with the exception of a 39-bp deletion and a mutation in the 5′ untranslated region. About half the patients are compound heterozygotes. Most frequently encountered, in about one-third of the alleles, is an R426H mutation.

### Molecular and Systemic Pathophysiology

Adenylosuccinate lyase catalyzes two steps in the synthesis of AMP and GMP (Fig. 1), the conversion of succinyl aminoimidazolecarboxamide ribotide (SAICAR) into aminoimidazolecarboxamide ribotide (AICAR) and the conversion of adenylosuccinate (S-AMP) into AMP. The deficiency results in accumulation in body fluids of SAICA-riboside and succinyl adenosine (S-Ado), the products of dephosphorylation, by 5′-nucleotidase(s), of the two substrates of the enzyme. Although ADSL deficiency might be expected to lead to decreased synthesis of adenine and guanine nucleotides, normal levels of the latter were measured in freeze-clamped liver, kidney and muscle of patients. This can be explained by residual activity of the enzyme and by circumvention of the defect by the purine salvage enzymes HGPRT and APRT. The symptoms of ADSL deficiency might thus be caused by neurotoxic effects of the accumulating succinyl purines. In most



### Adenylosuccinate Lyase Deficiency.

**Figure 1** Pathways of Purine Metabolism. 1, ADSL; 2, 5'-nucleotidase(s); 3, hypoxanthine-guanine phosphoribosyltransferase (HGPRT); 4, adenine phosphoribosyl-transferase (APRT)

patients, S-Ado/SAICA-riboside ratios are  $\sim 1$ . The observation of milder mental retardation in patients with similar SAICA-riboside levels but S-Ado/SAICA-riboside ratios above 2, as compared to  $\sim 1$  in severely affected subjects [2], suggests that SAICA-riboside is the offending compound and that S-Ado could protect against its toxic effects. Hitherto however, all attempts to demonstrate neurotoxicity of the succinyl purines have failed.

### Diagnostic Principles

Due to the marked clinical heterogeneity in ADSL deficiency, screening for the defect should be performed in unexplained psychomotor retardation and neurological disease. Diagnosis is based on the presence of S-Ado and SAICA-riboside in urine and/or cerebrospinal fluid. Both are normally undetectable. A modified Bratton-Marshall test [4] on urine is the most practical. False positive results may be found in patients receiving medications, particularly sulfonamides or antiepileptics. Final diagnosis requires HPLC and UV detection [1].

### Therapeutic Principles

With the aim of correcting the hypothetical depletion of purine nucleotides in ADSL-deficient tissues, some patients have been treated with oral adenine and allopurinol, the latter to avoid conversion of adenine to the poorly soluble 2,8-dihydroxyadenine. No clinical or biochemical improvement was noted, with the exception of some acceleration of growth [2]. More recently, trials with ribose in a single patient showed a reduction of seizure frequency, which was not sustained.

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## ADHAPS Deficiency

► Rhizomelic Chondrodysplasia Punctata

## Adhesion of the Labia Minora

► Labial Fusion

## ADHH

► Hypocalcaemia with Hypercalciuria, Autosomal Dominant

## ADHR

► Osteomalacia

## Adiposity

► Obesity

## ADOA

► Optic Atrophy, Autosomal Dominant, Kjer Type



## ADP

► ALA Dehydratase Porphyria

## ADPKD

► Polycystic Disease (Kidney)

## Adrenal Hyperplasia, Congenital

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### Synonyms

21-Hydroxylase deficiency-classical salt wasting (OMIM 201910) and 3 $\beta$ -Hydroxysteroid dehydrogenase deficiency classical (OMIM 201810); Steroidogenic acute regulatory protein deficiency (OMIM 201710); CAH

### Definition and Characteristics

Congenital adrenal hyperplasia is a group of autosomal recessive diseases whose common feature is an enzymatic defect in the steroidogenesis pathway. Three forms of congenital adrenal hyperplasia with salt wasting and hypotension have been described: (i) 21-Hydroxylase deficiency-classical salt wasting (OMIM 201910), which causes salt-wasting with life-threatening vomiting and dehydration occurring within the first weeks of life. It is also the most common cause of ambiguous genitalia due to prenatal virilization of genetically female (XX) infants; (ii) 3 $\beta$ -Hydroxysteroid dehydrogenase II (HSD 3 $\beta$ 2) deficiency is an uncommon cause of CAH and results from loss of function of one of the key enzymes in adrenal cortisol synthesis. This form of CAH can cause salt wasting adrenal crises in infancy and is the only form that produces sexual ambiguity in both sexes; (iii) Congenital lipoid adrenal hyperplasia is the most severe form of congenital adrenal hyperplasia. Affected individuals do not synthesize any steroid hormones leading to a severe salt-wasting syndrome that is fatal if not treated in early infancy. All affected infants are phenotypic females because of the lack of production of testosterone.

### Prevalence

Rare disease.

### Genes

- 21 hydroxylase gene (CYP21 gene); Gene map locus 6p21.3; inheritance autosomal recessive;
- 3 $\beta$ -Hydroxysteroid dehydrogenase II gene (HSD3 $\beta$ 2 gene); Gene map locus 1p13.1; Inheritance autosomal recessive;
- Steroidogenic acute regulatory gene (StAR gene), Cytochrome P450 side chain cleavage enzyme (P450scc); Gene map locus 8p11.2; Inheritance autosomal recessive.

### Molecular and Systemic Pathophysiology

Deficient activity of the enzyme 21-hydroxylase (21-OH) reduces cortisol and aldosterone synthesis leading to elevated ACTH levels and hyperplasia of the adrenal cortex. Aldosterone deficiency results in urinary salt loss with impaired K<sup>+</sup> and H<sup>+</sup> secretion and affected infants develop hypotension with hyperkalemia and metabolic acidosis in the first week of life. Ability to maintain systemic blood pressure is further compromised by cortisol deficiency. The early symptoms of this form of CAH are spitting and poor weight gain, but most infants with severe CAH develop vomiting and shock by the first two or three weeks of life. The steroid precursors, progesterone, 17-hydroxypregnenolone, and 17-hydroxyprogesterone (17OHP) are increased in the circulation. Since 21-OH activity is not involved in synthesis of androgens, a fraction of the elevated 17-hydroxypregnenolone is converted to dehydroepiandrosterone (DHEA), androstenedione, and testosterone beginning in the third month of fetal life. This results in virilization in female infants that is evident at birth.

3 $\beta$ -HSD II mediates three parallel dehydrogenase/isomerase reactions in the adrenal glands that convert  $\Delta$ 4 to  $\Delta$ 5 steroids: 17-Hydroxypregnenolone to 17-Hydroxyprogesterone, DHEA to androstenedione and pregnenolone to progesterone. 3 $\beta$ -HSD II also converts androstenediol to testosterone in the testes. Deficient activity of the enzyme reduces cortisol with or without aldosterone synthesis leading to elevation of ACTH levels. The increased ACTH results in large elevations of pregnenolone, 17-hydroxypregnenolone, and DHEA. Severe forms of 3 $\beta$ -HSD deficiency with combined aldosterone and cortisol deficiency can result in life-threatening salt-wasting crisis in early infancy. The excess fetal production of DHEA causes virilization in genetic females. Underproduction of testosterone in the testis causes sexual ambiguity in genetic males. It is the only form of CAH that can produce genital ambiguity in both sexes.

Most cases of lipoid adrenal hyperplasia are due to mutations of the gene for a protein called steroidogenic acute regulatory protein (StAR) which transports cholesterol into the mitochondria. Deficiency results in impaired synthesis of all three categories of adrenal steroids (cortisol, mineralocorticoids, and sex steroids) and testosterone in the testis. The absence of cortisol and aldosterone leads to salt wasting crisis in infancy. High levels of ACTH lead to adrenal hyperplasia with lipid accumulation and to hyperpigmentation. Lipid accumulation also damages the testes and ovaries so that even with appropriate adrenal hormone replacement, gonadal function and fertility cannot be preserved.

### Diagnostic Principles

Salt-wasting forms of adrenal hyperplasia are accompanied by low serum aldosterone concentrations, hyponatremia, hyperkalemia and elevated plasma renin activity (PRA) secondary to hypovolemia. Further diagnosis of specific types of salt wasting congenital adrenal hyperplasia depends on the demonstration of inadequate production of cortisol, aldosterone, or both in the presence of an excess of precursor hormones. High serum concentration of 17-hydroxyprogesterone (usually >1,000 ng/dL) and urinary pregnanetriol (metabolite of 17-hydroxyprogesterone) with classic clinical features like ambiguous genitalia in females, normal genitalia in males with precocious puberty, salt wasting and hyperpigmentation are suggestive of 21-hydroxylase deficiency. Diagnosis of 3 $\beta$ -HSD CAH is usually made because of the appearance of ambiguous genitalia at birth or by development of a salt-wasting crisis in the first month of life. In this form of CAH, pregnenolone, 17-hydroxypregnenolone, and DHEA, are elevated. Steroidogenic acute regulatory protein deficiency is suggested by the finding of an elevated ACTH, with decreased cortisol, DHEA and testosterone in the setting of salt wasting.

### Therapeutic Principles

Patients with volume depletion, hyponatremia, or hyperkalemia should receive an intravenous isotonic saline solution, as needed, to restore their intravascular volume. Dextrose may be necessary if the patient is hypoglycemic. After the patient's condition is stabilized, all patients should be treated with long-term glucocorticoid or aldosterone replacement (or both) as necessary. The goal of therapy of adrenal hyperplasia is the replacement of glucocorticoid and mineralocorticoids to prevent hypovolemia and hypotension and to suppress precursor hormones that cause virilization. Infants with ambiguous genitalia will require surgical evaluation.

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## Adrenal Hypoplasia, Congenital

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### Synonyms

X-linked Addison's disease; Congenital adrenal hypoplasia with hypogonadotropic hypogonadism; Cytomegalic adrenocortical hypoplasia

### Definition and Characteristics

Congenital adrenal hypoplasia is a rare inherited disorder with genetic heterogeneity which generally presents within the first year of life with variable signs and symptoms, including vomiting and malaise, hypotension from hypovolemia and hyperpigmentation [1,2].

Three forms of congenital adrenal hypoplasia have been identified, as follows:

1. An X-linked form (OMIM 300200) is caused by a mutation or deletion of the DAX1 gene (dosage-sensitive sex reversal adrenal hypoplasia congenita critical region of the X chromosome, also called the AHCH gene) on the X chromosome. This form is usually associated with hypogonadotropic hypogonadism and failure to undergo puberty in boys. If the deleted region includes the contiguous glycerol kinase gene, psychomotor retardation and Duchenne type muscular dystrophy is also seen.
2. The autosomal recessive form (OMIM 184757) is from a mutation of the gene that codes for steroidogenic factor 1 (SF-1) on chromosome 9q33. This is associated with ambiguous genitalia in genetic males.
3. An autosomal recessive form of uncertain etiology (OMIM 240200) has also been identified.

### Prevalence

Rare disease.

## Genes

DAX1, steroidogenic factor (SF1), Gene map locus Xp21.3-p21.2, 9q33, Inheritance X linked, Autosomal recessive.

## Molecular and Systemic Pathophysiology

The roles of DAX1 and the undefined autosomal recessive gene in development of the adrenal cortex are not fully understood. DAX1 appears to be necessary for differentiation of the definitive adult adrenal cortex but not the fetal adrenal cortex, since the latter is preserved in patients who have deletions of DAX1. DAX1 acts as a transcriptional repressor for SF-1 and other genes involved in steroidogenesis. SF-1 is a transcriptional activator regulating steroidogenesis and male sexual differentiation and DAX1 is one of its principal targets.

## Diagnostic Principles

The most difficult aspect of adrenal insufficiency is clinical suspicion because signs and symptoms can be insidious or subtle. A cosyntropin stimulation test confirms the diagnosis of adrenal insufficiency. A spot urine or a 24-h urine for sodium, potassium, and creatinine, along with simultaneous serum sodium concentrations and creatinine concentrations, will determine whether inappropriate natriuresis is occurring. High-resolution karyotype may also be helpful.

## Therapeutic Principles

Patients are generally hypovolemic and may be hypoglycemic; therefore, initial therapy should consist of intravenous normal saline and dextrose. In cases of hypotension, a bolus dose of isotonic fluids over the first hour may be necessary to restore blood pressure. This can be repeated if the blood pressure remains low. Once electrolytes, blood sugar, cortisol, 17-hydroxyprogesterone and ACTH concentrations are obtained, the patient should be treated with glucocorticoids based on suspicion of adrenal insufficiency, since it may be life preserving.

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## Adrenal Insufficiency

A

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## Synonyms

Addison's disease; Morbus Addison (for primary forms of adrenal insufficiency); Adrenocorticotrophic pituitary insufficiency (for secondary forms of adrenal insufficiency)

## Definition and Characteristics

Adrenal insufficiency (AI) is a heterogeneous group of diseases leading to a functional impairment of the hypothalamic pituitary adrenal (HPA) axis. Eventually, there is a lack of glucocorticoids and/or mineralocorticoids. AI is termed "primary," when the disease process is located within the adrenal glands, "secondary" when the pituitary is the site of failure, or "tertiary" when the hypothalamus hosts the cause of the disease. In addition, there is a group of disorders that can not be classified within this scheme, but are characterized by relative hypocortisolism. In these cases, the need of glucocorticoids exceeds the capacity of the HPA axis, such as in critically ill patients when the strong feedback by cortisol prevents the adequate rise in ACTH secretion.

## Prevalence

Congenital adrenal hypoplasia, the demyelinating X-linked lipid metabolism disorders: adrenoleukodystrophy and adrenomyeloneuropathy, and other causes of primary adrenal insufficiency, such as unresponsiveness to corticotropin, have a low prevalence. On the other hand, iatrogenic forms of AI are frequent. Autoimmune adrenalitis is the most common cause of primary AI in developed countries (70%). Secondary AI compromises the largest patient population with AI.

## Genes

A monogenetic form of this syndrome, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED, APS type I), is due to mutations in the autoimmune regulatory (AIRE) gene located on chromosome 21q22.3.

Isolated familial glucocorticoid deficiency may be due to ACTH resistance and consists of two distinct genetic syndromes, both of which being inherited as autosomal recessive traits. Inactivating mutations of the ACTH receptor (MC2R) gene or mutations in other

genes are causes for isolated resistance to ACTH. Allgrove syndrome (triple A syndrome) may be due to mutations in the AAAS gene on chromosome 12q13, which codes for the alacrima-achalasia-adrenal insufficiency-neurologic disorder (ALADIN) protein.

Hereditary or congenital adrenal dysfunction is particularly important in the pediatric patient population and is in the majority of cases due to steroid 21-hydroxylase deficiency. Isolated hypoaldosteronism can occur as a consequence of corticosterone 18-methyl oxidase II deficiency. Hyporeninemia and renal tubular acidosis type IV are also associated with hypoaldosteronism. Adrenal hypoplasia congenita (AHC) can occur in an X-linked trait due to a mutation in the DAX-1 gene. Hypogonadotropic hypogonadism or premature puberty can be combined with this disorder or the only clinical presentation.

Susceptibility to develop APS type II, a polygenetic disorder, is conferred by genes in the human leukocyte antigen (HLA) region on the short arm of chromosome 6. Different susceptibility and resistance alleles of the MHC class II have been identified so far. Other candidate genes include the cytotoxic T lymphocyte antigen 4 (CTLA4) coding region of chromosome 2 on q33.

### Molecular and Systemic Pathophysiology

In rare cases, AI is secondary to monogenic defects. The most important cause of AI is, however, autoimmune adrenalitis. It occurs isolated or in combination with other autoimmune diseases in autoimmune polyendocrinopathy syndrome (APS) (Table 1).

Other causes of AI include bilateral adrenal tumors due to chronic infectious, granulomatous or tumorous diseases, including postprimary tuberculosis, sarcoidosis, toxoplasmosis, histoplasmosis, or metastatic infiltration (e.g., lung or breast cancer, malignant melanoma). Destruction of the adrenal cortex can also be the result of hemorrhage during meningococemia. Also adrenocortical glucocorticoid secretion is frequently impaired in chronic systemic diseases, including amyloidosis and AIDS.

Iatrogenic AI includes bilateral adrenalectomy and treatment with special drugs. Secondary AI most frequently results from suppression of the HPA axis by and subsequent correction or withdrawal of endogenous (Cushing's syndrome) or exogenous (iatrogenic) glucocorticoids. Other causes include hypopituitarism following neurosurgery or irradiation to control neoplastic lesions (pituitary adenoma, craniopharyngeoma). In addition, vascular lesions, trauma, Sheehan's syndrome, and apoplexy can also lead to impaired pituitary function. "Idiopathic" hypopituitarism is either due to mutations in genes expressed by the corticotrophs, such as prop-1, or due to hypophysitis, e.g., in autoimmune triple H syndrome.

Tertiary AI is a rare form of adrenal insufficiency and mostly due to irradiation, hemorrhage, tumors, and ischemia. The glucocorticoid resistance syndrome is an end-organ resistance, effectively presenting as glucocorticoid deficiency. Since aldosterone is not only stimulated via ACTH, secondary and tertiary AI is usually limited to glucocorticoid deficiency.

The clinical presentation of AI can vary, depending on age of manifestation and underlying disorder. While symptoms of primary AI in the majority of cases are determined by hypocortisolism and hypoaldosteronism, secondary and tertiary AI result only occasionally in hypoaldosteronism. On the other hand, in secondary and tertiary forms, AI is very often complicated by somatotrophic, gonatotrophic, and thyrotrophic insufficiency, and often the last deficiency develops in hypopituitarism. All forms of adrenal insufficiency may present as an acute adrenal crisis or as chronic state with exacerbations. Symptoms include poor feeding in infants, weakness, failure to thrive, weight loss, fatigue, nausea and vomiting, diarrhea, orthostatic hypotension with dizziness from postural or persistent hypotension to hypovolemic shock due to dehydration. Other signs may be fever, abdominal pain, or hypoglycemia. Patients with chronic primary AI present with hyperpigmentation (creases of palms, nail lunulae, buccal mucosa, breast areolas and nipples, and scars), because of extensive ACTH levels. Enzyme deficiencies of CAH,

**Adrenal Insufficiency. Table 1** Autoimmune disorders associated with Addison's disease

Autoimmune endocrine diseases	Autoimmune diseases of other tissues
Autoimmune adrenalitis	Skin/ectodermal manifestations (chronic mucocutaneous candidiasis, vitiligo, alopecia, nail dystrophy, keratokconjunctivitis, enamel dysplasia)
Autoimmune thyroid disease	
Autoimmune hypergonadotropic	
Hypogonadism	
Diabetes mellitus type I	Chronic atrophic gastritis (with pernicious anemia, hypergastrinemia with benign carcinoids)
Chronic hypoparathyroidism	
Autoimmune hypophysitis	Celiac disease with malabsorption
	Autoimmune hepatitis

**Adrenal Insufficiency. Table 2** Differentiation between primary, secondary, and tertiary adrenal insufficiency

Adrenal insufficiency	Primary	Secondary	Tertiary
Cortisol, baseline	<5 µg/dL	<10 µg/dL	<10 µg/dL
Cortisol, baseline during crisis	<18 µg/dL	<18 µg/dL	<18 µg/dL
Plasma ACTH, baseline	High	Low	Low
Plasma renin, baseline	High	Normal	Normal
Aldosterone, baseline	Low	Normal	Normal
Cortisol 60 min after ACTH	<20 µg/dL	<20 µg/dL	<20 µg/dL
Cortisol 30 or 60 min after CRH	<20 µg/dL	<20 µg/dL	<20 µg/dL
Plasma ACTH 30 or 60 min after CRH	High	Minor response	delayed
Cortisol after insulin-induced hypoglycemia	<20 µg/dL	<20 µg/dL	<20 µg/dL
Plasma ACTH after insulin	High	Minor response	Minor response

hyperandrogenism leads to virilization in girls and premature puberty or acne conglobata in boys.

### Diagnostic Principles

Early laboratory findings in AI may be lymphocytosis, eosinophilia, and neutropenia before hyperkalemia and hyponatremia develop. In addition, azotemia and metabolic acidosis may point to the diagnosis of AI. Hormone measurements are given in Table 2.

### Therapeutic Principles

Since routine laboratory studies do not necessarily demonstrate abnormalities, waiting for hormone analyses should not delay therapeutic intervention during adrenal crisis and be initiated immediately after the blood tests. Hypovolemic shock requires rapid replacement of sodium, glucose and water deficits. The therapeutic goal is an optimal and dynamic replacement of glucocorticoids and, if necessary, mineralocorticoids, depending on stress-related needs. All patients and their close relatives and friends need careful education. Usually, patients tolerate glucocorticoid therapy very well. Treatment of choice is hydrocortisone orally. To simulate the circadian rhythm of glucocorticoid secretion, split doses are given (Table 3).

Patients should take the first dose early in the morning and adopt their plan to the working time or sport exercises. In slight stress, before surgery, dental treatment, or during periods of intercurrent infection, the dosage has to be doubled or even tripled. During severe stress, such as infection or major surgery, replacement doses up to 200 mg hydrocortisone per day are required, sometimes, even continuous intravenous infusion. After overcoming this situation, the hydrocortisone doses should be returned to the normal replacement regimen within a few days. When doses higher of 60 mg hydrocortisone per day are given, no separate mineralocorticoid replacement is needed.

**Adrenal Insufficiency. Table 3** Example for glucocorticoid replacement therapy

Glucocorticoid	Morning	Noon	Afternoon
<b>Primary AI</b>			
Hydrocortisone	15 mg	5–10 mg	5 mg
Cortison acetate	25 mg	–	12.5 mg
Prednisone	5 mg	–	–
<b>Secondary and tertiary AI</b>			
Hydrocortisone	10 mg	5 mg	–

Otherwise, 0.05–0.1 mg fludrocortisone should be added in primary AI. Since these patients are frequently not quite able to conserve electrolytes, they should be put on a sodium-enriched diet. Treatment with corticotropin in subcutaneous injections conserves androgen secretion but bears the risk of allergic side effects and anaphylaxis. Therefore, female Addisonian patients have a better well-being when given DHEA in daily doses between 50 and 100 mg.

Adrenal crisis is often precipitated by acute stress. Therefore, appropriate increase in hydrocortisone replacement serves to restore glucocorticoid function. Slight elevation of TSH can be present in adrenal crisis and, independently, in autoimmune thyroid disease. If adrenal insufficiency is suspected, cortisol replacement has to be started earlier than treatment for hypothyroidism, because replacement of levothyroxin thrives the metabolism and may worsen the patient's condition in AI. Salt and volume loss are treated by intravenous infusion of 5% glucose in normal saline solutions lacking potassium. Cortisol should be administered, starting with a bolus of 100 mg.

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## Adrenal Insufficiency, Secondary

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### Synonyms

Central hypocortisolism; Adrenocorticotrophic insufficiency

### Definition and Characteristics

Adrenal insufficiency (AI) is a heterogenous group of diseases leading to a functional impairment of the hypothalamic pituitary adrenal (HPA) axis. AI is termed “secondary” when the pituitary is the site of failure, or “tertiary” when the hypothalamus hosts the cause of the disease. In clinical routine, very often the term *secondary adrenal insufficiency* is used for all pituitary or hypothalamic disorders and also for states of adrenal insufficiency after high-dose or long-term treatment with glucocorticoids.

### Prevalence

Secondary AI compromises the largest patient population with AI.

### Genes

“Idiopathic” hypopituitarism may be caused by mutations in genes expressed by the corticotrophs, such as *prop-1*, *DAX-1*, *pit-1*, and others.

### Molecular and Systemic Pathophysiology

Suppression of the HPA axis by and subsequent correction or withdrawal of endogenous (Cushing’s syndrome) or exogenous (iatrogenic) glucocorticoids is the most common cause of secondary AI. Other causes include hypopituitarism following neurosurgery or irradiation to control neoplastic lesions (pituitary adenomas, craniopharyngeoma, meningiomas, metastasis) while tumors of the pituitary or adjacent structures themselves may

impair the function of pituitary corticotrophs. In addition, granulomatous diseases (e.g., sarcoidosis and others), vascular lesions, trauma, Sheehan’s syndrome, apoplexy, or hemorrhage into tumors can also lead to impaired pituitary function. “Idiopathic” hypopituitarism is either due to genetic defects of genes expressed by the corticotrophs or due to hypophysitis, e.g., in autoimmune triple H syndrome.

The clinical presentation of secondary AI can vary, depending on age of manifestation and the underlying disorder. Although aldosterone is mainly regulated by the renin-angiotensin-aldosterone system, secondary and tertiary AI are not necessarily limited to glucocorticoids and – in women – androgen deficiency. In addition, secondary AI is very often complicated by somatotrophic, gonatotrophic, thyreotropic insufficiency, and central diabetes insipidus and often the last to develop in hypopituitarism. Isolated forms of secondary AI exist and occur more frequently in idiopathic forms of hypopituitarism. However, AI may present as an acute adrenal crisis or as a chronic state with exacerbations. Typical symptoms include poor feeding in infants and failure to thrive. Other symptoms are algos, weakness, arthralgias, fatigue, nausea and vomiting, abdominal pain, diarrhea, weight loss, and orthostatic hypotension with dizziness. Other features may be fever, hyponatremia, and hypoglycemia.

### Diagnostic Principles

Early laboratory findings in AI may be lymphocytosis, eosinophilia, and neutropenia before hyponatremia and hyperkalemia develop. In addition, azotemia, metabolic acidosis, and low plasma glucose may point to the diagnosis of AI. Hormone measurements are given in [Table 1](#).

### Therapeutic Principles

Since routine laboratory studies do not necessarily demonstrate abnormalities, waiting for hormone analyses should not delay therapeutic intervention during adrenal crisis and initiated immediately after the blood tests. Salt and volume loss are treated by intravenous infusion of 5% glucose in normal saline solutions lacking potassium. Cortisol should be administered, starting with a bolus of 100 mg. Perspective, the therapeutic goal is an optimal and dynamic replacement of glucocorticoids and, if necessary, mineralocorticoids and androgens, depending on stress-related needs. All patients and their close relatives and friends need careful education. Treatment of choice is hydrocortisone orally. To simulate the circadian rhythm of glucocorticoid secretion split doses are given, e.g., 10 mg–5 mg–0 mg, sometimes less, sometimes 12 mg per qm body surface or more, depending on symptoms,

**Adrenal Insufficiency, Secondary. Table 1** Differentiation between primary, secondary, and tertiary adrenal insufficiency

Adrenal insufficiency	Primary	Secondary	Tertiary
Cortisol, baseline	<5 µg/dL	<10 µg/dL	<10 µg/dL
Cortisol, baseline during crisis	<18 µg/dL	<18 µg/dL	<18 µg/dL
Plasma ACTH, baseline	High	Low	Low
Plasma renin, baseline	High	Normal	Normal
Aldosterone, baseline	Low	Normal	Normal
DHEAS, baseline	Low	Low	Low
Postmenopausal gonadotropins	High	Low	Low
Cortisol 60 min after 250 µg ACTH	<20 µg/dL	<20 µg/dL	<20 µg/dL
Cortisol 30 or 60 min after 100 µg CRH	<18 µg/dL	<18 µg/dL	<18 µg/dL
Plasma ACTH 30 or 60 min after CRH	High	Blunted response	Delayed or good response
Cortisol after insulin-induced hypoglycemia	<20 µg/dL	<20 µg/dL	<20 µg/dL
Plasma ACTH after insulin	High	Minor response	Minor response

lymphocyte count, electrolytes, electrolyte diuresis, and 24-h urinary excretion of cortisol.

Patients should take the first dose early in the morning and adopt their plan to the working time or sport exercises. In slight stress, before surgery, dental treatment, or during periods of intercurrent infection, the dosage has to be doubled or even tripled. During severe stress, such as infection or major surgery, replacement doses up to 200 mg hydrocortisone per day are required, sometimes even continuous intravenous infusion. After overcoming this situation, the hydrocortisone doses should be returned to the normal replacement regimen within a few days. Female patients with AI have a better well-being when given DHEA or low-dose testosterone.

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## Adrenocorticotrophic Pituitary Insufficiency

### ► Adrenal Insufficiency

## Adrenogenital Syndrome

### ► Steroid 21-Hydroxylase Deficiency

## Adrenoleukodystrophy

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## Synonyms

Formerly Schilder's disease

## Adrenocorticotrophic Insufficiency

### ► Adrenal Insufficiency, Secondary

## Definition and Characteristics

X-linked recessive disease that primarily affects young boys with an onset between 3 and 10 years and exhibits progressive behavioral, cognitive, visual, auditory and gait abnormalities (juvenile or childhood cerebral

form). Death usually occurs within three years. Most develop clinical signs of adrenocortical insufficiency and after the onset of neurologic symptoms. Adolescent and adult forms also occur.

## Prevalence

1:25,000 in males.

## Genes

The ABCD1 (formerly ALD) gene on Xq28 has ten exons and encodes a peroxisomal integral membrane ABC half-transporter, ABCD1 or ALDP. A large number of mutations have been identified: about one-half are missense and one-quarter are frameshift mutations; exon 5 appears to be a mutational hot spot. Mutations in ABCD1 do not correlate with specific phenotypes in that the identical mutation can result in the AMN, ALD or Addisonian phenotypes in the same family. Modifier genes or environmental factors are suspected to contribute to the phenotypic variability [1].

## Molecular and Systemic Pathophysiology

The precise cellular role of ABCD1 is unclear. There is some evidence that ABCD1 can homodimerize or heterodimerize with other peroxisomal membrane proteins, and that overexpression of one may compensate for a deficiency of another. The expression of the ABCD1 transcript is highest in the adrenal gland and intermediate in brain. ABCD1 is most prominent in adrenal cortex, microglia, astrocytes, endothelial cells, and oligodendrocytes of the corpus callosum and internal capsule. How the absence of ABCD1 relates to the biochemical signature of all phenotypes: elevations in abnormal saturated very long chain ( $\geq C22$ ) fatty acids (VLCFA), is uncertain. The peroxisomal beta oxidation system is responsible for initiating the degradation of VLCFA. The abnormal VLCFA had been assumed to be due to decreased peroxisomal degradation primarily through decreased activity of its acyl-CoA synthetase (lignoceroyl-CoA ligase), but there is also evidence for increased synthesis by the microsomal elongation system. Recent data derived from knockout mice have cast doubt on the primacy of the former and the postulate that ABCD1 may transport VLCFA or its acyl-CoA synthetase across the peroxisomal membrane. These data also raise questions about the putative pathogenic role of VLCFA [2].

The systemic pathophysiology of ALD (or AMN) appears to be a complex pathogenetic fabric in which VLCFA, abnormal membrane fluidity, myelin instability, axonal dysfunction, inflammation/immune activation and perhaps age-related steroid fluctuations conspire to wreak havoc in the central nervous system (CNS). The endocrine failure is due to primary atrophy and apoptotic death of adrenocortical and testicular

Leydig cells, presumably caused by the cytotoxic effects of free VLCFA.

We have proposed that dysmyelinative foci (loss of myelin and oligodendrocytes without an appreciable cellular reaction) constitute the initial myelin lesion of ALD and might be due to the incorporation of saturated VLCFA into myelin, which can lead to its spontaneous breakdown. Free saturated VLCFAs are extremely insoluble, particularly at normal body temperature; they adversely affect the viscosity of erythrocyte and adrenocortical cell membranes, disrupt model membranes, and are toxic to a number of cell types. The toxicity of free fatty acids varies directly with their length and degree of saturation. Most of the emphasis in ALD has been on C26:0 and C24:0, but longer chain lengths also occur. The sources for the VLCFA are both endogenous and exogenous. The greatest excess occurs in ganglioside, PLP, cholesterol ester and phosphatidylcholine fractions, the latter even in "normal" white matter. The cholesterol esters are found in macrophages of actively demyelinating areas, not in normal areas, which indicates that they are secondary players in the dysmyelination. VLCFA in any of the other three myelin components would be reasonable candidates to destabilize the myelin sheaths, once a certain threshold is reached. PLP is the most appealing candidate, both for the dysmyelination and particularly for the transition to inflammatory demyelination [3].

The inflammatory demyelination appears to involve an initial innate immune response to the insoluble lipids that may simulate a bacterial pathogen, in which macrophages and astrocytes produce cytokines, particularly TNF- $\alpha$ ; this promotes a compromise of the blood-brain barrier and an influx of sensitized lymphocytes. An adaptive immune response then supervenes and several pathogenic elements seem to participate: an MHC-dependent TH-1 response, MHC-unrestricted CD1 lipid presentation, CD8 CTLs (probably unconventional), and oxidative damage by peroxynitrite and 4-hydroxynonenal, with resultant oligodendroglial lysis and loss of myelin. It is noteworthy that, despite biochemical and ultrastructural evidence for the involvement of brain, peripheral nerve, adrenal cortex, and testis, the only inflammatory site in ALD or AMN that converts to ALD is the brain. Hence, a CNS-specific antigen, such as PLP, is particularly appealing [4,5].

## Diagnostic Principles

Cerebral signs or symptoms with or without adrenocortical failure in a young male confirmed by an elevation of VLCFA, particularly C26:0, in plasma.

## Therapeutic Principles

Replacement therapy for adrenal insufficiency. Low fat diet combined with Lorenzo's oil (glyceryl trioleate-trierythrate) can rapidly lower plasma VLCFA and may

be beneficial. Bone marrow, or stem cell at present, transplantation is effective in pre-clinical or mildly affected patients. Highly immunosuppressive protocols, including anti-oxidants such as N-acetylcysteine, are under study in more neurologically compromised patients. Gene therapy is in the developmental stage.

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## Adrenoleukodystrophy

► Leukodystrophy

## Adrenomyeloneuropathy

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## Synonyms

Adult variant of adrenoleukodystrophy; ALD; AMN

## Definition and Characteristics

X-linked recessive disease in which men in their third to fourth decade, with or without adrenocortical or testicular dysfunction, develop difficulty walking due to spastic paraparesis and sensory ataxia that progresses slowly over years to eventuate in a wheelchair-bound existence; a milder peripheral neuropathy usually co-exists. Their neurological symptomatology may be restricted to this myeloneuropathy (pure AMN) or they may develop clinical signs or MRI lesions of cerebral white matter disease (cerebral AMN) that manifests as mild psychomotor deficits to visual or auditory abnormalities to dementia to a rapidly fatal ALD phenotype. Voiding abnormalities and impotence are common. Female heterozygotes may become symptomatic with a milder course and later onset of neurological deficits.

## Prevalence

1:20,000 in males and 1:15,000 in females.

## Genes

See ► Adrenoleukodystrophy.

## Molecular and Systemic Pathophysiology

See essay on ► Adrenoleukodystrophy.

The systemic pathophysiology of AMN (or ALD) appears to be a complex pathogenetic fabric in which Very long chain Fatty acids (VLCFA), abnormal membrane fluidity, myelin instability, axonal dysfunction, inflammation/immune activation and perhaps age-related fluctuations in steroid levels somehow conspire to wreak havoc in the central nervous system (CNS). In AMN the major CNS lesion is a myelopathy, but adrenal and testicular dysfunction usually co-exist. The endocrine failure is due to primary atrophy and apoptotic death of adrenocortical and testicular Leydig cells, presumably caused by the cytotoxic effects of free VLCFA.

The precise pathophysiology of the myelopathy is unknown, but neuropathologic and neurophysiologic data are most consistent with a primary “dying-back” axonopathy. The predominant spinal lesion is one of bilaterally symmetrical long tract degeneration, most commonly affecting the gracile tracts of the posterior columns (which carry the ascending large proprioceptive and vibratory sensation fibers of the dorsal root ganglia (DRG) from the legs) and the crossed lateral corticospinal tracts (which carry the descending large pyramidal fibers from the cerebrum). The tract degeneration consists of equivalent losses of axons and myelin sheaths that are greatest and seen earliest in the cervical gracile tracts and the lumbar

corticospinal tracts. That is, the axonal degeneration is most severe in the axonal compartment most distant from the parent cell body (e.g., DRG for gracile tracts) and progressively becomes equally severe in more proximal segments (“dying-back” toward the cell body) [1]. The parent neurons in the lumbar DRG, and presumably those of the pyramidal tracts, are atrophic but not appreciably lost at autopsy – which makes therapeutic intervention a realistic possibility if the pathophysiologic mechanism can be identified [2]. It has been postulated that, when VLCFA become incorporated into axonal membranes their viscosity/fluidity is adversely affected. An alternate, and perhaps not mutually exclusive, pathophysiologic mechanism would be an abnormality in axoplasmic transport. The recent discovery of abnormal mitochondria (lipidic inclusions) in DRG of AMN patients raises the possibility of decreases in energy needed for axoplasmic transport [2]. If ALDP were found to be transported down the axon, this could provide a most desirable pathophysiologic link between the gene defect and the neuropathologic data.

### Diagnostic Principles

Gait difficulties with or without adrenocortical, rarely testicular, failure in a young adult male. Confirmed by an elevation of VLCFA, particularly C26:0, in plasma.

### Therapeutic Principles

Replacement therapy is needed for adrenal insufficiency. Androgen replacement therapy is more controversial. Low fat diet combined with Lorenzo’s oil (glyceryl trioleate-trierucate) can rapidly lower plasma VLCFA and may be beneficial. Bone marrow, or stem cell at present, transplantation is not recommended for AMN, but is being considered if AMN begins to convert to ALD. Gene therapy is in the developmental stage and not yet available [3].

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## ADSL Deficiency

- Adenylosuccinate Lyase Deficiency

## Adult-Onset Diabetes

- Metabolic Syndrome

## Adult Polyglucosan Body Disease

- Glycogen Branching Enzyme Deficiency

## Adult Tapeworm Infection

- Taeniasis

## Adult T-Cell Leukemia/Lymphoma

- T-Cell Leukemia/Lymphoma, Adult
- T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Adult-Type Hypolactasia

- Lactose Intolerance

## Adult Variant of Adrenoleukodystrophy

- Adrenomyeloneuropathy



## Afferent Loop Syndrome

- ▶ Postgastrectomy Syndrome

## Agglutination of the Labia Minora

- ▶ Labial Fusion

## AFL

- ▶ Hepatic Steatosis

## Aggressive NK Cell Leukemia

- ▶ Lymphocyte Leukemia, Large Granular

## AFLD

- ▶ Hepatic Steatosis

## Aggressive T-Cell LGL Leukemia

- ▶ Lymphocyte Leukemia, Large Granular

## AFTNs

- ▶ Hyperthyroidism due to Thyroid Autonomy

## Aging Macula Disorder

- ▶ Macular Degeneration, Age-related

## AGAT Deficiency

- ▶ Arginine-Glycine Amidinotransferase Deficiency

## Agnogenic Myeloid Metaplasia

- ▶ Myelofibrosis
- ▶ Primary Myelofibrosis

## Age-related Macular Degeneration

- ▶ Macular Degeneration, Age-related

## AGS

- ▶ Alagille Syndrome

## Age-related Maculopathy

- ▶ Macular Degeneration, Age-related

## AHO

- ▶ Pseudohypoparathyroidism Type 1A

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## AIDS

- ▶ Acquired Immunodeficiency Syndrome

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## AIED

- ▶ Inner Ear Disease, Autoimmune

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## AIH

- ▶ Hepatitis, Autoimmune

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## AIHA

- ▶ Anemia, Hemolytic Autoimmune

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## AIS

- ▶ Androgen Insensitivity Syndrome

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## AISA

- ▶ Anemia, Sideroblastic Acquired Idiopathic

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## AIVR

- ▶ Accelerated Idioventricular Rhythm

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## Akinetic Crisis of Parkinson's Disease

- ▶ Neuroleptic Malignant Syndrome

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## ALA Dehydratase Porphyria

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### Synonyms

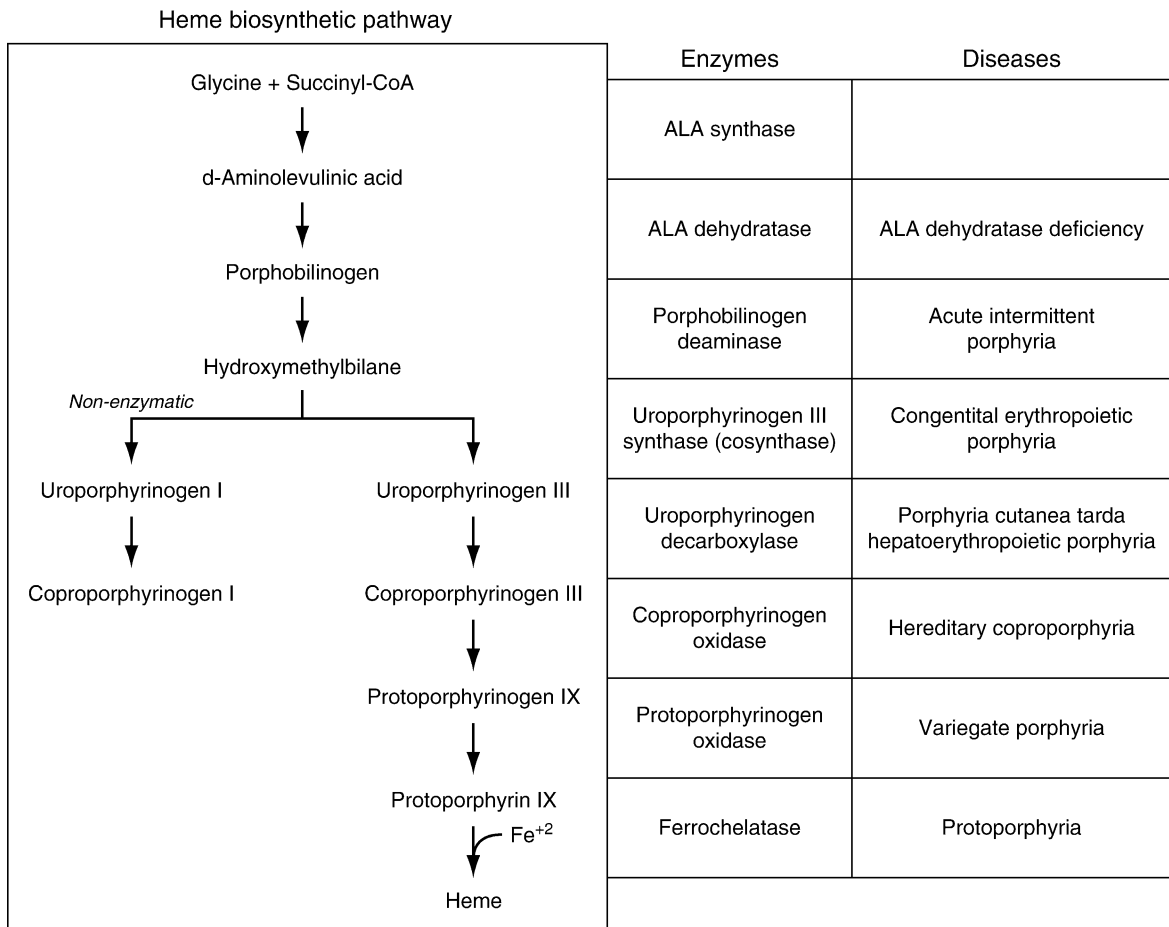
Doss porphyria; Plumboporphyria; ADP

### Definition and Characteristics

$\delta$ -aminolevulinic acid dehydratase porphyria (ADP) is a rare disorder caused by a profoundly decreased activity of  $\delta$ -aminolevulinic acid dehydratase (ALAD), also known as porphobilinogen synthase (PBGs). ALAD catalyses the second step in the heme biosynthetic pathway, namely the condensation of two molecules of  $\delta$ -aminolevulinic acid (ALA) into one of porphobilinogen (PBG) (Fig. 1).

ADP has an autosomal recessive inheritance and all of the well-documented cases thus far described have been males. Affected patients present with a variety of neurovisceral symptoms. Cutaneous manifestations have not been described in ADP [1]. The abdominal symptoms are very similar to those of the other acute porphyrias (acute intermittent porphyria, hereditary coproporphyria, variegate porphyria) and include episodes of colicky abdominal pain, nausea, vomiting, and constipation. Other neurologic manifestations include autonomic neuropathy, polyneuropathy, psychiatric symptoms or convulsions. Precipitating factors such as exposure to porphyrogenic drugs have not been evident in most reported cases.

Heterozygotes, who have ~50% of the normal activity of ALAD, are asymptomatic, but may have enhanced susceptibility to lead, and to the toxic effects of other chemicals such as 4,6-dioxoheptanoic acid (succinylacetone), iron, trichloroethylene, and styrene that can adversely affect the ALAD activity [2].



**ALA Dehydratase Porphyria. Figure 1** The heme biosynthetic pathway.

### Prevalence

Fewer than a dozen cases have been reported so far. The prevalence of heterozygous ALAD deficiency is estimated to be less than 1% in Germany and 2% in Sweden.

### Genes

The human ALAD gene is found on chromosome 9 (9q34). It is 16 kb in length with two promoter regions and two alternative first exons, 1A and 1B, that generate housekeeping and erythroid-specific transcripts, respectively. Both transcripts encode the same amino acid sequence. The promoter region upstream of the housekeeping exon 1A is GC-rich and contains three potential Sp1 elements and a CCAAT box. Further upstream there are three potential GATA-1 binding sites and an AP-1 site. The promoter region upstream of the erythroid-specific exon 1B has several CACCC boxes and two potential GATA-1 binding sites [3]. These two promoter regions associated with human ALAD gene generate housekeeping and erythroid-specific transcripts by alternate splicing.

A common ALAD polymorphism, K59N, termed ALAD2, is seen in ~20% of Caucasians. ALAD2 retains normal enzyme activity but may be associated with increased susceptibility to lead toxicity.

Most, if not all, ADP cases described to date have inherited a different ALAD mutation from each unrelated parent and thus are compound heterozygotes. Eleven ALAD mutations, mostly point mutations, have been identified so far. (Cardiff; [www.hgmd.cf.ac.uk](http://www.hgmd.cf.ac.uk)).

### Molecular and Systemic Pathophysiology

ADP is often classified as an hepatic porphyria, although the site of overproduction of ALA is not established and would not be expected to be limited only to the liver. The human enzyme is believed to be a homo-octamer with a subunit size of 31-kDa. The enzyme requires an intact sulfhydryl group and one zinc atom ( $\text{Zn}^{2+}$ ) per subunit for full activity.

Human ALAD exists as an equilibrium of functionally distinct quaternary structure assemblies, known as “morphoeins,” in which one functional homo-oligomer has the ability to dissociate, change conformation and

reassociate into a different oligomer. A high activity octamer assembly and a low activity hexamer assembly have been described in human ALAD, which are in dynamic equilibrium. In ADP, the ALAD conformation has been shown to shift towards the less active hexamer assembly [4].

ALAD is the principal lead binding protein in erythrocytes, and inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure. Succinylacetone (which accumulates in hereditary tyrosinemia type I) is the most potent inhibitor of ALAD, and ~40% of patients with this form of tyrosinemia develop signs and symptoms similar to ADP.

### Diagnostic Principles

Production, plasma levels, and urinary excretion of ALA are increased markedly in the face of near normal PBG levels. In contrast, other hepatic porphyrias show elevations in ALA and PBG to a similar extent.

All suspected cases should undergo a measurement of erythrocyte or lymphocyte ALAD activity. Erythrocyte ALAD activity is markedly reduced, and is not restored by the *in vitro* addition of dithiothreitol, which helps distinguish this disease from lead poisoning. Heterozygous parents have approximately half-normal activity of ALAD and normal urinary ALA [2]. All confirmed cases should ideally undergo mutational analysis, especially if they have first degree relatives.

Lead poisoning should be excluded by finding normal blood lead levels and showing that ALAD activity is not restored by dithiothreitol. Hereditary tyrosinemia should be excluded in young children.

### Therapeutic Principles

Hemin therapy was effective in most reported cases with acute attacks, as evidenced by clinical improvement along with decreases in urinary or serum levels of ALA. In one case weekly infusions of hemin were required to prevent recurrent attacks [5]. Limited experience shows that glucose is not very effective, but may be tried for mild symptoms. Porphyrigenic drugs should be avoided in all patients with ADP. Supportive care is similar as for other acute porphyrias [1].

There has been a single case report of liver transplantation in a Swedish child with severe disease. It is contentious whether liver transplant was of benefit or not.

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## Alagille Syndrome

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### Synonyms

AGS; Syndromic bile duct paucity; Arteriohepatic dysplasia; Watson-Miller syndrome

### Definition and Characteristics

Autosomal dominant developmental disorder which may include liver, heart, eye, kidney, craniofacial, skeletal, and central nervous system (CNS) abnormalities [1]. These include most commonly paucity of interlobular bile ducts, peripheral pulmonary artery stenosis, posterior embryotoxin, characteristic facies, and butterfly vertebrae.

### Prevalence

One in 100,000 live births. This may underestimate the true incidence with respect to phenotypically mild cases.

### Genes

Caused by mutations in the JAG1 gene, which encodes a cell surface ligand, Jagged1, for Notch family receptors. Most patients have null alleles, suggesting that JAG1 haploinsufficiency causes the disorder in these cases.

### Molecular and Systemic Pathophysiology

The disorder is caused by mutations in the JAG1 gene, leading to haploinsufficiency in most affected patients [2,3]. JAG1 encodes a cell surface ligand, Jagged1, for the Notch family receptors. While there is nearly complete penetrance, expression is quite variable. JAG1 mutations can be identified in 70% of patients, and are inherited in 30–50%. Mutations have been identified in almost all of the 26 exons of the gene, and include total gene deletions (6%) as well as

protein-truncating (insertions, deletions, and nonsense mutations) (82%) and missense mutations (12%). Most (72%) of the reported mutations lead to frameshifts and a premature termination codon. During both mouse and human development, JAG1 is strongly expressed in the regions of heart, kidney, eye, and developing nervous system which are ultimately affected. Interestingly, JAG1 is not expressed in developing hepatocytes or bile ducts, but rather the adjacent portal veins and hepatic arteries. This may link abnormal angiogenesis to the resulting bile duct paucity. Mice with homozygous deletion of Jag1 die during embryogenesis from defects in vascular remodeling, while Jag1+/- mice only exhibit abnormalities in eye development. Interestingly, mice doubly heterozygous for a Jag1 null allele and a Notch2 hypomorphic allele (expressed in adjacent hepatoblasts which may be bile duct precursors) exhibit a phenotype similar to Alagille syndrome; this work may give further insight into the variable phenotypic expression in humans [4].

### Diagnostic Principles

This diagnosis should be considered in all infants with neonatal cholestasis, as well as older patients with cholestatic liver disease and other features of the syndrome. The characteristic facies includes a broad forehead, deep-set eyes, mild hypertelorism, a straight nose, and a small pointed chin. The diagnosis may be made after using liver biopsy to identify paucity of interlobular bile ducts (defined as a ratio of bile ducts to portal tracts  $\leq 0.9$ ), combined with cardiac ultrasound, plain radiography, and ophthalmologic examination. It is generally accepted that, in addition to bile duct paucity, three of the following cardinal features should be present to make the diagnosis in a proband: cholestasis, characteristic facies, posterior embryotoxin, butterfly vertebrae, and consistent renal or cardiac disease. Family members with as few as one to two consistent clinical features should also be evaluated. JAG1 mutational analysis in the proband will facilitate this. Approximately 89% of patients who meet the overall criteria for AGS have bile duct paucity. Paucity may develop over time in infants with AGS, as the liver disease progresses.

### Therapeutic Principles

The majority of the morbidity in AGS is due to the cardiac and/or liver disease, and therapy is tailored accordingly. Most early mortality (before age 6) is related to the presence of complex congenital heart disease, while late mortality is primarily due to advanced liver disease. Recently, intracranial bleeding has also been reported in 12–14%. The subset of patients with chronic cholestatic liver disease tend to have the most severe clinical course, and will benefit

from supportive care including medium chain triglyceride containing formulas as infants and fat soluble vitamin supplementation. Most presenting during infancy will remain jaundiced, with growth failure and pruritis; 10–50% will progress to cirrhosis. Pruritis can be extreme, and an indication for liver transplantation. Hypercholesterolemia is also common, and does not typically respond to medical therapy. Biliary diversion may significantly alleviate both pruritis and hypercholesterolemia, and should be considered prior to liver transplantation in patients who have not developed cirrhosis [5]. Indications for liver transplantation may include intractable pruritis, complications of cirrhosis, synthetic liver failure, or growth failure; this amounts to 21–50% of patients who present with liver disease in infancy. It should be noted, however, that growth failure may not improve after liver transplantation. Post-transplant survival has been reported in the range of 79–92%.

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## β-Alanine-α-Ketoglutarate Aminotransferase Deficiency

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### Synonyms

BAKAT

\*deceased



## Definition and Characteristics

Autosomal recessive? A nearly complete deficiency of BAKAT is hypothesized in patients with primary hyper- $\beta$ -alaninemia. A partial deficiency of BAKAT is associated with Cohen's syndrome.

## Prevalence

The defect is very rare. Only one patient has been reported with a nearly complete deficiency [1] and one patient with a partial deficiency (50% of normal activity) [2].

## Genes

The gene locus is unknown.

## Molecular and Systemic Pathophysiology

The one reported boy with the putative nearly complete BAKAT deficiency suffered from hypotonia, hyporeflexia, generalized therapy-resistant tonic clonic seizures and intermittent lethargy and died in infancy. The patient with a proven partial deficiency of BAKAT had intermittent seizures, lethargy and Cohen's syndrome.

BAKAT is generally assumed to be the same enzyme as GABA transaminase (GABAT), but the clinical and metabolic phenotypes of deficiencies of these enzymes differ. Linear growth is normal or increased in GABAT deficiency but decreased in BAKAT deficiency. The  $\beta$ -alanine levels in the patient with the putative nearly complete BAKAT deficiency were two to three times normal, in plasma and CSF and 100 times normal in urine. Since the concentrations of malonic semialdehyde in urine were not increased, the block in the metabolic pathway is expected to be at the transamination step. In the patient with the partial deficiency, elevated levels of  $\beta$ -alanine were present in urine, but in plasma and CSF they were only seen after a 12 hours fasting period. The activity of BAKAT in the fibroblasts was decreased to 70% of control values. In the patients with GABAT deficiency, the  $\beta$ -alanine concentration in CSF was only eight times normal [3]. The symptoms in patients with hyper- $\beta$ -alaninemia presumably reflect the agonistic effect of  $\beta$ -alanine on GABA receptors in the nervous tissue (see also the Fig. 1 in the chapter on  $\beta$ -aminoisobutyrate-pyruvate aminotransferase deficiency).

## Diagnostic Principles

Hyper- $\beta$ -alaninemia in combination with increased concentrations of  $\beta$ -aminoisobutyric acid, GABA and taurine in urine are indicative of BAKAT as well as GABAT deficiency, but in BAKAT deficiency  $\beta$ -alanine in CSF is 100 times higher than in GABAT deficiency. Increased concentrations of the relevant amino acids in the body fluids can easily be identified by quantitative amino acid analysis.

## Therapeutic Principles

In the patient with presumed BAKAT deficiency, the metabolic but not the clinical abnormalities improved on treatment with 10 mg/day of pyridoxine orally. In the patient with proven partial BAKAT deficiency in fibroblasts, both the metabolic and the clinical symptoms improved dramatically on 100 mg/day of pyridoxine.

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## Albers-Schönberg Disease

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## Synonyms

Marble bones disease [1]; Autosomal dominant osteopetrosis type II; Osteosclerosis fragilis generalisata

## Definition and Characteristics

An autosomal dominant form of osteopetrosis localized on chromosome 16p13.3.

## Prevalence

The prevalence of Albers-Schönberg disease is estimated at about 1/100,000 individuals [2].

## Genes

The CLCN7 chloride channel gene on chromosome 16p13.3 [3].

## Molecular and Systemic Pathophysiology

The CLCN7 chloride channel is a protein with several transmembrane domains. It has an important function in the bone resorbing cell (osteoclast). This multinucleated cell attaches to the bone thus creating an extracellular compartment. Acidification of this compartment is essential for the bone resorption process. The acidic environment is created by transfer of protons over the plasma membrane by a vacuolar-type ATPase

protonpump. The function of the CLCN7 chloride channel is to compensate for the potential generated over the membrane by transferring Cl<sup>-</sup> anions. Missense mutations in the gene encoding CLCN7 were found in patients with Albers-Schönberg disease. These mutations most likely resort a dominant-negative effect as CLCN7 are known to act as dimers.

## Diagnostic Principles

The clinical picture is highly variable ranging from individuals that are asymptomatic to patients with a very high fracture rate. Osteoarthritis of the hip and mandibular osteomyelitis can also occur. Radiologically it manifests with segmentary osteosclerosis mainly affecting the vertebral endplates (“rugger jersey spine”), the iliac wings with endobones and the skull base.

## Therapeutic Principles

No therapeutic intervention effective in increasing the bone resorption in these patients is currently available.

### ► Osteopetrosis

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## Albinism

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## Definition and Characteristics

Albinism defines a genetically and clinically heterogeneous group of diseases characterized by reduction in melanin in the skin, hair and eye (oculocutaneous albinism, OCA, mostly autosomal recessive), or primarily in the eye (ocular albinism, OA, X-linked recessive).

## Prevalence

Among the different forms of albinism OCA2 has the highest prevalence of 1:37,000 in Caucasians, 1:15,000 in African-Americans, and 1:3,900 in Southern Africans with Bantu-speaking origin.

## Genes

Tyrosinase gene (Tyr), MIM 203100; P gene, MIM 203200; Tyrosinase-related protein-1 gene (TYRP1), 203290; Membrane-associated transporter protein (MATP), MIM 606574; HPS1 gene, MIM 604982; Beta-3 A-adaptin gene (ADTB3A), MIM 603401; HPS3 gene, MIM 606118; HPS4 gene, MIM 606682; HPS5 gene, 607521; HPS6 gene; MIM 607522; CHS1 gene; MIM 214500; OAI gene MIM 300500 (1).

## Molecular and Systemic Pathophysiology

Mutations of at least 12 different genes are responsible for albinism [1,2] (Table 1). Tyrosinase is the rate-limiting enzyme in melanin synthesis. Single base, missense, nonsense, frameshift and splice site mutations result in absent (in OCA1A) or reduced tyrosinase activity (in OCA1B). Mutations of OCA2 encoding the human homologue of the pink-eyed dilution gene cause OCA2. OCA2 encodes a transmembrane protein involved in generation and maintenance of the melanosomal pH. Mutations of TYRP1 result in OCA3. TRP-1 has DHICA oxidase activity and stabilizes tyrosinase and DOPACHrome tautomerase activity. Hermansky-Pudlak syndrome (HPS) is genetically heterogeneous. HPS type 1 is caused by mutations of HPS1 encoding a transmembrane protein of 79 kDa which is involved in biogenesis of lysosomes and lysosome-related organelles. In other patients with HPS mutations in ADTB3A encoding the  $\beta$ 3A subunit of AP3, an adaptor protein complex implicated in protein trafficking, were detected [3,4]. The gene associated with ►Chediak-Higashi syndrome (CHS), LYST, encodes a 430 kDa protein involved in fusion/fission events of lysosomes and related organelles. Mutations of OA1 cause OA1. The OA1 protein interacts with heterotrimeric G<sub>i</sub> proteins and appears to be involved in intracellular signaling, reorganization of the late endosomal compartment and melanosomal biogenesis [5].

## Diagnostic Principles

Albinism is most often detected by the characteristic ocular changes that are iris translucency, nystagmus and reduced visual acuity due to diminished amounts of retinal melanin and foveal hypoplasia. In OCA1A patients have white hair, skin and blue irides at birth and there is no pigment production throughout the life. Due to residual tyrosinase activity (detectable by the DOPA reaction of hair bulbs) the hair color of patients

**Albinism. Table 1** A selection of genes and loci of albinism

Type of albinism	MIM#	Human chromosome	Human locus	Encoded protein	Murine locus	Functional role in pigmentation
OCA1	203,100	11q14–21	<i>TYR</i>	Tyrosinase	<i>albino (c)</i>	Melanogenic enzyme
OCA2	203,200	15q11–13	<i>OCA2</i>	Melanosomal membrane protein <sup>1</sup>	<i>pink-eyed dilution (p)</i>	Stabilization of melanosomal pH
OCA3	203,290	9q23	<i>TYRP1</i>	Tyrosinase-related protein (TPP-1)	<i>brown (b)</i>	Melanogenic enzyme/stabilizing factor
HPS	604,982	10q24	<i>HPS1</i>	Membrane protein	<i>pale ear (ep)</i>	Lysosome/melanosome structure/function
CHS	214,500	1q43	<i>CHS1</i>	Membrane protein	<i>beige (bg)</i>	Lysosome/melanosome structure/function
OA1	300,500	Xp22.3–22.3	<i>OA1</i>	Melanosomal membrane protein	<i>OA1 (oa)</i>	Intracellular signaling/melanosomal biogenesis

<sup>1</sup>Modified from Oetting and King [2].

with OCA1B changes from white to blond during the first decade and may even become brown. These individuals may also tan and their visual acuity may improve. Prenatal and postnatal detection of genomic tyrosinase mutations is possible by allele-specific hybridization and PCR. Patients with the typical OCA2 have yellow hair, creamy skin and blue irides at birth. The ethnic background determines the final development of pigment. Individuals with OCA3 (formerly known as rufous albinism) have reddish skin and hair with minimal visual disturbance. Albinism associated with accumulation of ceroid-like pigment in the reticuloendothelial system and a bleeding diathesis due to a platelet storage pool deficiency is characteristic for HPS. CHS is a multisystemic disorder with features of OCA, haematologic, neurologic abnormalities, and problems with infection. Although OA primarily involves the eye it actually represents another form of OCA as cutaneous melanocytes display histologically giant melanosomes.

### Therapeutic Principles

Photoprotection is essential to minimize the risk of cutaneous cancers especially in patients with OCA1 and OCA2. Topical broad-spectrum sunscreens, physical sun protection and sunglasses are necessary and regular clinical examination on a yearly basis are advised.

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## Albinism with Hemorrhagic Diathesis and Pigmented Reticuloendothelial Cells

### ► Hermansky-Pudlak Syndrome

## Albright Hereditary Osteodystrophy

### ► Pseudohypoparathyroidism Type 1A

## Albright Syndrome

### ► Fibrous Dysplasia

## Alcalosis

### ► Alkalosis

## Alcohol Disorders

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### Synonyms

Acute alcohol disorders; Chronic alcohol disorders

### Definition and Characteristics

1. Alcohol intoxication: Acute alcohol-related psychopathological alterations.
2. Alcohol abuse: Repeated consumption pattern being associated with somatic and/or mental health problems.
3. Alcohol dependence (“alcoholism”): Repeated consumption pattern being associated with increase of tolerance, withdrawal symptoms, “craving,” loss of control and preference of alcohol consumption compared with other activities.
4. Alcohol-related complicating transitory and chronic psychopathological syndromes: Any other psychiatric consequence being caused by alcohol consumption such as transitory or chronic alcohol-related psychotic, cognitive and/or affective syndromes.

### Prevalence

Substantial intercultural differences, highest in alcohol-“permissive” cultures such as Germany, France, Spain and Italy with a range of about 2–5% of the general population for both alcohol abuse and dependence.

### Genes

Alcoholism is a complex disorder with both genetic and environmental risk factors. Multiple genes have been demonstrated to modulate the susceptibility for alcoholism (Table 1). An important hypothesis is that people with alcohol dependence experience less aversive alcohol effects which is associated with (i) a genetically

**Alcohol Disorders. Table 1** Genes that may have an influence on alcohol use and dependence in humans [5]

ADH	Alcohol dehydrogenase
ALDH2	Aldehyd dehydrogenase
GABRA	Gamma-aminobutyric acid A receptor
OPRM	$\mu$ -opioid receptor
5-HTT	Serotonin transporter
PER2	Period gene
NPY	Neuropeptide Y

determined or environmentally caused serotonin neurotransmission deficit leading to reduced GABAergic sedation or (ii) a lack of a genetically determined slow alcohol metabolism (protective effect of the ALDH2–2 allele) [1,2].

### Molecular and Systemic Pathophysiology

Alcohol increases GABA and neurosteroid release and enhances the function of an extrasynaptically located GABA(A) receptor mediating inhibitory ionic currents [3]. Additionally, alcohol is an antagonist at the glutamatergic NMDA receptor which is upregulated in the course of alcohol dependence [2] whereas the GABA(A) receptor density declines (which is reversible in case of long-term sobriety); this results in typical glutamatergic withdrawal symptoms such as tremor, perspiration, agitation, nausea, vomiting, epileptic seizures and delirium, which is defined as additional clouding of consciousness, psychotic features, disorientation and autonomic nervous system dysfunction [3].

Acute alcohol consumption, similar to other psychotropic substances inducing dependence, increases the striatal release of dopamine (“reward system”) which is associated with “craving” (via stimulation of  $\mu$ -opiate receptors). Repeated dopaminergic stimulation leads to sensitization of the reward system and thus increases the attractiveness of alcohol and environmental cues being associated with its consumption, resulting in reduced capacity to control consumption [2].

Continued inadequate alcohol consumption can induce global atrophy of the brain most frequently affecting the frontal cortex and cerebellum [2] which is likely to be associated with deterioration in cognitive function and long term prognosis. Reduction in brain volume is at least partially reversible.

### Diagnostic Principles

Taking a drinking history (amount of alcohol consumed, time of the first alcoholic drink of the day, pattern of drinking, presence of withdrawal symptoms). Determining MCV, gamma-glutamyl transferase, blood alcohol level and CDT, which is considered as the most reliable indicator [4]. Reporting comorbid conditions (depression, anxiety or other neuropsychiatric symptoms, gastrointestinal and cardiovascular symptoms, sexual dysfunctions) and social problems.

### Therapeutic Principles

1. *Alcohol intoxication:*
  - Symptomatic treatment, sobering up.
2. *Alcohol abuse:*
  - Brief intervention by general practitioner (providing information, giving advice, “motivational interviewing”).

3. *Alcohol dependence:*

- Acute detoxification: Benzodiazepines and other *tranquilizers* (e.g. Clomethiazole) can be used to alleviate symptoms of acute alcohol withdrawal, they also prevent epileptic seizures.
- Long term treatment: *Acamprosate* (NMDA-receptor antagonist) which is supposed to antagonize the (psychologically) conditioned central nervous system excitation. The blockade of  $\mu$ -opioid receptors by substances such as *naltrexone* may help to reduce “craving” and “comfortable” effects of alcohol. Supporting evidence with regard to abstinence and relapse is weak for the alcohol aversive drug *disulfiram* (inhibitor of aldehyd dehydrogenase).

Drug treatment should always be integrated with a comprehensive psychosocial (maintenance) therapy programme including institutions such as outreach clinics and self-help groups; thorough treatment of comorbid medical and mental disorders.

4. *Alcohol-related complicating transitory and chronic psychopathological syndromes:*

- Symptomatic treatment.

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**Alcohol-induced Hepatitis**

- Steatohepatitis, Alcoholic

**Alcohol-responsive Myoclonus**

- Myoclonus-Dystonia

**Alcoholic Fatty Liver**

- Hepatic Steatosis

**Alcoholic Fatty Liver Disease**

- Hepatic Steatosis

**Alcoholic Hepatitis**

- Steatohepatitis, Alcoholic

**Alcoholic Steatohepatitis**

- Steatohepatitis, Alcoholic

**ALD**

- Adrenomyeloneuropathy
- Leukodystrophy

**Aldolase B Deficiency**

- Fructose Intolerance, Hereditary

**Alexander Disease**

- Leukodystrophy



## ALF

► Liver Failure, Acute

## Alkalemia

► Alkalosis

## Alkalosis

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### Synonyms

Alcalosis; Alkalemia

### Definition and Characteristics

Alkalosis is characterized by an arterial blood pH > 7.44. Metabolic alkalosis is due to a primary elevation of the plasma  $\text{HCO}_3^-$  concentration. Respiratory alkalosis is defined by a primary reduction of  $P_{\text{CO}_2}$  due to hyperventilation (Fig. 1) [1].

Symptoms include peripheral paraesthesia, tetany and muscular cramps due to the fall in ionized calcium in serum (stronger binding of calcium to serum proteins). Primary respiratory alkalosis may lead to dizziness and fainting due to cerebral vasoconstriction [2].

### Prevalence

While alkalosis due to genetic defects is rare, metabolic alkalosis caused by volume depletion is a common side effect of natriuretic treatment.

### Genes

Mutations causing metabolic alkalosis without volume expansion [4]

Inactivating mutations in

- The renal  $\text{Na}^+/\text{Cl}^-$  cotransporter NCC (SLC12A3): Gitelman's disease
- The renal  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  cotransporter NKCC2 (SLC12A1): type I Bartter syndrome

- The renal ROMK K-channel (KCNJ1): type II Bartter syndrome
- The renal CLC-Kb chloride channel (CLCNK): type III Bartter syndrome
- Barttin (BSND), a  $\beta$ -subunit of  $\text{ClC-K}$ -channels: type IV Bartter syndrome
- In the cystic fibrosis transmembrane conductance regulator, CFTR: Cystic fibrosis
- The intestinal down-regulated-in-adenoma, DRA (SLC26A3), chloride/bicarbonate exchanger
- Gain-of-function mutations in the calcium-sensing receptor (CaSR): type V Bartter syndrome

Mutations causing metabolic alkalosis with volume expansion [4]

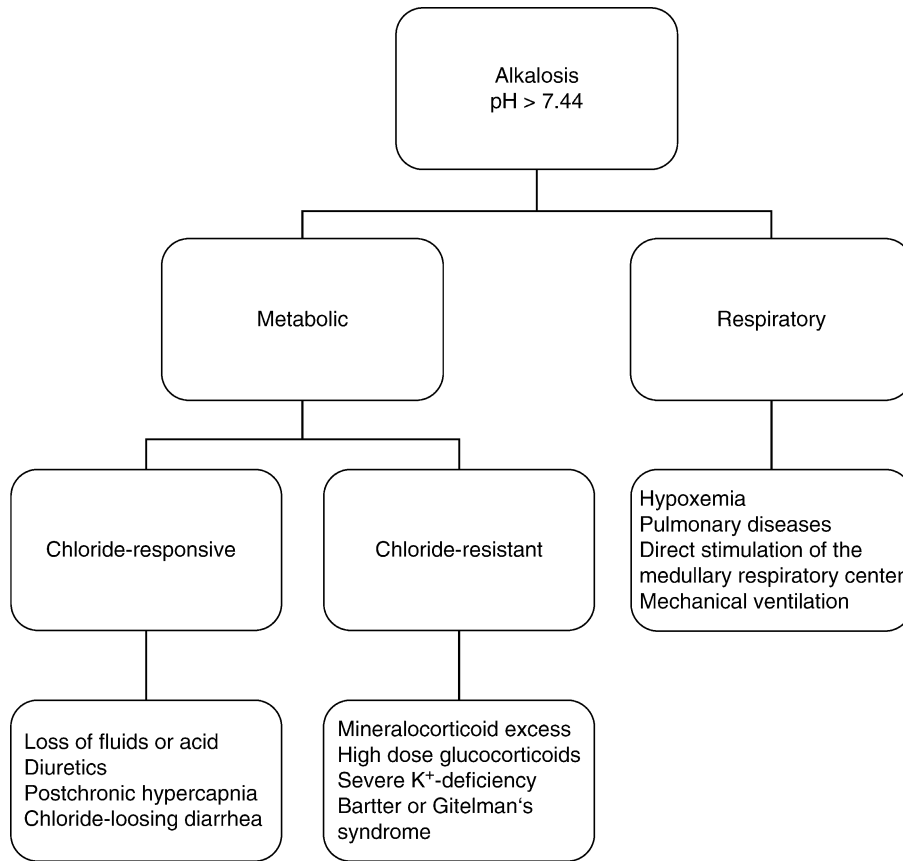
- Mutations in the steroid  $11\beta$ -hydroxylase resulting in a chimeric gene with a 5' promoter sequence of the  $11\beta$ -hydroxylase gene fused to the distal 3' aldosterone-synthase sequence: glucocorticoid remediable hyperaldosteronism
- Gain-of-function mutations in the  $\beta$ - or  $\gamma$ -subunits of the epithelial sodium channel ENaC: Liddle's syndrome
- Mutations in the  $11\beta$ -hydroxysteroid dehydrogenase type 2 ( $11\beta\text{HSD2}$ ): apparent mineralocorticoid excess

### Molecular and Systemic Pathophysiology

**Metabolic Alkalosis:** Metabolic alkalosis is caused by hydrogen ion loss from the gastrointestinal tract or in urine. Alkali administration or enhanced  $\text{HCO}_3^-$  reabsorption due to volume-, potassium- or chloride depletion induce metabolic alkalosis [1].

**Chloride-responsive Alkalosis:** Primary loss of salt and consecutive extracellular (ECL) volume depletion activate the renin-angiotensin-aldosterone system, stimulate salt retention in kidney and other organs, and increase urinary potassium and acid excretion thereby promoting hypokalemia. Hypokalemia together with aldosterone stimulate renal acid excretion (ammonia-genesis and distal proton secretion). The most common causes are loop or thiazide diuretics reducing salt absorption. Loss of acidic gastrointestinal fluid (e.g. vomiting) causes higher plasma  $\text{HCO}_3^-$  and ECL depletion. Chloride loss maintains metabolic alkalosis by enhancing proximal tubular  $\text{Na}^+$  (and  $\text{HCO}_3^-$ ) reabsorption, by lowering  $\text{HCO}_3^-$  secretion from type B intercalated cells, and by increasing proton secretion. Excessive salt loss in sweat causes ECL depletion in cystic fibrosis [1,3].

**Chloride-resistant Alkalosis:** Primary hyperaldosteronism enhances renal salt reabsorption and potassium secretion as well as acid excretion. The syndromes of apparent mineralocorticoid excess share the features of hyperaldosteronism without aldosterone elevation.



**Alkalosis. Figure 1** Two major forms of alkalosis have to be distinguished, induced primarily by a change in metabolic functions or by a primary increase in respiration. Respiratory alkalosis can be initiated by a variety of events acting either directly on the respiratory center in the brainstem or stimulating peripheral chemo- or mechanosensors leading to increased respiratory drive. Metabolic alkalosis can be further subdivided in chloride-responsive and chloride-resistant forms. In general, chloride-sensitive forms are caused by an initial loss of salt and extracellular volume depletion which secondarily increases aldosterone activity, salt retention, potassium wasting and excessive acid excretion. This form of metabolic alkalosis can be treated with NaCl substitution. In contrast, chloride-resistant forms are due to an inappropriately increased aldosterone or aldosterone-like activity with similar mechanisms causing hypokalemia and alkalosis as in chloride-sensitive forms. However, alkalosis is treated by NaCl restriction and antagonizing aldosterone(-like) activity [1,3].

Gain-of-function mutations of the  $\beta$  and  $\gamma$ -ENaC subunits lead to excessive salt reabsorption. 11 $\beta$ HSD2 prevents activation of the mineralocorticoid receptor by cortisol and its absence results in hyperabsorption of salt and excessive excretion of potassium and acid [1,3,4].

*Respiratory Alkalosis:* CO<sub>2</sub>-sensitive chemoreceptors in the brainstem and in the carotid and aortic bodies regulate respiratory drive. PCO<sub>2</sub> changing ambient pH is the most important stimulus for central chemoreceptors. Respiratory alkalosis arises from increased ventilatory drive due to hypoxemia or anemia, acidic cerebral pH or other stimuli such as pain, anxiety, stimulation of lung mechanoreceptors or direct stimulation of the respiratory center.

Physiologic compensation to hypocapnia involves acutely the fall in plasma HCO<sub>3</sub><sup>-</sup> by tissue buffering within few minutes and chronically by decreasing HCO<sub>3</sub><sup>-</sup> reabsorption and activating renal HCO<sub>3</sub><sup>-</sup> secretion. Hypoxic stimulation of peripheral chemoreceptors causes hyperventilation and rise in arterial and cerebral pH. Cerebral alkalosis limits hyperventilation unless arterial PO<sub>2</sub> falls below 50–60 mmHg or hypocapnia is not apparent because of pulmonary diseases.

Pulmonary disease (pneumonia, pulmonary fibrosis, pulmonary embolism) cause respiratory alkalosis by stimulating mechanoreceptors in the lung, chest wall, and airways causing hyperventilation. Direct stimulation of the medullary respiratory center is due to partly unknown mechanisms [1].

## Diagnostic Principles

Measurement of blood  $\text{HCO}_3^-$ , arterial pH and  $P_{\text{CO}_2}$ . Urinary chloride concentration is an important parameter for differential diagnosis (95% of cases are caused by diuretics or chloride losses from the gastrointestinal tract). Chloride levels greater than 30 mmol/L suggest chloride-resistant forms such as primary hyperaldosteronism. Serum renin and aldosterone levels help to distinguish from apparent mineralocorticoid excess syndromes. Normotensive or hypotensive patients with chloride-resistant metabolic alkalosis may require genetic testing for Bartter or Gitelman's syndromes. Sweat tests when cystic fibrosis is suspected [1,3].

## Therapeutic Principles

**Metabolic Alkalosis:** Treatment of underlying etiology. In chloride-responsive forms, ECL volume has to be restored, potassium monitored, and potassium-sparing diuretics may be used. In chloride-resistant forms, NaCl should be restricted and mineralocorticoid activity reduced (mineralocorticoid receptor antagonists, ENaC inhibitors), suppression of ACTH in glucocorticoid-remediable with dexamethasone. In Bartter and Gitelman syndromes non-steroidal anti-inflammatory drugs may reduce renal chloride loss [1,2,5,3].

**Respiratory Alkalosis:** Treatment of the underlying etiology. In symptomatic patients with anxiety-hyperventilation syndrome rebreathing into a paper bag is the acute treatment of choice. In severe hypoxemia due to high altitude, oxygen should be supplied, symptoms can be ameliorated with acetazolamide [2,5].

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## Allergic Conjunctivitis

► Conjunctivitis, Allergic

## Allergic Contact Dermatitis

► Contact Allergy  
► Contact Dermatitis, Allergic

## Allergic Contact Eczema

► Contact Dermatitis, Allergic

## Allergic Rhinitis

► Rhinitis, Allergic

## Allergy

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## Synonyms

Type I hypersensitivity

## Allergic Angiitis

► Leukocytoclastic Vasculitis

## Definition and Characteristics

Allergic disease is caused by a dysregulated immune response against common, ubiquitous antigens, termed allergens, such as pollen, animal dander, pharmaceuticals or latex. The disorder is categorized by the organ

of disease manifestation and includes asthma, atopic dermatitis, allergic rhinitis, food allergy and anaphylaxis. The predisposition to produce IgE antibodies to allergens is termed atopy. Many factors affect the onset of allergic disease, including genetic susceptibility and environmental factors.

## Prevalence

Allergic disorders are common in affluent, western countries with a high degree of industrialization, affecting up to 40% of children and 30% of adults [1].

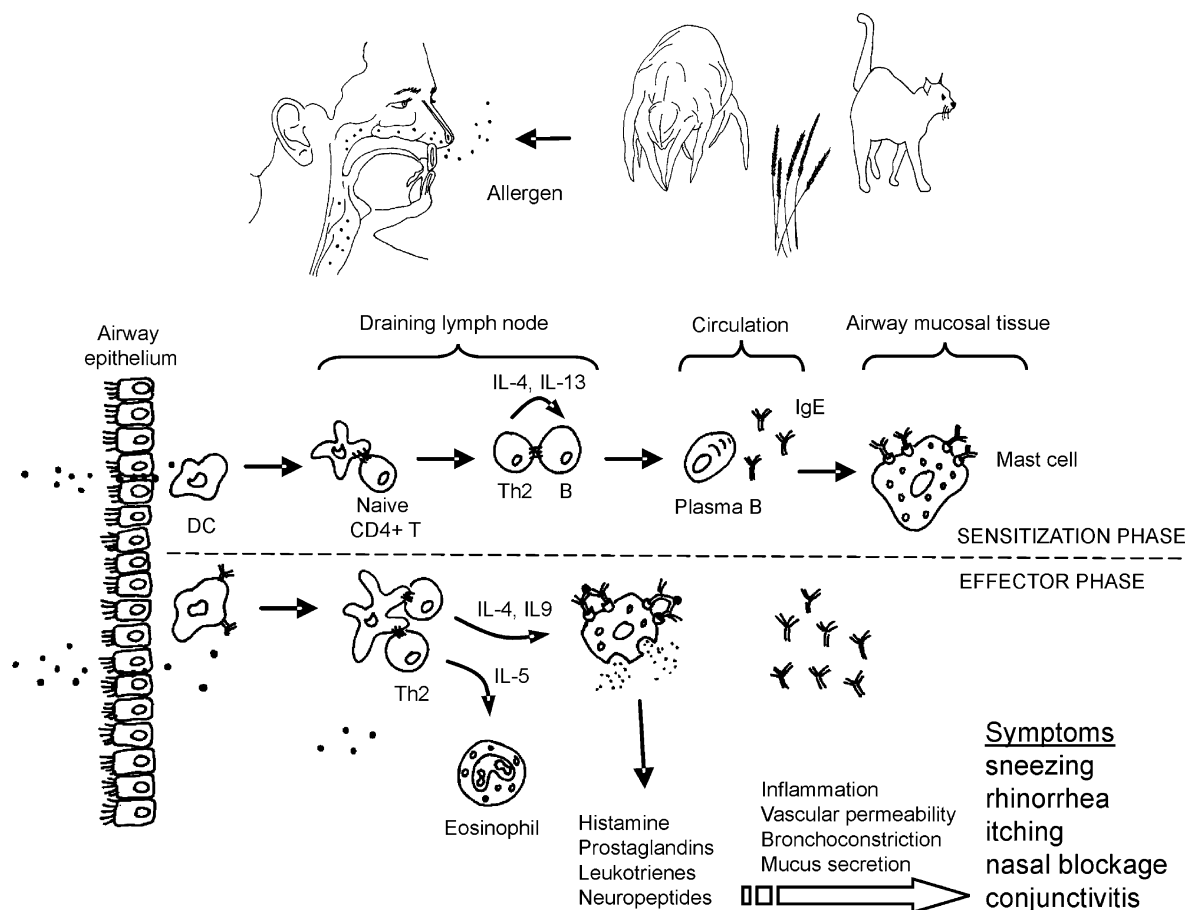
## Genes

Many genes may influence susceptibility to allergy, however, no single gene with complete penetrance has been identified. Rather, allergy occurs through complex interactions involving various genes and environmental risk factors. Among the genes associated with atopy are e.g., CTLA4 (2q33), IL-3, IL-4, IL-5, IL-9, IL-13, CD14 (5q23–q33), HLA-D, TNF- $\alpha$ (6p21.1–p23), Fc $\epsilon$ RIb (11q13), STAT6, SCF and IFN- $\gamma$ (12q14–q24.33).

## Molecular and Systemic Pathophysiology

The allergic response is a consequence of complex signaling cascades and interactions between several cells of the immune system. Repeated exposure to allergenic compounds is required to trigger a hypersensitivity response, as exemplified by allergic rhinitis below. Allergic rhinitis is an inflammatory disorder of the upper airways, clinically characterized by inflammation of the nasal mucosa and symptoms such as sneezing, rhinorrhea, itching and nasal blockage [2]. The allergic response can be divided into two phases, the sensitization phase and the effector phase [3]. The first encounter with otherwise harmless antigens, such as inhalation of pollen or animal dander, results in sensitization and mounting of an inappropriate immune response towards the antigen (Fig. 1).

Allergens that cross the airway epithelial cells are taken up by nasal and bronchial mucosal antigen-presenting cells, mainly dendritic cells (DC), situated above and beneath the basement membrane of the respiratory epithelium [4]. The initial response to allergen in an atopic individual may be influenced by the local tissue environment, such as human thymic stromal



**Allergy. Figure 1** Cellular and molecular processes involved in the immune response in allergic rhinitis.

lymphopoietin (TSLP) or prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) produced by epithelial cells, which may influence the local balance of Th1/Th2 polarizing agents. DCs process the allergens and present them to allergen specific, naive CD4<sup>+</sup> T-cells in the draining lymph nodes, which subsequently become polarized proliferating effector T-helper type 2 (Th2) cells that produce cytokines such as IL-4, IL-5, IL-9 and IL-13. Within the Th2-cytokine environment, allergen specific B-cells switch their antibody production towards IgE upon cell–cell contact with T cells which involves recognition of allergen/MCH by the TCR, CD80/CD86 costimulation and ligation of CD40 by CD40L-expressing T cells. Circulating allergen specific IgE binds to various FcεRI<sup>+</sup> effector cells of the immune system, such as tissue mast cells and blood basophils. It is not until repeated exposure to allergens, during the effector phase, that the clinical symptoms emerge. In this phase, antigen-presenting cells, such as DCs, also process and present internalized allergens to specific memory CD4<sup>+</sup> T-cells generated during the sensitization phase. The activated effector memory T-cells further amplify the IgE production by producing Th2 cytokines. Simultaneously, intact allergen directly activates mast cells in connective tissues and basophils in blood by binding to surface IgE antibodies bound to FcεRI. Allergen induced cross-linking of FcεRI initiates a signaling cascade that cause exocytosis of preformed mediators, such as histamine, leukotrienes and prostaglandins, as well as production of various cytokines, e.g., IL-4 [5]. T-cell derived cytokines, such as IL-5, also promote eosinophil growth, differentiation and activation. Large numbers of activated eosinophils migrate into areas of allergen challenge and release, for instance, the toxic mediators major basic protein (MBP), eosinophilic cationic protein (ECP) and peroxidase (EPO), which may be responsible for tissue damage in later stages of the effector phase. Eosinophils also produce IL-4 and IL-13, which may further enhance the allergic response, as well as lipid mediators and chemoattractants. Production of Th2 cytokines and degranulation of mediators from mast cells and basophils, as well as activation of eosinophils etc. are all events that trigger the allergic inflammation. Other characteristics of allergic rhinitis include exudation of plasma proteins in the nasal and bronchial airways as a result of increased vascular permeability and the involvement of neuropeptides and nerve fibers in the nasal mucosa.

### Diagnostic Principles

The clinical diagnosis of allergic rhinitis depends on display and history of symptoms, which may be complemented with a skin prick test and detection of allergen specific IgE in blood.

### Therapeutic Principles

Allergen avoidance, drug therapy (such as antihistamines, corticosteroids) and allergen immunotherapy (vaccination with allergen extracts).

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## Alopecia

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### Synonyms

Baldness; Hair loss

### Definition and Characteristics

Alopecia is characterized by partial or complete loss of hair. Hair loss is induced by various conditions such as hereditary disorders, aging, hormonal imbalance, internal and infectious diseases, intoxication and trauma. It is most noticeable on the scalp but can occur anywhere on the body where hair grows. Men are more frequently affected than women. Baldness can be classified into several types including androgenetic alopecia (AGA) referred to as female-pattern baldness (FPB) or male-pattern baldness (MPB), alopecia areata (AA), toxic alopecia (TA), scarring alopecia (SA) and



trichotillomania (TTM). Alopecia is generally caused by inactivation or destruction of the hair follicles preceded by a gradual shrinkage and miniaturizing. Until now, it has been believed that hair follicles can only form during embryonic development and that each individual is born with a fixed number of hair follicles. In 1998 Gat et al. reported findings on *de novo* hair follicle morphogenesis in adult skin and this has created possible strategies for the regeneration and reactivation of miniaturized hair follicles [1]. Increasing interest is being focused on  $\beta$ -catenin as a potential molecular candidate.

### Prevalence

By the age of 30, 30% of white men have androgenetic alopecia; by the age of 50, 50% do. White men are four times more likely than black men to develop premature balding.

### Genes

Some types of alopecia are considered to be genetically determined. In autosomal recessive alopecia universalis and papular atrichia a “hairless” gene (HR) has recently been cloned. In androgenic alopecia an initial autosomal dominant inheritance is superseded by polygenic inheritance. Functional mutations in the upstream promoter regions of the AR gene have been found and may alter transcription and translation in the affected scalp. Moreover, mutations of genes affecting plasma or tissue androgen concentration and/or alteration in the genes coding estrogen receptors, progesterone receptors, follicle stimulating hormone, sex hormone binding globulin and insulin like growth factor 1 are thought to be involved in the inheritance of AGA. The role of the HR gene in AGA development has not been proved. Recently, the loss of  $\beta$ -catenin has been postulated to have a major impact on hair follicle morphogenesis [2] and the precise link between androgenetic alopecia and catenin has been studied intensively. Changes to  $\beta$ -catenin regulation have been demonstrated mainly in cancer development, where mutations of the  $\beta$ -catenin gene CTNNB1 result in disruption of a large number of cellular functions leading to loss of growth control and neoplastic change. However  $\beta$ -catenin mutations also induce benign tumor growth, as has been described for example in pilomatricomas and trichofolliculomas [3].

### Molecular and Systemic Pathophysiology

Catenins have emerged as molecular sensors that integrate cell-cell junctions and cytoskeletal dynamics with signaling pathways that govern morphogenesis, tissue homeostasis, and even intercellular communication between different cell types within a tissue [4]. Generally,  $\beta$ -catenin has a dual function. It plays a

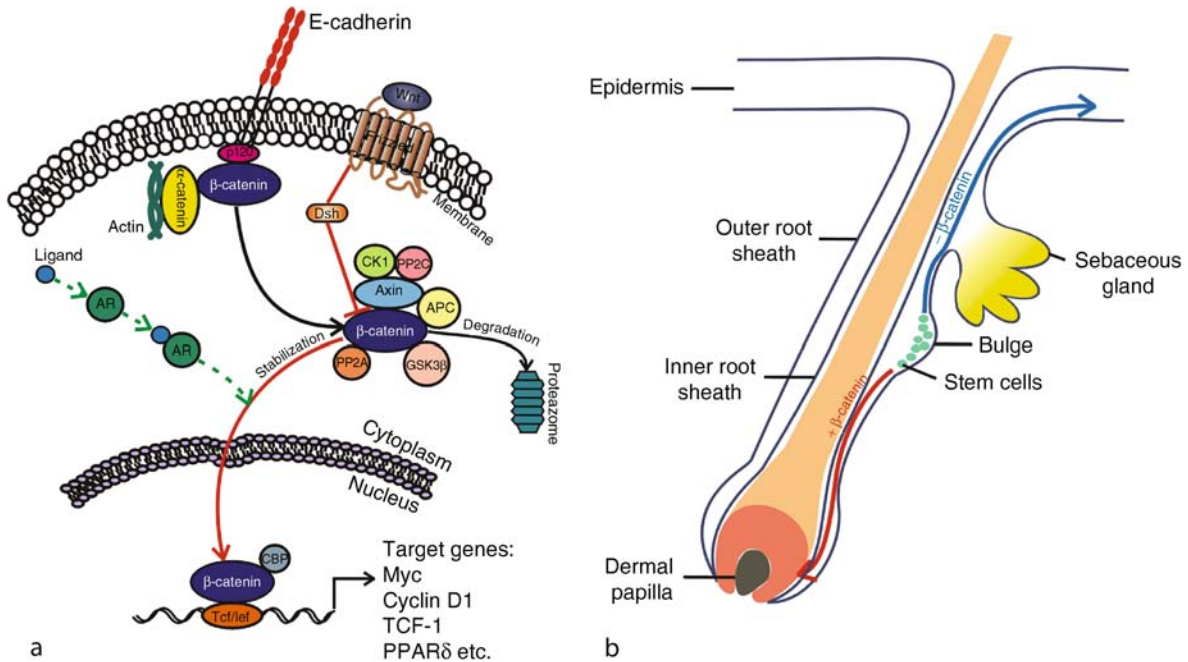
key role in cell-cell adhesion by linking cadherins to  $\alpha$ -catenin and the actin cytoskeleton. In the absence of a Wnt signal,  $\beta$ -catenin is constitutively down-regulated by a multicomponent destruction complex containing GSK3 $\beta$  (glycogen synthase kinase 3  $\beta$ ), axin and a tumor suppressor APC (adenomatous polyposis coli). These proteins promote the phosphorylation of serine and threonine residues in the NH<sub>2</sub>-terminal region of  $\beta$ -catenin. The  $\beta$ -catenin protein is then degraded by casein kinase CK1 and protein phosphatases PP2A and PP2C through the ubiquitin proteasome pathway. Wnt signaling inhibits this process, leading to an accumulation of  $\beta$ -catenin in the nucleus which promotes the formation of transcriptionally active complexes with members of the Tcf/lef family (T-cell factor/lymphoid enhancer factor) (Fig. 1a). In skin, the lef1/ $\beta$ -catenin complex is thought to regulate the differentiation of bulge stem cells to either hair follicles or epidermal cells (Fig. 1b): the complex of  $\beta$ -catenin and lef-1 forms a transcription factor that binds to the cell DNA activating the genes instructing the cell to become a hair follicle [1]. The absence or interference with Wnt seems to favor an epidermal or sebocyte cell fate. Moreover, it has been shown that mature skin cells expressing the constitutive form of  $\beta$ -catenin act like embryonic or stem cells, and start to produce aberrant new follicles throughout the interfollicular epidermis. Conversely, ablation of the lef1 gene or  $\beta$ -catenin expression impairs hair follicle morphogenesis. A study which investigated  $\beta$ -catenin in the scalp of patients suffering from AGA has revealed decreased expression of the protein compared to healthy individuals. Furthermore, the pattern of  $\beta$ -catenin expression showed membranous or weak cytoplasmic, but no nuclear protein location in the hair follicle [5]. Androgens and their receptors have been shown to influence  $\beta$ -catenin subcellular distribution and its translocation to the nucleus; however mechanisms of the nuclear translocation are not fully understood. It is possible that altered AR/ $\beta$ -catenin interaction might contribute to the hair follicle impairment.

### Diagnostic Principles

The diagnosis of alopecia is usually made clinically. Phototrichogram is a technique that analyzes the scalp under high-power magnification to give information on hair density, follicular unit composition and degree of miniaturization densitometrically. In case of diagnostic doubt, laboratory and histopathological examinations of scalp biopsies are sometimes necessary.

### Therapeutic Principles

So far scientists have sought how to decelerate further hair thinning and to increase scalp coverage with



**Alopecia. Figure 1** (a) Protein  $\beta$ -catenin connects actin filaments to the cadherins that make up adherens junctions that bind cells together. The axin/GSK3 $\beta$ /APC complex normally promotes the degradation of any cytoplasmic  $\beta$ -catenin excess. The stabilization of free pools of  $\beta$ -catenin by Wnt leads to entry into the nucleus and interaction with the Tcf/lef family of transcription factors to promote specific gene expression. In pathophysiological conditions aberrant  $\beta$ -catenin/Tcf signaling might be modulated by agonist-bound AR; (b) Hair follicle stem cells in the bulge differentiate in the presence of  $\beta$ -catenin into follicular keratinocytes.

limited success. This is in part because no way was known to induce the adult scalp to generate new hair follicles. Stabilization of the natural  $\beta$ -catenin within skin cells and activation of the Wnt pathway just long enough for formation of new follicles in alopecic scalp may open new possibilities for the treatment of alopecia based on gene therapy.

### Acknowledgments

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## Alopecia, Androgenetic

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### Definition and Characteristics

Androgenetic alopecia (AGA; syn. male/female-pattern hair loss = MPHL/FPHL) is a clinically specific and pathogenetically fixed form of hair loss affecting both men and women of all ages during or after puberty.

AGA is a potentially reversible disease with hair growth reduction and resulting hair loss in androgen-dependent and genetically predetermined hair follicles in the fronto-temporal and vertex-region of the male scalp (defined as male pattern hair loss; MPHL), and preferentially in the cranio-parietal region of women (defined as female pattern hair loss; FPHL). Although the typical gender-specific pattern expression follows in ca. 85–90% the one that is characteristic for the

related gender, deceptively, 5–10% each can show the pattern of the opposite gender or mixed patterns.

Both conditions, whose interpretation as a “disease” state is mainly justified by the substantial and widely underestimated individual degree of psychological suffering associated with it, develop over years in clinically observable phases: MPHL, as classified by Norwood-Hamilton, develops with thinning of the hair in the fronto-temporal area with slow retraction of the front-hair border into occipital direction and continuation in the vertex area with circular thinning of the hair and further confluence of both areas to almost complete baldness of the whole scalp except a small occipital “corona.” In FPHL, thinning develops diffuse in the top-area of the scalp, classified in three grades by Ludwig, however, complete baldness is never observed [1].

### Prevalence

AGA commonly starts to develop at the age of 20–25 years, even though rare cases of much earlier start points are seen (usually coinciding with the onset of puberty and the associated surge in androgen production), and the prevalence increases up to 50% at the age of 50 years [1]. However, in the personal experience of these authors, the prevalence of at least minimal variants of AGA in both sexes at age 50 is considerably higher than customarily reported figures in the literature.

### Genes

The genetic involvement of AGA is undoubted, though poorly understood, in contrast to increasing knowledge gained about androgen involvement. Some information is available about genetic association of 5 $\alpha$ -reductase type 1 and 2 genes with presence of AGA, and polymorphism of the AR gene is also associated with MPHL. However, the AR gene is located on the x-chromosome which makes it difficult to explain the strong penetrance of the baldness phenotype in fathers and sons. Also, no single gene has been identified so far convincingly as key genetic determinant of AGA, and polygenic inheritance with variable penetrance (e.g. on the basis of combinations of several mutations) is much more probable [1]. In addition, in FPHL, the importance of a relative lack of activity of locally produced estrogens (e.g. via insufficient aromatase activity) may have been underestimated [2].

### Molecular and Systemic Pathophysiology

The two basic pathogenesis mechanisms leading to AGA are widely appreciated to-date:

(i) increased conversion of circulating testosterone within the papilla of genetically predisposed

hair follicles in androgen-sensitive scalp skin territories to dihydrotestosterone (DHT) by intrafollicular 5 $\alpha$ -reductase and (ii) overexpression of hair follicle related androgen receptor (AR) [1,3]. However, at least in FPHL, insufficient estrogen-stimulation may also be relevant (estrogens prolong anagen). Also, rather than abnormalities in local DHT production and/or AR expression, the target cell response to (normal) AR stimulation may be altered, e.g. by the excessive production of hair growth-inhibitory agents such as TGF $\beta$ 2 [2].

Irrespective of the – as yet quite unclear – initial phases of AGA pathogenesis, the two characteristic pathophysiological events are shortening of the phase of active hair growth (anagen) e.g. by excessive AR stimulation, and hair follicle miniaturisation, likely by excessive emigration of inductive fibroblasts from the follicular dermal papilla. These events conspire to prematurely induce catagen, and thus to induce the characteristic, clinically appreciable telogen effluvium, and terminal-to-vellus conversion of hair follicles in androgen-sensitive scalp skin, transforming previously well-pigmented, thick, long hair shafts into tiny, non-pigmented, hardly visible, fibrous fluff [2,3]. It is important to emphasize that, even in the massively balding scalp, the actual number of hair follicles does not dramatically decline and that, in principle, vellus hair follicles permanently retain the full capacity to cycle and to reconvert into terminal follicles, and that they retain as many epithelial stem cells as are needed to achieve both.

The as yet unsolved key enigma remains how, when, and where exactly excessive AR stimulation and/or signalling shifts the intra- and perifollicular balance between anagen-shortening/catagen-inducing agents (e.g. BMP2/4, FGF5, follistatin, TGF $\beta$ 1, TGF $\beta$ 2, prolactin, pro-NGF, BDNF and NT-3), and anagen-promoting/catagen-inhibitory agents (e.g. IGF-1, HGF, noggin) and how clinically undesired shifts in this local signalling balance, and in the subsequent imbalance in the trafficking of follicular papilla fibroblasts, can be therapeutically manipulated with highest efficacy and lowest risks [2,3].

### Diagnostic Principles

The diagnosis is largely clinical: hair thinning along the male or female pattern, increased terminal-to-vellus conversion, and telogen effluvium, positive family history for AGA. Sensible laboratory tests, especially in patients with FPHL, include DHEAS, free testosterone, SHBG, TSH, ferritin, iron, and zinc so as to detect and treat concomittant or aggravating factors, such as excessive adrenal androgen production, low iron and/or zinc stores, and abnormal thyroid dysfunction. Telogen effluvium-promoting drugs (e.g. beta-blockers,

lithium, androgens, thyrostatic agents, tamoxifen) must be recorded and, if possible, eliminated. Contrary to its common use in clinical practise, a routine trichogram (plucking of hairs with their roots and evaluation under light microscope for ratio of anagen/telogen/dystrophic hair) often provides only information of poor accuracy/reliability and is thus dispensable, while a professionally executed phototrichogram (evaluation of anagen/telogen ratio, hair count, hair density and cumulative hair shaft diameter by digital pictures taken with epiluminescence microscopy and digital software analysis) can be very useful, especially for objective follow-up of the response to treatment.

### Therapeutic Principles

Available therapeutic principles are still limited to two FDA-approved drugs, the oral 5-alpha-reductase inhibitor, finasteride (1 mg/day) and the topically applied potassium-channel opener, minoxidil (2–5%). While the latter can be used both in men and women, the former has been FDA-approved only for use in men. However, some recent case reports question the long-held dogma that finasteride is exclusively working in men [2]. Even though this has only been poorly examined in clinical studies, in the experience of the current authors, topical long-term application of 17-β-estradiol also is a very effective therapy for halting or slowing the progression of FPHL [2].

An ever-increasing array of topical agents has been suggested as alternative or supplementary therapy for AGA (incl. e.g. 17-alpha-estradiol, melatonin, caffeine, carnitine-tratrate, and a wide variety of plant/herbal extracts). However, for all these agents, professionally executed, long-term, prospective clinical studies with a randomized, prospective, double-blinded, cross-over design remain to be performed so as to convincingly document efficacy and safety.

In addition, MPHL is ideally suited for corrective surgery with hair follicle autotransplants from androgen-insensitive occipital scalp skin. Even though hair transplants are increasingly advocated by some authorities also for use in women with AGA, the poor (if not impossible) demarcation of androgen-insensitive scalp skin territories questions the justification of this approach. Also, growing hope that “hair follicle cloning” (i.e. for example, the *de novo* generation of hair follicles by injection of isolated and in vitro-propagated autologous hair follicle cell populations) may become a useful therapy for AGA, appear, in our view, ill-advised, since there is really no need at all to induce any new hair follicle in AGA, since the real challenge is to reconvert vellus follicles into terminal ones, and to counteract premature anagen termination [2].

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## Alpha-1 Antiprotease Deficiency

### ► α-1 Antitrypsin Deficiency

## Alpha-Fucosidase Deficiency

### ► Fucosidosis

## Alpha-Mannosidase B Deficiency

### ► α-Mannosidosis

## Alpine Scurvy

### ► Pellagra

## Alport Syndrome

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### Synonyms

Nephropathy and deafness



## Definition and Characteristics

Disorder of basement membranes arising from mutations in different type IV collagens. The clinical picture is dominated by renal manifestations and malformations of the eye and the cochlea [1]. Alport syndrome shows considerable genetic and clinical heterogeneity. Occurrence and severity of the auditory and renal features vary in individuals. Different modes of inheritance have been described.

## Prevalence

Alport syndrome accounts for 1–2% of patients reaching end-stage renal disease (ESRD) in Europe. The prevalence is estimated to be 1:5,000 in the US [2]. The X-linked form accounts for approximately 85% of all Alport cases [3].

## Genes

COL4A3, COL4A4 or COL4A5.

## Molecular and Systemic Pathophysiology

The autosomally recessively inherited form of Alport syndrome can be caused by mutations in COL4A3 as well as in COL4A4. Collagen IV is the major structural component of the basement membranes of kidney, eye, lung, brain and cochlea. Patients show nephritis, often progressing to renal failure and end stage renal disease (ESRD), ocular abnormalities and/or hearing impairment, which is sensorineural, bilateral and initially affecting high frequencies, but spreading to other ranges later on.

An autosomally dominantly inherited form of Alport syndrome has also been reported to be caused by mutations in COL4A3 and COL4A4 [3]. Dominant Alport syndrome belongs to a group of nephropathies comprising e.g. benign familial hematuria, Fechtner syndrome, Epstein syndrome and branchio-oto-renal (BOR) syndrome, thus aggravating phenotype genotype correlations.

The major, X-linked form of Alport syndrome is caused by mutations in COL4A5 localized on Xq22 [4].

The mechanisms of pathogenesis in different forms of Alport syndrome and in different affected tissues are still obscure.

## Diagnostic Principles

According to clinical symptoms and biopsy of kidney. Due to the fact that type IV collagens are comprised of multiple exons (e.g., COL4A5: 51 exons spanning over 250 kb genomic DNA) and over 300 mutations are known so far, molecular genetic analysis is laborious and costly.

## Therapeutic Principles

So far, the only therapy is dialysis or kidney transplantation. Some studies on other therapeutic options have been published [5].

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## Alport Syndrome – Diffuse Leiomyomatosis Complex

► Hematuria

## Alport Syndrome – Mental Retardation Complex

► Hematuria

## ALS

► Amyotrophic Lateral Sclerosis



## Altered Levels of Coagulation Factors and Arterial Thrombosis

►Thrombosis, Arterial, at Altered Levels of Coagulation Factors

## Alveolar Lipoproteinosis

►Pulmonary Alveolar Proteinosis

## Alveolar Phospholipidosis

►Pulmonary Alveolar Proteinosis

## Alveolar Proteinosis

►Pulmonary Alveolar Proteinosis

## Alzheimer Disease

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### Synonyms

Dementia of Alzheimer type; Alzheimer's disease

### Definition and Characteristics

Alzheimer's disease (AD) represents the most common neurodegenerative disease in the elderly. Clinically it is characterized by a progressive loss of cognitive

functions. It begins with a fluctuating forgetfulness, and progresses to a pervasive loss of memory going along with declining activities of daily living, behavioral and personality changes. In late stages, the patients typically show muscle wasting and loss of mobility. The average duration of the disease is approximately 7–10 years.

Pathological hallmarks are neurodegeneration in selectively vulnerable brain regions accompanied by proteinaceous inclusions mostly associated with an inflammatory response [1]. The pathological inclusions consist either of abnormal phosphorylated tau protein, aggregating in form of neurofibrillary tangles (NFT), or deposits of the 40–42 amino acid long  $\beta$ -Amyloid ( $A\beta$ ) peptides assembled in oligomers forming extracellular senile plaques. The distribution of neuritic plaques varies widely from one individual to another. Neurofibrillary tangles and neuropil threads, in contrast, exhibit a characteristic distribution pattern, going along with brain regions showing neurodegeneration, permitting the differentiation of six different stages (I–VI).

### Prevalence

Among people aged 65, 2–3% show signs of the disease, while 25–50% of people aged 85 have symptoms of AD. Approximately every five years after the age of 65, the probability of having the disease doubles.

### Genes

Alzheimer disease (AD) is a genetically complex and heterogeneous disorder. Established genetic factors implicated in AD include mutations in Amyloid precursor protein (APP) (chromosome 21), presenilin (PS) 1 (chromosome 14) and PS 2 (chromosome 1). Autosomal dominant mutations in these genes (familial AD) usually induce an earlier disease onset than in sporadic cases, with the majority of mutations affecting  $\beta$ - and  $\gamma$ -secretase cleavages of APP to increase the level of all  $A\beta$  species or the relative amounts of toxic  $A\beta_{42}$ . Individuals with duplications of only the APP gene or with trisomie 21 develop AD relatively early in life. The presence of the ApoE4 allele (chromosome 19) is the only so far identified common risk factor for sporadic AD. Several lines of evidence suggest that additional susceptibility genes exist for both early- and late-onset AD, however, none of the more than three dozen putative AD loci proposed to date have been consistently replicated in follow-up analyses [2].

### Molecular and Systemic Pathophysiology

The first hypothesis trying to explain the pathogenic mechanisms underlying progressive neurodegeneration in AD was the “cholinergic hypothesis”. It suggests that AD is mainly caused by reduction of acetylcholine

(a major excitatory neurotransmitter). As the medications with AChE-inhibitors, increasing ACh levels, have neither halted nor reversed the disease, the cholinergic hypothesis has not maintained widespread support.

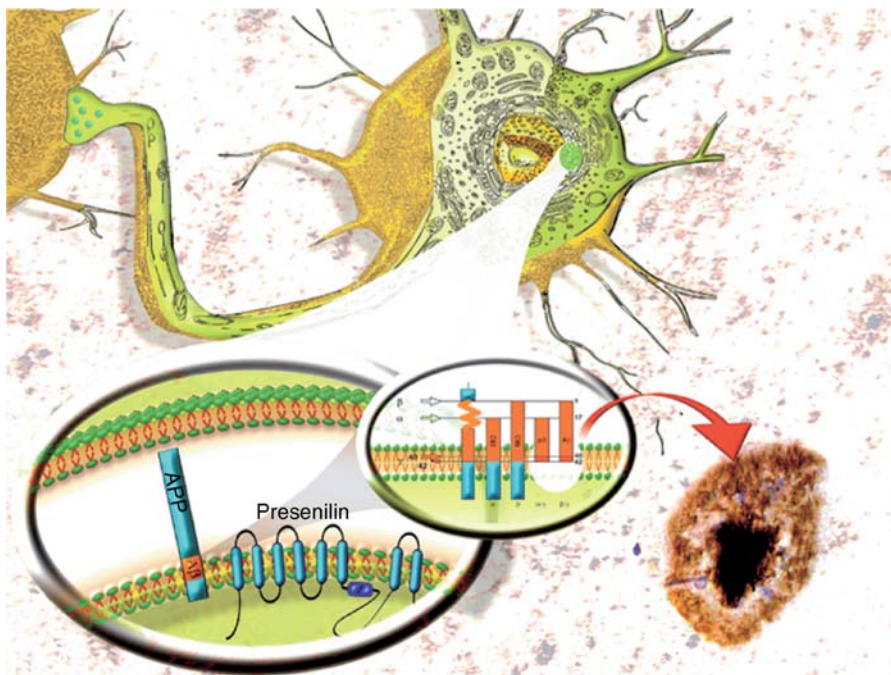
The “tau hypothesis” is supported by the long-standing observation that the occurrence of NFT, but not the deposition of amyloid plaques correlates well with neuron loss. However, more recent data suggest that abnormal tau phosphorylation and tau aggregation is triggered by A $\beta$ , whereas changes in tau pathophysiology have no major impact on A $\beta$  generation or aggregation. Furthermore, genetic analyses did not serve any evidence that tau may affect the risk for AD so far.

At the moment, the majority of researchers support the amyloid hypothesis, suggesting that A $\beta$  is the primary causative agent, whereby it is currently under debate which state of A $\beta$  aggregates represents the toxic species: the mature aggregated polymer or any specific oligomeric species [4]. This hypothesis is strongly

supported by genetic studies, showing that the majority of familial AD mutations are located in APP, PS1 or PS2 genes, causing an elevated generation of A $\beta$ 42.

APP is a type I transmembrane protein. During maturation it is processed by different secretases [5]. Cleavage by either  $\alpha$ -secretase or, alternatively, the  $\beta$ -secretase,  $\beta$ -site APP-cleaving enzyme 1 (BACE1), results in membrane-retained C-terminal fragments, which are subsequently cleaved within the transmembrane region by the  $\gamma$ -secretase multiprotein complex containing presenilin. Cleavage of APP by  $\alpha$ - and  $\beta$ -secretase results in the release of A $\beta$  peptides and the APP intracellular domain (AICD) whereas  $\alpha$ -cleavage prohibits A $\beta$  generation (Fig. 1).

Although the molecular mechanisms of APP processing are well understood, it is still unclear which changes in normal cell physiology of elderly people cause the accumulation of A $\beta$ . Plausible causes include alterations of subcellular transport, axonal transport damage, or changes in lipid or calcium homeostasis [6].



**Alzheimer Disease. Figure 1** The pathogenic role of APP in AD. Schematic structure of a neuron with synaptic contacts is shown. APP is a type I transmembrane protein localizing to different intracellular compartments, including the endoplasmic reticulum (ER), Golgi apparatus, plasmamembrane and endosomal compartments in the cell soma, dendrites and axons. During maturation it is processed by different secretases. Cleavage by either  $\alpha$ -secretase or, alternatively, the  $\beta$ -secretase, results in membrane-retained C-terminal fragments (C83 and C99), which are subsequently cleaved within the transmembrane region by the  $\gamma$ -secretase multiprotein complex containing presenilin (small and large insets). Cleavage of APP by  $\gamma$ - and  $\beta$ -secretase results in the release of A $\beta$ , whereas  $\alpha$ -cleavage prohibits A $\beta$  generation (small inset). In the course of AD, A $\beta$  oligomerizes and aggregates in Amyloid plaques. Although it is clear that the generation of A $\beta$  represents one of the key events in the course of AD, the mechanisms how A $\beta$  causes neurodegeneration in specific vulnerable brain regions is not yet understood.

## Diagnostic Principles

Diagnosis of AD is primarily based on clinical tests of memory and intellectual abilities (for example the mini mental state examination). The accuracy of AD diagnosis is about 85–90%, but a definitive diagnosis must await post mortem examination of brain tissue. Physical tests, including blood and cerebrospinal fluid tests of phosphorylated tau and Aβ as well as neuroimaging (MRI and PET) are mainly performed to rule out differential diagnoses, but can provide a supporting role in diagnostic accuracy.

## Therapeutic Principles

Up to now, there is no treatment available to cure AD. Besides different psychosocial interventions, current medications include acetylcholinesterase (AChE) inhibitors or NMDA antagonists. Both have only a small benefit for the patients and do not slow disease progression. AChE-inhibitors cause an increase of acetylcholine (ACh) levels at the synapse, and are thought to partially rescue the loss of the cholinergic neurons. NMDA antagonists reduce the calcium influx at glutamatergic synapses, preventing neuronal excitotoxicity and thus possibly neuronal death in AD. Novel potential treatments for Alzheimer's disease with the potential to lower Aβ42 are currently under investigation. They include compounds inhibiting β- or γ-secretase, modulating γ-secretase in a way that less Aβ42 is generated and preventing oligomerization of Aβ. Vaccination with synthetic Aβ-species caused a dramatic reduction of β-amyloid plaques in animal models.

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## Amaurosis, Leber Congenital

► Leber Congenital Amaurosis

## AMD

► Macular Degeneration, Age-related

## Amenorrhea

► Malnutrition  
► Dysmenorrhea

## β-Aminoisobutyrate-Pyruvate Aminotransferase Deficiency

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## Synonyms

BAIBPAT

## Definition and Characteristics

Benign polymorphism leading to a permanent hyper-β-aminoisobutyric aciduria (hyper-β-AIBuria) in healthy individuals.

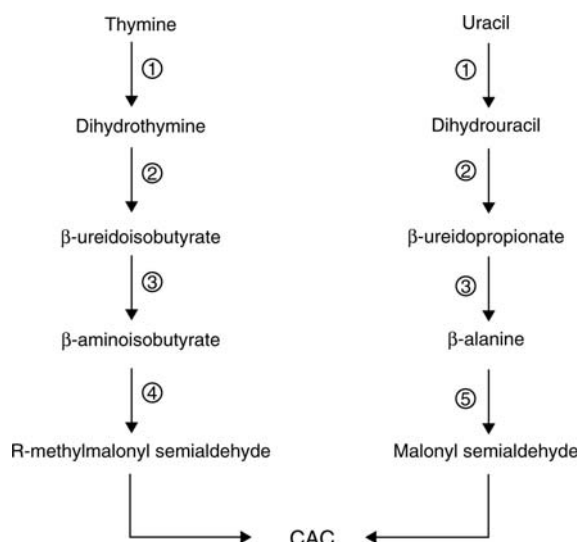
## Prevalence

Genetic high excretors of β-AIB are found with a frequency of 1–10% in Western European populations and up to 80% in Micronesian and Mongoloid populations in Southeast Asia.

## Genes

Hyper-β-AIBuria is thought to be a benign genetic polymorphism at a single locus with non-random distribution in human populations, the lowest frequencies being found in Caucasians, the highest in Micronesians. Inheritance is by an incompletely recessive gene (Fig. 1).

\*deceased



**β-Aminoisobutyrate-Pyruvate Aminotransferase Deficiency.** **Figure 1** Scheme of the pyrimidine degradation pathway and the enzymes involved in the catalysis of each step. ① dihydropyrimidine dehydrogenase; ② dihydropyrimidinase; ③ β-ureidopropionase; ④ (R)-(-)-β-aminoisobutyrate-pyruvate aminotransferase; ⑤ β-alanine-α-ketoglutarate aminotransferase; CAC, citric acid cycle.

### Molecular and Systemic Pathophysiology

A permanent hyper-β-AIBuria (excretion in children above 79, in adults above 22 mmol/mol creatinine) is thought to be caused by a deficiency of R(-)-β-aminoisobutyrate-pyruvate aminotransferase (BAIBPAT) in the liver [1]. The β-AIB found in urine is almost exclusively the R-isomer, which originates from thymine. In the kidney the R-isomer is both filtered by the glomerulus and secreted by the tubule cells. In plasma of Caucasians the concentration of the S-isomer, originating predominantly from valine and to a lesser extent from thymine, is usually fourfold that of the R-isomer due to active renal reabsorption. A linear relationship between the R- and S-enantiomers of β-AIB in urine has been reported [2]. R-β-AIB derived from thymine is transaminated by BAIBPAT to R-methylmalonyl semialdehyde (R-MMSA), which for the greater part is converted to propionyl-CoA and subsequently carboxylated. The methylmalonyl-CoA thus formed is isomerized to succinyl-CoA, an intermediate of the citric acid cycle. The smaller part of the R-MMSA may be racemized and the resulting S-MMA will be transaminated to S-BAIB presumably via aminobutyrate aminotransferase [2,3].

### Diagnostic Principles

Hyper-β-AIBuria can be identified by quantitative amino acid analysis of urine. The measurement of the

activity of BAIBPAT in the liver of patients is not indicated. On the other hand, as hyper-β-AIBuria can also be caused by increased tissue-breakdown, it is important to exclude a neoplastic condition [4].

### Therapeutic Principles

Patients with BAIBPAT deficiency do not need to be treated.

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## AMN

► Adrenomyeloneuropathy

## Amnestic Disorder

► Wernicke Korsakoff Syndrome

## AMS

► Mountain Sickness, Acute

## Amyloid Nephropathy

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### Synonyms

Renal amyloidosis

## Definition and Characteristics

Amyloidosis is a disorder of protein folding in which soluble proteins aggregate and deposit as insoluble fibrils in extracellular areas within various tissues. Renal involvement is quite common in systemic amyloidosis and frequently the major source of morbidity is amyloid nephropathy, which usually progresses to end-stage kidney disease [1].

The leading types of renal amyloidosis are immunoglobulin light chain (AL) and amyloid A (AA), and, rarely, familial or hereditary amyloidosis. AL amyloidosis, also known as primary amyloidosis, is derived from a fragment, or less frequently, from immunoglobulin light chain itself, whereas in a rare form of amyloidosis (AH) the deposits are truncated immunoglobulin heavy chains. AA amyloidosis, also called reactive or secondary amyloidosis, occurs in patients with chronic inflammatory disorders, including rheumatoid arthritis, familial Mediterranean fever (FMF), inflammatory bowel disease, and chronic infections [1–3]. The acute phase reactant serum amyloid A protein (SAA) forms AA amyloid fibrils through a process of cleavage, misfolding, and aggregation into a highly ordered abnormal  $\beta$ -sheet conformation.

In the kidney, amyloid deposition is primarily found in glomerular mesangium and capillary loops, but it may also be seen in the small arteries, arterioles, and tubular basement membranes. The clinical manifestations include proteinuria, ranging from nonnephrotic to massive (as high as 30 g/day), hypoalbuminemia, and renal insufficiency.

## Prevalence

The exact prevalence is unknown and seems to be quite variable throughout the world. The annual incidence rate is reported to be 2–12 per million population. Prevalence of renal amyloidosis is 1–4% in kidney biopsy series, 12–17% among patients with nephrotic syndrome, and <1% among patients with end-stage kidney disease undergoing renal replacement therapies.

## Genes

Genetic studies have revealed some abnormalities in amyloidogenic proteins: Polymorphisms, variant molecules caused by missense mutations, deletions, and premature stop codons, and genetically determined post translational modifications. Some mutations in genes coding nonamyloidogenic proteins can also play a permissive role in deposit formation. An increased risk for the development of AL amyloidosis has been reported for both  $V\lambda 3r$  and  $V\lambda 6a$  genes. Also, M694V and SAA1 $\alpha$  homozygote genotypes have been found to be associated with AA amyloidosis in patients with FMF.

## Molecular and Systemic Pathophysiology

In contrast to the heterogeneous structures of the known amyloidogenic proteins, all amyloid fibrils have similar ultrastructural morphology and histochemical properties [4]. Marked refolding and highly ordered self-assembly into protofilaments of the various precursor proteins result in amyloid fibrils. Amyloid deposits are rich in restricted subsets of heparan and dermatan sulphated glycosaminoglycans and proteoglycans associated non-covalently with the fibrils. These are reported to play a role in amyloidogenesis, such as influencing protein folding and/or promoting fibril stability, since they are present universally, show close temporal relationship with the fibrils, and have restricted heterogeneity. Another universal constituent of amyloid deposits is the nonfibrillar normal plasma glycoprotein serum amyloid P, a member of the pentraxin family of calcium-dependent ligands and binding proteins that includes C-reactive protein, which is presumed to play a role in the pathogenesis and persistence of amyloid. Serum amyloid P protects fibrils from several proteases *in vivo* and prevents proteolytic reabsorption of the amyloid deposits.

The mechanisms of cellular injury and tissue damage are not completely understood. In addition to deleterious effects of physical substitution of parenchymal tissue by amyloid deposits, soluble prefibrillar aggregates may also exert cytotoxic effects through oxidative stress or apoptotic pathways [2].

## Diagnostic Principles

A kidney biopsy is often the method by which renal amyloidosis is identified. The absence of enlarged kidneys should not decrease suspicion of renal amyloidosis as the kidneys seem to be of normal size in most patients [1]. The histological demonstration of amyloid deposits, which is usually accomplished by staining with Congo red dye that produces an apple-green birefringence under polarized light, is required for the diagnosis. Electron microscopy shows that amyloid is composed of rigid, nonbranching fibrils of 8–12 nm in diameter [4,5]. Immunofluorescence or immunohistochemical staining of tissue, using antibodies that are directed against known amyloidogenic proteins, is used to differentiate the type of amyloidosis. In selected cases in which definitive typing cannot be made by the use of routine methods, microcharacterization by mass spectrometry and amino acid sequence analysis of the amyloid fibril proteins in the tissues may be considered.

## Therapeutic Principles

The successful treatment of amyloidosis should focus on reducing the supply of the amyloid precursor protein and supporting or replacing the function of the compromised organs. In order to select the appropriate



therapies, it is fundamental to identify the type and extent of the amyloid deposits. AL amyloidosis aims at the treatment of the underlying B cell dyscrasia to reduce the production of amyloid forming monoclonal immunoglobulin light chains (e.g., high-dose melphalan followed by autologous stem cell transplantation). In AA amyloidosis, therapeutic modality should address treatment of the underlying inflammatory process to keep SAA within normal range. Colchicine has been the most successful drug for this purpose, especially in patients with FMF. It is important to keep in mind that renal replacement therapies including dialysis and kidney transplantation, which are successfully performed in patients who have developed end-stage kidney disease secondary to amyloidosis, should not preclude administration of treatments against amyloid production.

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## Amyloidoses, Cutaneous

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### Definition and Characteristics

Amyloidoses are rare disorders characterized by the extracellular deposition of amyloid in various organs leading to organic damage and dysfunction. The skin may be involved as the only organ – localized cutaneous amyloidosis – or in the course of systemic (generalized) amyloidosis. Within these two categories, several clinical variants can be distinguished and on pathogenetic grounds be classified as primary or secondary manifestations, and also be divided into hereditary and nonhereditary forms (see Table 1).

The various types of cutaneous amyloidoses differ in their clinical appearance, in the type of amyloid that is deposited, in the course of the disease and the patient's

outcome, which in systemic amyloidosis depends on the internal organs involved.

### Prevalence

Amyloidoses are rare diseases and the prevalence and incidence differ dependent on the type of amyloidosis. The incidence of primary systemic amyloidosis is reported to be about eight patients per million per year.

### Genes

Genetic aberrations in hereditary syndromes associated with amyloidoses are still under investigation, but some are well documented: Familial Mediterranean fever with amyloidosis is a rare autosomal recessive disorder, caused by mutations in the MEFV gene (Mediterranean fever gene) on chromosome 16p. Muckle–Wells syndrome as an autosomal dominant disorder is reported to be linked to mutations in the CIAS gene on chromosome 1q. Familial primary cutaneous amyloidosis (lichen amyloidosis and macular amyloidosis) may be linked to chromosome 5p13.1–q11.2, and 1q23, at least in a subset of families.

### Molecular and Systemic Pathophysiology

Amyloid is a protein complex derived from many different precursor proteins. Ultrastructurally, it is composed of straight, nonbranching fibrils, measuring 6–10 nm, whose peptide component shows a  $\beta$ -pleated sheet pattern. Additionally, each amyloid molecule contains a nonfibrillary component, the serum amyloid P component (SAP), which binds to all types of amyloid deposits and protects them from degradation by proteolytic enzymes and phagocytic cells. Precursor proteins of amyloid among others are immunoglobulin light chains (amyloid L), polypeptide hormones (proinsulin, precalcitonin), prealbumins (i.e., transthyretin, senile amyloid),  $\beta$ 2-microglobulin, keratin filaments (amyloid K), and serum amyloid A protein (Amyloid A) [1].

Histochemically amyloid shows specific staining properties with Congo red (apple-green birefringence in polarized light) and thioflavine T (yellow-green fluorescence) and metachromatically stains with crystal violet and methyl violet [2]. Furthermore, immunohistochemical staining for cytokeratins may be used in cases of cutaneous amyloidosis in which amyloid K is suspected. In this context immunohistochemical identification of the SAP with antibodies might be of interest, but was demonstrated so far only in animals. In most cases of cutaneous amyloidosis, immunoglobulins, in particular IgM, and complement C3 can be detected by immunofluorescence microscopy.

In primary localized cutaneous amyloidosis, which includes macular, papular [lichen amyloidosis (Fig. 1)]

**Amyloidoses, Cutaneous. Table 1** Classification of amyloid and biochemical nature of fibril proteins

Clinical syndrome	Fibril proteins and precursors
<i>Systemic amyloidosis</i>	
Associated with immunocyte dyscrasia	
Primary systemic (occult dyscrasia)	AL fibrils form monoclonal immunoglobulin light chains
Myeloma associated	
Associated with chronic active diseases (secondary or reactive systemic amyloidosis)	AA fibrils from serum amyloid A protein (SAA)
Hereditary syndromes	
Predominantly neuropathic forms (autosomal dominant)	Transthyretin variant or apolipoprotein A1 or gelsolin
Familial amyloid polyneuropathy	
Nonneuropathic forms (autosomal dominant)	Apolipoprotein A1 or lysozyme or fibrinogen $\alpha$ -chain
Ostertag type	
Predominantly nephropathic forms	
Familial Mediterranean fever (autosomal recessive)	AA fibrils from SAA
Muckle-Wells type	AA fibrils from SAA
Predominantly cardiomyopathic forms	Transthyretin variant
Cardiomyopathy with persistent atrial standstill	Unknown
Senile systemic amyloidosis	Transthyretin from plasma
<i>Localized (organ-limited) amyloidosis</i>	
Hereditary syndromes	
Hereditary cerebral hemorrhage with amyloidosis	
Icelandic type	Cystatin C fibrils
Dutch type	$\beta$ -Protein fibrils
Periarticular, bony, and renal amyloid in chronic hemodialysis patients	$\beta_2$ -Microglobulin from plasma
Cerebral amyloid angiopathy and cortical plaques in Alzheimer's disease, senile dementia, Down's syndrome	$\beta$ -Protein fibrils
Sporadic Creutzfeld-Jakob disease, kuru	Prion protein
Focal senile amyloidosis	
Heart atria	Atrial natriuretic peptide
Joints	Unknown
Seminal vesicles	Seminal vesicle exocrine protein
Prostate	$\beta_2$ -Microglobulin
Ocular deposits (corneal, conjunctival)	Unknown
Endocrine amyloidosis (APUD organs, APUDomas)	
Elderly noninsulin-dependent diabetics, benign insulinomas of the pancreas, normal aged pancreas	Islet amyloid polypeptide fibrils (homology) with calcitonin gene-related peptides
Medullary carcinoma of the thyroid	Precalcitonin-related fibrils
Nodular (skin, lung, genitourinary tract)	AL fibrils derived from monoclonal immunoglobulin light chains
Primary localized cutaneous (macular amyloidosis and lichen amyloidosis)	Keratin-derived
Secondary localized cutaneous (microscopic deposits secondary to a variety of cutaneous lesions)	Keratin-derived

Taken from [1].

and the rare nodular forms, two different kinds of amyloid – amyloid K and amyloid L – are deposited.

Except in the nodular form, in which fibrils are of amyloid L type and are thought to derive from local

aberrant light chain material production by clonally expanded plasma cells in the course of extramedullary plasmacytoma, amyloid K is the protein deposited in all other cases of localized cutaneous amyloidosis



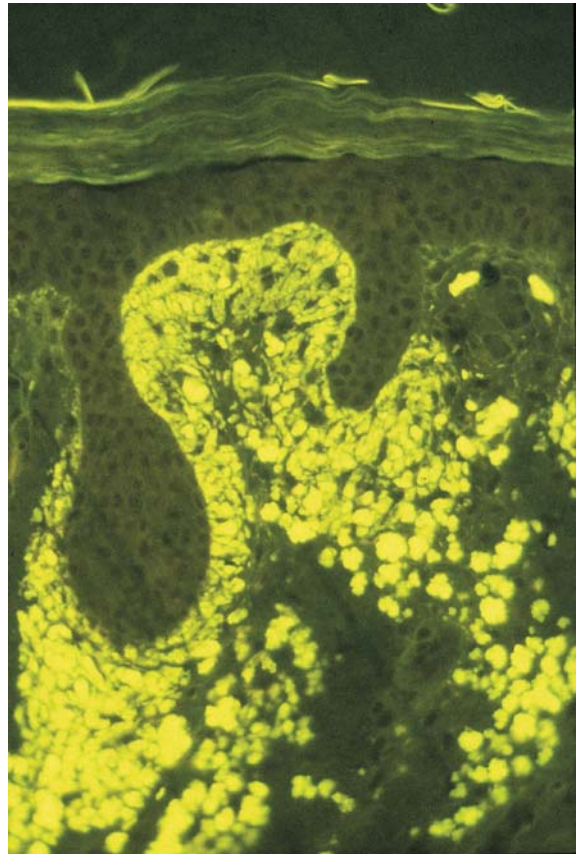
**Amyloidoses, Cutaneous. Figure 1** Primary localized cutaneous amyloidosis-lichen amyloidosis.

including secondary localized cutaneous amyloidosis, which occurs in association with benign and malignant neoplastic skin diseases. This can be demonstrated by the binding of antikeratin autoantibodies to the deposited proteins in direct immunofluorescence (DIF) (Fig. 2).

Furthermore, IgM-antikeratin autoantibodies can be detected in the serum of patients, who suffer from localized cutaneous amyloidosis. The mechanism of amyloid K-deposition in these forms is still debated, but the basal epidermal keratinocyte seems to play the major role in the histogenesis. Basal keratinocytes show degenerative changes leading to the accumulation of modified keratin – tonofilaments in the upper dermis. It still remains unknown how tonofilaments transform into mature amyloid K by switching from an  $\alpha$ -helical structure to a  $\beta$ -pleated sheet pattern, which is responsible for the binding of SAP and thereby for the resistance to degradation by proteolytic enzymes and phagocytes. Clinically, this mechanism leads to the formation of skin-colored and/or brownish, pruritic papules and plaques preferentially on the extensor surfaces of the patient's extremities and trunk.

In systemic amyloidoses (SA), many different kinds of amyloid (Table 1) are described to be deposited in the mesenchymal component of internal organs and sometimes also in the skin and mucosa. In this chapter, the authors want to dedicate attention to the most common forms of SA, amyloidosis L (AL) and amyloidosis A (AA). In AL (Fig. 3), which can be primary (primary systemic amyloidosis, occult dyscrasia) or associated with multiple myeloma, immunoglobulin light chains are the precursor molecules.

In AA, genetic mutations (like in Muckle-Wells syndrome) as well as chronic inflammatory or neoplastic processes lead to the deposition of amyloid that is derived from the serum amyloid A molecule, a



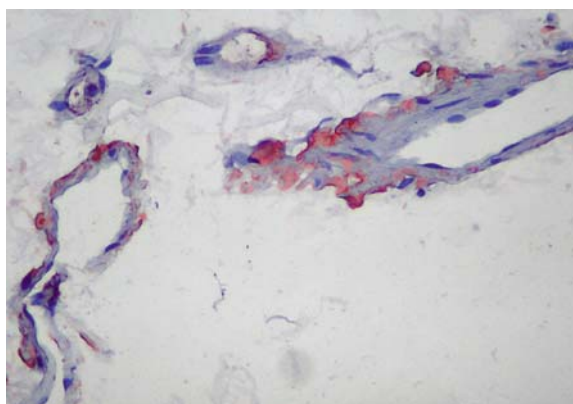
**Amyloidoses, Cutaneous. Figure 2** Amyloid deposits in the dermis in nodular cutaneous amyloidosis Thioflavin T Stain, (100 $\times$ ).



**Amyloidoses, Cutaneous. Figure 3** Periorbital and perioral suffusions in a patient with systemic amyloidosis L.

mediator for inflammation. In detail, Il-1 is liberated in chronic inflammatory diseases, which stimulates hepatic cells for serum amyloid A production and secretion. Serum amyloid A is then phagocytized and





**Amyloidoses, Cutaneous. Figure 4** Deposits of amyloid in vessel walls of the subcutaneous fat in systemic amyloidosis (AL) (200×).

transformed to amyloid A by macrophages, which is finally exocytized and deposited in the mesenchyme. Because of the systemic oversupply of the amyloid precursor molecules in the circulation, they are preferentially deposited in vascular and perivascular structures (Fig. 4), causing dependent organic dysfunction (i.e., peripheral neuropathy, hepatomegaly, cardiac and renal failure) by inhibition of nutritional supply and hemorrhage. Cutaneous involvement in systemic amyloidosis, when present, shows purpuric papular lesions at the sites of friction and characteristically suffusions in the periorbital region (Fig. 3).

### Diagnostic Principles

The clinical appearance of waxy, skin-colored and/or hemorrhagic papules or plaques, especially on the extremities and the face in periorbital areas (Fig. 3), as well as organ symptoms (i.e., congestive cardiomyopathy, renal failure with proteinuria, hepatosplenomegaly, and neuropathy) should refer to the diagnosis of amyloidosis. Histopathology and immunohistochemical stains on skin or organ biopsies should confirm the diagnosis. Only in special cases, direct immunofluorescence (with antikeratin autoantibodies) and electron microscopy are necessary to demonstrate amyloid deposition and to rule out differential diagnoses. Molecular biologic methods are necessary to characterize the type of deposited amyloid, if necessary. It is obligatory to investigate the patient for any inflammatory, neoplastic, or hereditary disease, which can be the source of amyloid production and deposition.

### Therapeutic Principles

In localized cutaneous amyloidosis therapy is difficult, and dermabrasion, carbon dioxide laser treatment, or surgical excision revealed recurrence. Retinoids (Etrinate) and dimethyl sulfoxide seem to be successful in

some cases. Therapeutic options in systemic amyloidoses, which often run a catastrophic course, are the causal or symptomatic treatment of the underlying disease. In AL, a reduction of precursor molecules, i.e., circulating free immunoglobulin light chains, by more than 50% was shown to be associated with substantial survival benefit, regardless of the type of chemotherapy used [3]. Therapy that lowers the amyloidogenic precursor molecules in the serum of AL can stop further accumulation of amyloid deposits, but clinical improvement following chemotherapy seems to be delayed. As a rule, if the underlying disease is controlled or healed, systemic amyloidoses may show a benign course. A new therapeutic approach seems to be Ro 63–8695 (CPHPC), which is a competitive inhibitor of SAP binding to amyloid fibrils. Furthermore, CPHPC is described to crosslink and dimerize SAP molecules in the serum, leading to their rapid clearance by the liver. This mechanism should potentially remove SAP from amyloid deposits, which then can be degraded by proteolytic enzymes and phagocytes. Therefore, CPHPC could be a new therapeutic option for all forms of amyloidoses [4]. In addition, in hereditary forms of AA (especially in Muckle-Wells syndrome) systemic therapy with anakinra – an IL-1 receptor antagonist – may be a successful treatment, as patients treated with this drug have experienced a complete release of their symptoms and resolution of organ dysfunction [5].

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## Amylopectinosis

► Glycogen Branching Enzyme Deficiency

## Amyotrophic Lateral Sclerosis

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### Synonyms

Lou Gehrig's disease; Motor neuron disease; MND; ALS

### Definition and Characteristics

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults. The average age of onset is 50 years; rare juvenile cases are also observed. ALS was first described in 1869 by the French neurologist Jean-Martin Charcot as a progressive, late-onset, lethal motor neuron disease. Characteristics are the degeneration of upper and lower motor neurons, indicated by "myelin pallor" representing loss of the axons of upper motor neurons as they descend from the brain to connect onto the lower motor neurons within the spinal cord. The most typical feature of ALS is the degeneration of cortical, bulbar and spinal motor neurons, excluding those that control the bladder and the eye movement. This leads to generalized muscle weakness and atrophy, speech and swallowing disabilities, progressive paralysis and ultimately death caused by respiratory failure. About 90% of all cases are sporadic, with unknown etiology. The remaining cases are familial, about 20% of which are associated with mutations in Cu/Zn-Superoxide Dismutase (SOD1) [1]. Familial ALS cases are indistinguishable from sporadic ALS on the basis of clinical and pathological criteria. Generally, ALS patients show large heterogeneity as far as symptoms, age of onset and disease duration are concerned.

### Prevalence

Incidence: 1–2 per 100,000; prevalence: 4–6 per 100,000.

### Genes

Most common to date are mutations in the gene encoding Cu/Zn-superoxide dismutase (SOD1). Other genes associated with ALS encode alsin and dynein/dynactin. The alsin gene has been found to be mutated in families with juvenile onset ALS (recessive mode of inheritance). Mutations in the dynein/dynactin complex have also been suggested to be associated with ALS.

Further genes proposed to be associated with ALS are angiogenin, peripherin, senataxin, survival motor neuron gene (SMN), vascular endothelial growth factor (VEGF), vesicle associated protein B (VAPB).

### Molecular and Systemic Pathophysiology

The best studied cause of familial ALS are mutations in the SOD1 gene. SOD1 is 32-kDa homodimer, an anti-oxidant enzyme, located mainly to the cytoplasm and the mitochondria, but is also secreted. Over 130 different ALS-causing mutations are known, most of them point-mutations acting with a dominant mode of inheritance. Each mutation affects differently the biochemical and biophysical properties of SOD1 in vitro. The proposed toxic properties of mutant SOD1 vary from accumulation of protein aggregates, as a consequence of misfolding or protein oxidation, to promotion of pro-oxidant chemistry, possibly mediated by incorrect or loosened binding of metals.

To date no clear-cut correlation has been made between a given mutation and severity of disease. All mutations cause the same phenotype, possibly because they all cause the same mitochondrial damage [2]. Transgenic mice expressing mutant SOD1 ubiquitously display severe neurodegeneration, representing a commonly used model for ALS. Although it is expressed in all cells, SOD1 mutations results in the selective loss of motoneurons. Recent studies show that the neurotoxic effect of mutant SOD1 requires alteration of function of non-neural neighboring cells that enhance motoneuronal damage. Expression within motor neurons was shown to be a primary determinant of disease onset, while the presence of mutant SOD1 in microglia had effect on later disease progression. Onset and progression thus represent distinct disease phases defined by mutant action within different cell types to generate non-cell-autonomous apoptosis of motor neurons [3].

Other genetic defects have been shown to be associated with ALS (see above, "Genes"). Mutations in dynein/dynactin presumably cause a disruption of axonal transport, indicating one possible mechanism of ALS pathogenesis. The other genes implicated in ALS encode proteins involved in a wide range of cellular processes, from oxidation to RNA processing, vesicular transport and angiogenesis. In most cases, genetic analyses have been performed on relatively small populations and, although there have been many gene association studies in ALS, only a few have led to the identification of candidates with repeatable result [4].

Increasing evidence indicates that cellular functions impaired as a consequence of mutant SOD1 converge on pathways that could be activated by other toxic factors in non-SOD1 linked and in sporadic ALS. These pathways include oxidative damage, protein misfolding, mitochondrial dysfunction, defective axonal transport, excitotoxicity, insufficient growth factor signaling, and inflammation [3].

### Diagnostic Principles

A variety of diseases can resemble ALS in its early stages. The diagnosis is therefore primarily based on the



**Amyotrophic Lateral Sclerosis. Table 1** Revised El escorial criteria for diagnosing ALS

ALS diagnostic category	Requirements
Definite ALS	LMN and UMN signs in three regions of the body
Definite familial ALS	LMN and UMN signs in one region of the body plus laboratory-supported identification of gene mutations associated with ALS
Probable ALS	LMN and UMN signs in two regions of the body (some UMN signs rostral to LMN signs)
Probable ALS (laboratory supported)	LMN and UMN signs in one region of the body plus electromyographic evidence of acute denervation of two or more muscles in two or more limbs
Possible ALS	LMN and UMN signs in one region of the body

LMN – lower motor neuron; UMN – upper motor neuron.

**Amyotrophic Lateral Sclerosis. Table 2** Requirements for the diagnosis of ALS: A together with B

A – the presence of	B – the absence of
(A:1) Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination, (A:2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and (A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination	(B:1) Electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and (B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

observed symptoms and signs in the patient, and a series of tests to rule out other diseases (see [Tables 1](#) and [2](#)). Symptoms are muscle weakness, atrophy of muscles, hyperreflexia, and spasticity with pyramidal signs, and the presence of upper and lower motor neuron signs in a single limb. If these symptoms are getting progressively worse, this is strongly suggestive. In order to exclude the possibility of other conditions, blood- and urine-tests and electromyography (EMG), nerve conduction velocity (NCV) or magnetic resonance imaging (MRI) testing may be needed [\[5\]](#).

### Therapeutic Principles

ALS cannot be cured. The first approved drug treatment for the disease is riluzole (Rilutek), which is believed to reduce damage to motor neurons by decreasing the release of glutamate. Treatments for ALS are designed to relieve symptoms and improve the quality of life for patients. Standard support therapy includes night-time breathing assistance early in the course of the disease and application of alternate feeding options once swallowing becomes difficult. Patients may eventually consider forms of mechanical ventilation (respirators). Medications to help reduce fatigue and depression, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm can be considered [\[5\]](#).

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## Analgesic Nephropathy

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### Synonyms

Phenacetin nephritis

### Definition and Characteristics

A slowly progressive decline in renal function secondary to chronic regular use of analgesic medications. Histology classically shows renal papillary necrosis and chronic interstitial nephritis.

### Prevalence

Phenacetin-containing analgesics were initially implicated as the cause of analgesic nephropathy; this led to the withdrawal of phenacetin from the market in many

industrialized nations during the 1980s. The general prevalence of analgesic nephropathy in these nations is estimated to be 1–5%. In nations such as Sweden in which over-the-counter sales of analgesic mixtures have also been banned, this prevalence is even lower. Eastern European countries are noted to have higher prevalence rates, presumably related to higher sales of analgesic mixtures. Though the majority of the epidemiological studies are methodologically flawed, lifetime cumulative intake of analgesics seems to correlate with increased incidence of end-stage renal disease.

### Molecular and Systemic Pathophysiology

The pathogenesis underlying analgesic nephropathy remains unclear although animal models and limited studies in humans have emphasized three main possible mechanisms: inhibition of prostaglandin production, renal medullary ischemia and direct cell injury.

Prostaglandins are hormones derived from arachidonic acid metabolism by two cyclooxygenase (COX) isoforms. COX-1 is expressed ubiquitously throughout the body while COX-2 has traditionally been viewed as inducible during inflammatory states. More recent data have demonstrated continuous low levels of COX-2 within the macula densa, thin ascending limb of the loop of Henle and endothelial cells of the kidney. In a state of low effective circulating volume, COX-2 expression is enhanced, leading to increased local prostaglandin production [1]. Prostaglandins, such as prostacyclin and PGE<sub>2</sub>, maintain proper renal hemodynamics in this setting by stimulating renin release and by attenuating afferent arteriolar vasoconstriction induced by angiotensin II and norepinephrine. The medullary pyramids are particularly at risk for ischemia given their delicate vascular supply that consists of tapering vasa recta capillaries derived from the efferent arterioles of juxtamedullary glomeruli. Non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit both COX isoforms and selective COX-2 inhibitors disable the compensatory actions of prostaglandins. This results in reduced overall renal perfusion though these effects may be more profound in the renal medulla. Analgesics also cause relative renal ischemia despite normal renal perfusion by decreasing hemoglobin oxygen affinity. Aspirin reduces red blood cell 2, 3-diphosphoglyceric acid levels. Phenacetin produces methemoglobinemia [2].

The medullary counter-current multiplier system that modulates urinary concentration may accumulate harmful levels of analgesic metabolites within the medulla. Animal studies have demonstrated increased concentration gradients of acetaminophen metabolites and salicylate between the renal cortex and medulla. Direct cell injury likely occurs through free radical formation especially in the setting of combined acetaminophen and aspirin ingestion. Prostaglandin H synthase localized in

the renal medulla transforms acetaminophen into reactive metabolites which in turn react with glutathione to form stable conjugated compounds. In the setting of concurrent aspirin use, the primary aspirin metabolite, salicylate, consumes glutathione supply resulting in increased free radical formation from acetaminophen metabolism. These free radicals react with oxygen to form superoxides that cause cellular membrane dysfunction [3]. COX inhibition may also shunt arachidonic acid metabolism to the lipoxygenase pathway. This process produces leukotrienes that instigate inflammation, resulting in chronic interstitial nephritis [4]. Recurrent insults lead to apoptosis of medullary interstitial cells and necrosis of the vasa recta. Eventually cortical interstitial fibrosis and tubular atrophy ensue.

### Diagnostic Principles

Analgesic nephropathy typically occurs in women suffering from chronic pain syndromes. Diagnosis is suggested by the presence of chronic kidney disease and positive history of daily analgesic intake for greater than one year; however, an accurate history of analgesic use is often difficult to obtain. Patients may suffer from recurrent urinary tract infections or renal colic secondary to urinary tract obstruction from sloughed necrotic papillary tissue. Urinalysis often demonstrates sterile pyuria and sub-nephrotic range proteinuria. Urinary concentration and acidification may also be impaired. Non-contrast computed tomography scans characteristically exhibit decreased renal size, “bumpy” renal contours and papillary calcifications [5].

### Therapeutic Principles

A more rapid decline in renal function has been noted in patients with ongoing analgesic use, underlying vascular disease and proteinuria at presentation. Preservation of renal function requires avoidance of further analgesic use and adequate control of possible concurrent diseases such as hypertension, diabetes and hypercholesterolemia. Prevention and prompt management of urinary tract infections and urinary tract obstructions are imperative.

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## Anankastic Personality Disorder

- Obsessive-compulsive Personality Disorder

## Anaplastic Thyroid Cancer

- Thyroid Cancer

## ANCA-associated Vasculitis

- Vasculitis, of Medium-sized Vessels

## ANCA-mediated Vasculitis

- Vasculitis, ANCA-mediated

## Ancell-Spiegler Cylindromas

- Cylindromatosis, Familial

## Andersen Disease

- Glycogen Branching Enzyme Deficiency

## Andersen Syndrome

- Periodic Paralyzes, Familial

## Andersen-Tawil Syndrome

- Long QT Syndrome

## Anderson's Disease

- Chylomicron Retention Disease

## Anderson-Fabry Disease

- Fabry Disease

## Androgen Insensitivity Syndrome

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### Synonyms

Testicular feminization, 46,XY sex reversal; Reifenstein syndrome; Mild androgen insensitivity syndrome; MAIS; Partial androgen insensitivity syndrome; PAIS; Complete androgen insensitivity syndrome; CAIS; AIS

### Definition and Characteristics

AIS manifests in an array of phenotypes from mild to partial or complete androgen insensitivity [1]. Complete androgen insensitivity syndrome (CAIS) is characterized by female external genitalia, usually

with small labial folds, a short blind ending vagina (3–10 cm), absence of Wolffian duct derived structures and prostate, absent/rudimentary uterus, gynecomastia, scanty/absent pubic/axillary hairs. In partial androgen insensitivity syndrome (PAIS), several different phenotypes are evident with predominantly female phenotype to ambiguous genitalia (determined by the extent of clitoromegaly and fusion of labia) or predominantly male phenotype with micropenis, perineal hypospadias and cryptorchidism. The later group of the patients is also termed as Reifenstein syndrome [2]. Males with mild androgen insensitivity syndrome (MAIS) usually have normal male genitals and internal male structures; however, during puberty they may experience breast enlargement, sparse facial and body hair, and inadequate enlargement of penis [3]. Some affected males may also have impaired sperm production resulting in oligozoospermia or azoospermia [4].

### Prevalence

**CAIS:** The estimate of the incidence varies from 1 in 20,000 to 1 in 64,000 individuals with a 46,XY karyotype.

**PAIS:** The incidence of PAIS is estimated to be 1 in 30,000 individuals with a 46,XY karyotype.

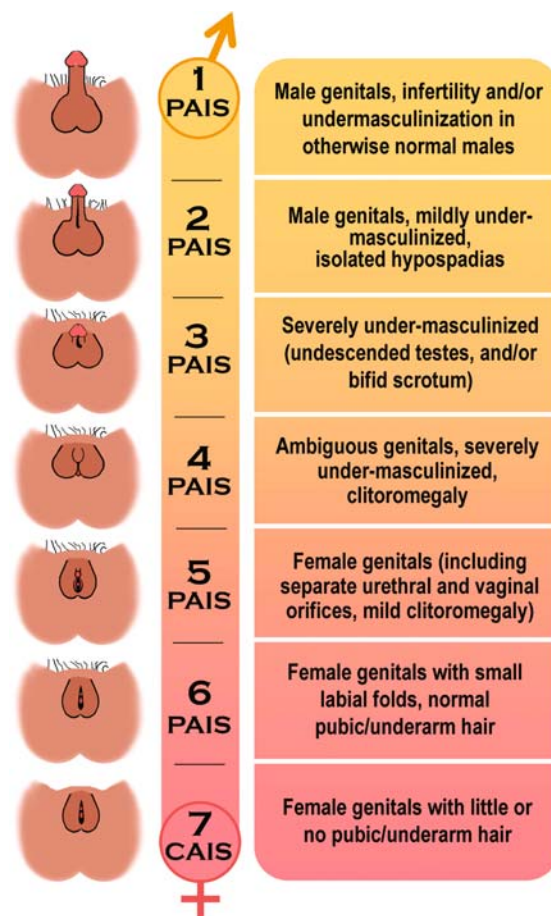
**MAIS:** The incidence is much lesser than CAIS and PAIS, however, the incidence has not been measured as yet.

### Genes

Deletions/point mutations in androgen receptor (AR) gene, mapped on Xq11–12, have been frequently reported in AIS (web: <http://www.mcgill.ca/androgendb/>) [5]. Mutations have been reported throughout the gene with deletions predominantly in exons 1 and 2, and substitutions in exons 2–8 of the gene. Certain nucleotide positions have been identified as mutation hotspots. Mutations in SRD5A2 gene in the background of AR mutations may result in phenotypic variations among the affected siblings sharing the AR mutation [1].

### Molecular and Systemic Pathophysiology

AIS results from the imperfect secondary sexual differentiation as a result of defective AR. The complete loss of the androgen action in CAIS results in the default development of the ovaries, followed by the breast development at puberty leading to overall female phenotype. The partial loss of androgen action in PAIS results in various phenotypes (Fig. 1), depending upon the overall exposure of the fetus to the androgens. The mild loss of androgen action in MAIS results in failure of proper enlargement of penis and testicular growth, and/or inadequate sperm production leading to infertility.



**Androgen Insensitivity Syndrome . Figure 1** Different grades of Androgen Insensitivity Syndrome (AIS) along with phenotypic appearance of external genital organ and clinical features. PAIS 1 is also referred as MAIS. AIS 6 and AIS 7 (also called as CAIS) differ only by the presence and absence of pubic hair, respectively.

### Diagnostic Principles

The diagnostic features of AIS are the presence of female external genitalia, ambiguous genitalia or undermasculinization in association with 46,XY karyotype, normal/elevated levels of androgens, elevated levels of LH and/or FSH. The individuals with CAIS are difficult to distinguish from their normal female counterparts at birth, however, the absence of menstruation onset and the absent/scanty pubic/axillary hair at puberty may indicate CAIS. The diagnosis is confirmed by the evaluation of hormone levels, followed by the confirmation of the abdominal testes by needle biopsy. The highest grade of PAIS (grade 6) can also be diagnosed in a similar way with the difference that pubic/axillary hair is of higher density. The presence of the ambiguous external genitalia at birth may indicate PAIS. This is confirmed by evaluation of hormone

levels, poor/normal breast development, appearance of normal pubic/axillary hair at puberty, and needle biopsy confirming testicular tissue. However, the PAIS should be distinguished carefully from the male pseudohermaphroditism arising as a result of inadequate androgen metabolism due to defective 5- $\alpha$  reductase enzyme. The undermasculinization resulting in smaller testicular volume, micropenis, reduced sperm count or the development of certain feminine characters such as gynecomastia, high-pitched voice and behavioral differences, in the otherwise normal looking males, may help to detect MAIS. The sequence analyses identifying a mutation in AR gene would confirm AIS.

### Therapeutic Principles

Therapeutic principles focus mainly on three aspects: surgical reconstruction of external genitalia, removal of abdominal gonads due to the risk of neoplasia, and the choice of appropriate hormone therapy. The development of external genitalia is one of the main aspects of sex differentiation taking place *in utero*. Therefore, it is not possible to initiate normal differentiation of external genitalia and fertility in the affected individuals. However, surgical reconstruction of the external genitalia may help to restore the normal sexual life in many patients. The individuals with CAIS have female external genitalia with short vaginal length, which may be inadequate for sexual intercourse. These individuals are invariably raised as girls after surgical restoration of the normal vaginal length. The gonads are surgically removed and estrogen therapy may be given to help the development of female secondary sexual characters. However, most of the patients do not need hormonal therapy because in the absence of androgen action, female secondary sexual characters develop by default. In PAIS, the restoration of the external genitalia involves more extensive manipulation. The external genitalia resembling female genitals or the ambiguous genitalia are surgically manipulated to construct the female genitals. Hypospadias or the micropenis may be reconstructed to male genitals, followed by the removal of gonads and testosterone therapy to favor male secondary sexual differentiation. In MAIS, surgical intervention is usually not required, except the correction of the gynecomastia in certain cases; however, androgen therapy may be advised to achieve masculinization.

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## Androgenetic Alopecia

### ► Alopecia, Androgenetic

## Anemia

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### Definition and Characteristics

Reduced hemoglobin concentration. Weakness, shortness of breath, palpitations, and headaches are common complaints. In elderly patients' heart failure, angina pectoris, intermittent claudication, or mental deterioration may occur. Clinical manifestations depend on the speed of onset and the severity of anemia. Pallor of the skin or mucous membranes and resting tachycardia may be present.

### Prevalence

It is a common clinical condition, with a wide variety of causes. No precise prevalence is available. In developing countries iron deficiency due to helminthic infections and malnutrition are major causes of anemia. There are considerable differences in the occurrence of hemoglobin disorders and red cell membrane disorders that leads to anemia in different parts of the world.

### Genes

Genes associated with hemoglobin disorders such as sickle cell anemia and thalassemias, red cell membrane defects and enzymatic defects, paroxysmal nocturnal hemoglobinuria, Fanconi anemia, and Diamond–Blackfan syndrome are specified in the chapters on these topics.



## Molecular and Systemic Pathophysiology

Anemia can be classified according to the underlying pathological condition. There are three classes of anemia; however, it should be stated that in many clinical situations more than one class coexist.

1. Anemia due to a reduced production of erythrocytes in the bone marrow as a result of bone marrow damage or reduced erythropoietin production. Red blood cells usually have a normal volume (normocytic anemia). Bone marrow may be infiltrated by malignant cells or it may be fibrotic, for instance due to myelofibrosis or radiation therapy. Erythropoietin production may be reduced in case of renal insufficiency. In case of inflammatory diseases the production of erythropoietin is suppressed by cytokines, which have a direct suppressive influence on the bone marrow as well. In hypothyroidism the oxygen need of tissue is reduced, also leading to a reduced erythropoietin production. Mild iron deficiency may also lead to bone marrow hypoplasia.
2. Anemia due to a maturation disorder of erythrocytes. Maturation defects are associated with an altered red cell volume: decreased when the hemoglobin production is impaired (microcytic), increased when there are nuclear defects in erythroid progenitor cells (macrocytic). Hemoglobin production is reduced in moderate and severe iron deficiency. There are many clinical conditions leading to iron deficiency. Hemoglobin production is impaired in thalassemias as a result of defective globin chain production. Defective heme synthesis occurs in sideroblastic anemia. Defects in the nucleus of erythroid progenitor cells may be the result of a variety of clinical conditions. Deficiencies of hydroxycobalamin (vitamin B12) or folate (vitamin B11) lead to macrocytic anemia, and can be the result of reduced intake, or a reduced uptake from the gut, for instance after bowel surgery or as a result of malabsorption. Intrinsic factor, which is produced in the stomach, is an essential factor for the uptake of B12 in the ileum. Antibodies against intrinsic factor cause B12 deficiency and macrocytic anemia in the case of pernicious anemia. Drugs that have an influence on DNA metabolism cause macrocytic anemia as well. Well-known examples are alkylating agents, methotrexate, and antiretroviral therapy. Alcohol has the same effect. The myelodysplastic syndrome is another possible cause of macrocytic anemia.
3. Anemia due to an increased turnover or loss of erythrocytes. In contrast to the other types of anemia the number of reticulocytes, young erythrocytes, is high in most conditions of this group. Exceptions are acute and chronic blood loss. In the first, erythrocyte production has not been upregulated yet, while in the latter iron is lost along with the erythrocytes

which limits erythrocyte production (in fact, a combination of blood loss, reduced red cell production, and a maturation defect due to iron deficiency). The red blood cells have a normal or slightly increased mean volume depending on the percentage of reticulocytes (which are larger than erythrocytes). Hemolytic anemia, which leads to an increased erythrocyte turnover, may be caused by membrane defects, enzymatic defects, hemoglobin disorders, autoimmune processes as well as mechanical factors. Membrane defects may be congenital (hereditary spherocytosis and elliptocytosis) or acquired (paroxysmal nocturnal hemoglobinuria). Examples of enzymatic defects are glucose 6 phosphate dehydrogenase deficiency and pyruvate kinase deficiency. Autoimmune hemolysis is seen in patients with systemic autoimmune disease, but also in patients with hematologic malignancies or infections. Hemoglobin disorders, sickle cell disease and thalassemias, may present with hemolytic anemia. A prosthetic heart valve is a well-known mechanical cause of hemolysis.

## Diagnostic Principles

Medical history, physical examination, and screening laboratory examination lead to the diagnosis in most patients. Screening laboratory examination should include measurement of hemoglobin concentration, mean corpuscular volume of erythrocytes, reticulocyte, leucocyte, and platelet counts. Examination of the blood film is often helpful. A higher bilirubin and a lower haptoglobin concentration are indicative for hemolysis. Bone marrow examination may be needed in case of unexplained reduced erythrocyte production. Additional tests for the diagnosis of hemoglobin disorders, enzymatic defects, membrane defects are mentioned in the chapters on these disorders.

## Therapeutic Principles

The treatment is dependent on the underlying condition.

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## Anemia, Diamond-Blackfan

### ► Diamond-Blackfan Anemia

## Anemia, Hemolytic Autoimmune

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### Synonyms

Anemia; AIHA; Idiopathic autoimmune hemolytic; Cold agglutinin disease; Paroxysmal cold hemoglobinuria

### Definition and Characteristics

Autoimmune hemolytic anemia (AIHA) is a disease in which the patient is producing antibodies against antigens present on his own red blood cells, causing them to be destroyed prematurely. The disorder can be classified by the isotype and temperature at which the antibodies react optimally with the red cell antigen: in warm AIHA the antibodies are mostly IgG and react at normal body temperature (37°C); in cold-reacting AIHA IgM antibodies are seen and react best at temperatures below 37°C. Cold AIHA can be further subdivided into cold agglutinin disease (CAS, cold hemagglutinin disease) and paroxysmal cold hemoglobinuria (PCH). Rarely, patients have mixed warm and cold autoantibodies. AIHA can occur by itself (primary or idiopathic) or in combination with another disease, or as a result of drug therapy (secondary) [1].

### Prevalence

AIHA has a prevalence of 1 in 100,000; warm type AIHA is the most common type [1]. CAS represents approximately 16–32% of AIHA cases, whereas PCH is reported in 2–10% of cases of hemolytic anemia. In 50% of the cases, AIHA is primary or idiopathic since its cause cannot be determined.

Approximately half of secondary warm and cold AIHA cases are associated with lymphoproliferative disorders. Autoimmune disorders are the next leading cause of warm AIHA, whereas infections are the most common cause of secondary cold AIHA. Primary CAS

is mostly seen in older adults (70 years and above), affecting more females than males.

### Genes

In humans, there is conflicting data as to the role of HLA-A1, B7 and B8 for susceptibility to this disease. Genetic studies in a certain strain of mice known as the New Zealand black (NZB) [2], which develop warm AIHA spontaneously in 25% of the cases, have revealed that the development of AIHA is under multigenic control and a combination of several susceptibility genes and modifying alleles with suppressive activities determine the outcome of disease features in the progeny. Susceptibility loci for development of AIHA mapped thus far include autoimmune hemolytic anemia (Aha), autoimmune anemia 1 (Aia 1), and Aia2, although none of the genes or gene products responsible for the associated phenotypes have yet been identified.

### Molecular and Systemic Pathophysiology

Several mechanisms are thought to result in the loss of tolerance to red cell antigens, including: (i) cryptic determinants, a result of conformational change on self red cells, or cross reactive foreign antigens mimicking epitopes on red cells leading to polyclonal T and B cell activation, (ii) genetic defects in central tolerance such as mutations in apoptotic machinery (mutations associated with Fas/Fas ligand), (iii) immunoregulatory disorders resulting in errors in peripheral tolerance such as depletion of CD4+CD25+ T regulatory cells or imbalance of cytokine (Th1/Th2) networks such as increased production of Th2 (IL-4 and IL-10) versus reduction in Th1 (IFN- $\gamma$ ) cytokine production or downregulation of IL-12 [3,4,5].

Most warm autoantibodies are directed against the Rhesus blood group antigen complex. The presence of autoantibodies on the patient's red cells results in recognition and binding of the Fc portion of the antibody molecule to the Fc-receptors on splenic macrophages and subsequent ingestion of the sensitized erythrocytes. In most cases the sensitized cells are only partially ingested, leaving characteristic cells of AIHA referred to as microspherocytes. These spherocytes are trapped in the splenic sinusoids and removed from circulation. If in addition to autoantibodies, the red cells are also coated with complement factor C3 split product (C3b), there is enhanced clearance through complement receptors present on the macrophages.

Cold IgM autoantibodies bind to the red cells in the extremities where the temperature can be lower, activate complement, and deposit C3b on the cell surface. These complement sensitized cells are cleared

extravascularly by the macrophages of the liver. In severe cases, the complete complement cascade is activated on the cell surface, resulting in intravascular hemolysis.

### Diagnostic Principles

Low hemoglobin, increased reticulocyte count and positive direct antiglobulin test (DAT) are the main diagnostic features of AIHA. Patients may develop symptoms such as fatigue and dizziness as a result of anemia. In cases of intravascular hemolysis, decreased haptoglobin, hemoglobinemia and hemoglobinuria can also be seen. Eluate studies and indirect antiglobulin tests are some of the additional assays used to define the antibody.

### Therapeutic Principles

In mild AIHA no treatment may be required. When intervention is necessary, corticosteroids (prednisone) represent the first line of treatment. Splenectomy may be considered in certain cases. Intravenous gammaglobulin has been used with mixed results. Rituximab (anti-CD20 antibody) has been used successfully in pediatric cases. Immunosuppressive therapy may be used if the other agents are ineffective. Blood transfusions may be necessary, although they are complicated because the autoantibodies are panagglutinins, so that crossmatching of red blood cells may be difficult.

If the hemolysis is thought to be drug-induced, the offending drug needs to be discontinued.

In cases of cold AIHA, keeping the patient warm may be sufficient. For more severe cases, corticosteroids are rarely effective. Splenectomy is not useful because the liver is the main site for clearance of complement-coated cells.

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## Anemia, Sideroblastic Acquired Idiopathic

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### Synonyms

Refractory anemia with ringed sideroblasts; RARS; AISA

### Definition and Characteristics

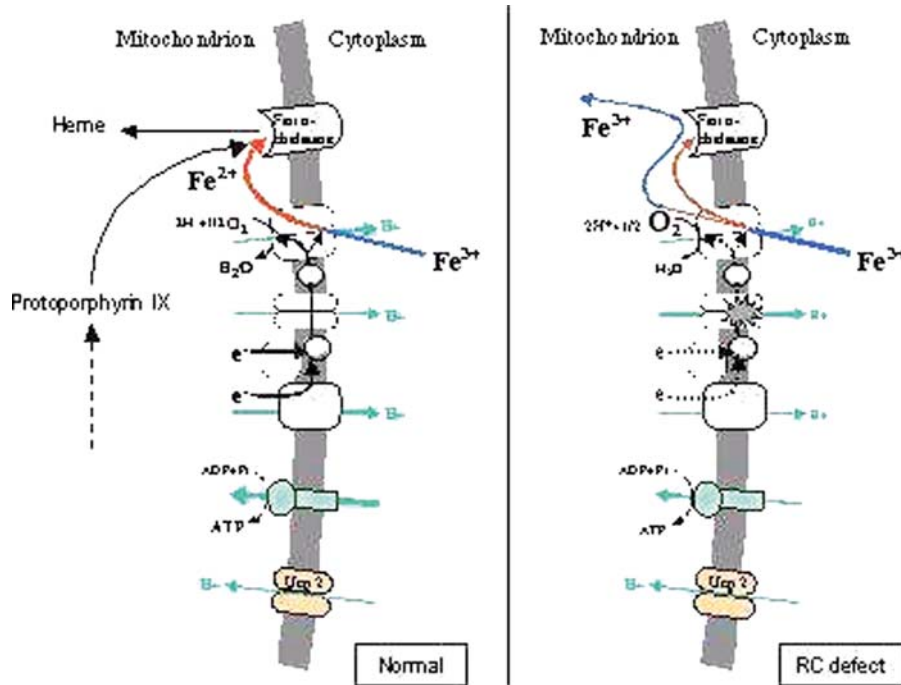
Clonal bone marrow disease arising from a multipotent hematopoietic stem cell. Red cell precursors show large abnormal iron granules surrounding the cell nucleus (“ringed sideroblasts”) [1]. This finding corresponds to massive iron accumulation in the mitochondria.

### Prevalence

Like other types of myelodysplastic syndrome (MDS), the incidence of AISA is strongly age-dependent. The majority of cases occur after age 65. Crude annual incidence is about 1/100,000 (Fig. 1).

### Molecular and Systemic Pathophysiology

Ferrochelatase utilizes only ferrous iron ( $\text{Fe}^{2+}$ ) for heme synthesis. In sideroblastic anemia, iron accumulates in the ferric form ( $\text{Fe}^{3+}$ ). This appears to be attributable to a failure of the respiratory chain (RC) to remove oxygen from the mitochondrial matrix efficiently. Oxygen consumption is stimulated in erythropoietic cells by uncoupling protein-2. A low oxygen concentration in the mitochondrial matrix helps to keep iron in the reduced form. A respiratory chain defect will decrease  $\text{O}_2$  consumption and will thus increase  $\text{O}_2$  in the mitochondrial matrix. If iron, which crosses the inner mitochondrial membrane as  $\text{Fe}^{2+}$ , becomes re-oxidised ( $\rightarrow\text{Fe}^{3+}$ ), it will be rejected by ferrochelatase and will thus accumulate in the mitochondrial matrix. RC dysfunction can be explained by mutations in mitochondrial DNA (mtDNA), because important RC subunits are encoded by mtDNA. Clonal mtDNA mutations, changing conserved nucleotides/amino acids, have been discovered in the bone marrow of patients with AISA [2,3]. They affect protein genes as well as mitochondrial transfer RNAs and mitochondrial ribosomal RNAs. They are acquired in the bone marrow and show heteroplasmy, i.e., coexistence of mutant and wild type mtDNA, which is typical of mitochondrial DNA disorders. Besides interfering with iron metabolism and heme synthesis, mitochondrial dysfunction can explain



**Anemia, Sideroblastic Acquired Idiopathic. Figure 1**

other features of AISA [4], like increased apoptosis of bone marrow cells [5] and megaloblastic changes in red cell precursors (because de novo pyrimidine nucleotide synthesis depends on a functioning respiratory chain).

### Diagnostic Principles

Bone marrow cytology, including iron staining, reveals ringed sideroblasts and other dysplastic changes. Reversible causes of sideroblastic anemia (e.g., alcoholism or lead poisoning) must be excluded. Clonal chromosomal abnormalities are detectable in up to 50% of patients. They apparently provide the growth advantage to the clone harboring the mitochondrial defect. There are no chromosomal changes specific for the sideroblastic phenotype.

### Therapeutic Principles

The only curative approach is allogeneic stem cell transplantation. Treatment with erythropoietin and G-CSF can diminish apoptosis of bone marrow cells, thereby improving blood counts. Because of secondary hemosiderosis, patients require iron chelation therapy.

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## Aneurysm, Aortic and Arterial

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### Definition and Characteristics

An aneurysm (AN) is defined as a widening of the vessel that is greater than 50% of its normal size [1]. An AN is classified as fusiform or secular. A fusiform



AN affects the entire circumference of the segment of the vessel resulting in a symmetric dilatation, whereas a secular AN involves only a portion of the circumference resulting in an outpouching of the vessel wall. Mycotic or infected ANs are arterial dilatations secondary to an infected embolus adhering to the wall of the AN. A dissecting aneurysm (DA) is defined as a hematoma that extends to or dissects the medial wall of a vessel secondary to a tear in the intima. DA can be classified (Stanford) as type A, in which the dissection involves the ascending aorta; type B, when the dissection is limited to the descending aorta. Aortic ANs are classified as thoracic, abdominal and thoracoabdominal. The sinus of Vasalva is a dilatation of one of the aortic sinuses between the aortic valve annulus and the sinotubular ridge; a common location is the right coronary sinus, which may rupture into the right ventricle. Other important ANs include the intracranial aneurysms which are usually secular (or berry) aneurysms located at the terminal internal carotid artery, middle cerebral artery bifurcation, and the top of the basilar artery. Aortic and arterial ANs commonly produce no symptoms and are usually detected on routine examinations as a palpable, pulsatile and nontender mass, or may present as an incidental finding on an imaging test performed for other reasons. The speed of AN growth can be unpredictable, and may enlarge steadily or exponentially with time and age. As it reaches a critical size, which is specific for each location, the chance of rupture is greatly increased and site specific symptoms start to occur. Rupture and dissection of ANs are often accompanied by sharp, excruciating pain and carries a high morbidity and mortality rate when it happens in the aorta and intracranially. Other complications include thromboembolism and compression of adjacent structures. Aortic dissection can result in occlusion of major arteries, compression of adjacent structures, acute aortic regurgitation and myocardial infarction [2].

### Prevalence

Studies found that 4.8% of men aged 65–69 had an AN and 10.8% of men aged 80–89 had an aortic AN. Prevalence of AN in the intracranial arteries is 2%, the abdominal aorta 1%, the iliac artery 0.003%, femoral artery 0.004%, and popliteal artery 0.008%.

### Genes

Mutations of the genes encoding fibrillin-1 and type III procollagen have been implicated in some cases. Linkage analyses have identified loci in chromosome 5q13–14 and 11q23.3–q24 in several families with familial clustering of aortic ANs.

### Molecular and Systemic Pathophysiology

In familial cases such as in Marfan and Ehlers-Danlos syndromes, cystic medial necrosis leads to the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material. This results in circumferential weakness and dilatation and the development of fusiform AN and dissection ANs. Aortic rupture and dissection may follow. Furthermore, the dilatation of aortic annulus may cause significant aortic insufficiency. Recently, it has been shown that excessive transforming growth factor- $\beta$  (TGF- $\beta$ ) contributes to progressive aortic rest enlargement [3]. Both polyclonal TGF- $\beta$  neutralizing antibody and losartan, an angiotensin receptor inhibitor that limits TGF- $\beta$  action, may prevent aortic enlargements in Marfan syndrome [3]. For non-familial cases, the underlying causes of ANs are likely multifactorial which may include systemic causes, inflammation, and atherosclerosis. It is hypothesized that AN formation and rupture are the result of elastin and collagen degradation by proteases such as plasmin, matrix metalloproteinases and cathepsin S and K [4]. These proteases are derived from the endothelial and smooth muscle cells locally, and also from immigrated inflammatory cells. Vasculitides that are associated with arterial ANs include Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease, Behcet's syndrome and spondyloarthropathies. Congenital aortic aneurysms may be primary or associated with bicuspid aortic valve or aortic coarctation.

### Diagnostic Principles

Aneurysms are suspected by a localized pulsatile mass and are usually diagnosed incidentally from an imaging test such as routine x-ray, ultrasound, CAT scan or MRI. Ultrasonography is the preferred modality for screening except for intracranial aneurysms. The diagnosis can be confirmed with CT scan, MRI and/or angiography.

### Therapeutic Principles

Medical therapy consists of cessation of smoking and treatment of hypertension and dyslipidemia. Surgical consideration depends on the general health of the patient as well as the chance of rupture of the particular aneurysm [5]. Once the aneurysm has reached a critical diameter and when symptoms start to occur, surgery is indicated.

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## Angelman Syndrome

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### Synonyms

MIM 105830; Former designation (now in disuse):  
“Happy puppet syndrome”

### Definition and Characteristics

Angelman syndrome (AS) is a neurogenetic disorder caused by genetic defects at 15q11–13. Characteristic features include severe mental retardation, lack of speech, unmotivated laughter, and ataxia.

### Prevalence

The disorder occurs in approximately 1/15,000–20,000 live births.

### Genes

E6-associated protein ubiquitin-protein ligase gene: UBE3A (MIM: 601623); Small nuclear ribonucleoprotein polypeptide N: SNRPN (MIM: 182279).

### Molecular and Systemic Pathophysiology

The genetic basis of AS is complex. The majority of patients (approximately 70%) have an interstitial deletion at 15q11–q13 affecting the maternally inherited chromosome 15. Approximately 5% of AS patients have an imprinting defect [1] and 3–5% have a paternal UPD15 [2]. Furthermore, mutations in the imprinted gene UBE3A account for approximately 10% of AS cases [3–5]. The genetic defect underlying the remaining 10% of cases remains unknown to date.

Patients with a deletion generally appear to be more severely affected than those with a patUPD15 or an imprinting defect; patients with a mutation in the UBE3A gene also present with severe and typical AS features [6]. On the basis of these observations it is thought that the functional loss of the maternal UBE3A gene alone appears to cause the major features of AS.

### Diagnostic Principles

Some typical clinical symptoms of AS become more and more evident after the first 2 years of life (e.g. seizures, lack of speech and movement disorders), however, experienced physicians would usually diagnose AS also in new-borns. A number of other syndromes may mimic some of the AS features, particularly the RETT syndrome, which can be considered as the main differential diagnosis.

The molecular diagnosis of AS is based on the analysis of the methylation status at SNRPN. An abnormal methylation pattern is detected in AS patients with the 15q11–q13 deletion, patUPD15 and imprinting defects. Microsatellite analysis allows to differentiate between these classes of genetic defects. Conventional methods are usually used for the detection of UBE3A mutations (such patients have normal methylation patterns at SNRPN).

The 15q11–13 deletion can also be detected by FISH analysis; and in rare cases a UPD can be detected by conventional cytogenetic investigations, i.e. if either A) a clear polymorphism is present on both chromosomes 15, or B) the two chromosomes 15 are replaced by a 15;15 Robertsonian translocation chromosome.

### Therapeutic Principles

No therapy is available. Severe seizures may be treated with anticonvulsive drugs. Physiotherapy and ergotherapy are recommended.

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## Angina

- ▶ Coronary Artery Disease
- ▶ Tonsillitis

## Angina Pectoris

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### Synonyms

Stenocardia

### Definition and Characteristics

Angina pectoris is chest pain or discomfort due to coronary heart disease (CHD) and is a symptom of myocardial ischemia. It occurs when the blood supply to the heart muscle does not meet its demand. This usually results from obstruction or spasm of the coronary arteries. In less frequent cases, angina can be caused by valvular heart disease, hypertrophic cardiomyopathy or uncontrolled high blood pressure.

### Prevalence

The prevalence of angina pectoris increases with age, being twice as common in men as in women. In men, the prevalence is 2–5% in the 45–54 year-old age-group and 11–20% in the age group 65–74; in women the respective prevalence is 0.5–1% and 10–14%. It can be estimated that the prevalence of angina pectoris in Europe is as high as 30,000–40,000 per one million total populations.

### Genes

Most common forms of CHD are believed to be multifactorial and to result from many genes, each with a relatively small effect working alone or in combination with modifier genes and environmental factors. Well described examples include familial forms of hypercholesterolemia often caused by mutations in the low-density lipoprotein (LDL) receptor or the apolipoprotein (apo) B gene (APOB). [Table 1](#) specifies candidate gene variants for CHD.

Recently, a 58-kilobase interval on chromosome 9p21 was found to be associated with CHD in more than 23,000 individuals. This interval contains no annotated genes and is not associated with established CHD risk factors. Homozygotes for the risk allele make up 20–25% of Caucasians and have an approximately 30–40% increased risk of CHD [1].

### Molecular and Systemic Pathophysiology

Inflammation plays a major role in all stages of atherosclerosis and CHD and participates in the local, myocardial, and systemic complications of atherosclerosis. As a response to diverse factors like bacterial

**Angina Pectoris. Table 1** Meta-analyses published since 2000 consisting of a total of at least 1,000 subjects

Candidate genes for coronary heart disease		
Gene	Risk allele	Reported risk ratio <sup>a</sup>
MTHFR	C677T	1.14–1.21
Cholesterol ester transfer protein (CETP)	TaqIB	0.78
Paraoxonase (PON1)	Q192R	1.14–1.21
Endothelial nitric oxide synthase (eNOS)	T-786C	1.31
Prothrombin	G20210A	1.21
APOB	Ins/Del (DD)	1.30
Glycoprotein IIIa	PI(A2)	1.10
APOE	ε4/ε4	1.42
ACE insertion/deletion	DD	1.16–1.21
APOB	SpIns/Del (DD), EcorI (AA)	1.19–1.73
PAI1	4G/5G	1.20
Fibrinogen β-chain	G-455A	0.68
Endothelial nitric oxide	Glu298Asp, Intron-4	1.31–1.34

<sup>a</sup>All relative risks were reported to be statistically significant from 1.0. References for each gene are published in [4].

products, vasoconstrictor hormones, proinflammatory cytokines, dyslipidemia, and others, the endothelial cells of the artery express adhesion molecules that promote adhesion and transmigration of blood leukocytes. The blood leukocytes communicate with endothelial and smooth muscle cells (SMCs) depending on mediators of inflammation and immunity such as prostanooids and other derivatives of arachidonic acid, and protein mediators, including cytokines and complement components.

As a consequence of the inflammatory ferment, SMCs migrate from the tunica media to the intima, proliferate and build a complex extracellular matrix. Moreover, they secrete matrix metalloproteinases (MMPs) which modulate various functions of vascular cells. As the lesion progresses, calcification may occur. In addition, cell death (including apoptosis) commonly occurs in the atherosclerotic lesion. Death and coalescence of lipid-laden macrophages can form the classic, lipid-rich “necrotic” core of atherosclerotic plaque [2,3].

### Diagnostic Principles

An accurate history is important and should routinely demand cardiovascular risk factors like hypertension, diabetes mellitus, smoking, and hypercholesterolemia and family history. Typically, angina is induced by effort or conditions that increase myocardial oxygen demand. General physical examination is often unremarkable, but can show findings suggesting lipid disorders (e.g. xanthelasma). Resting 12-lead ECG is normal in 50% of cases or can show unspecific findings. However, the detection of pathologic Q/QS waves strongly suggests an ischemic origin of symptoms. Treadmill or bicycle exercise stress test during 12-lead ECG monitoring which may reveal stress-induced ST-segment depression is the test of choice to diagnose myocardial ischemia in the majority of patients with suspected stable angina. Additional non-invasive stress tests can be obtained by myocardial perfusion scintigraphy, echocardiography, and cardiac magnetic resonance imaging. Multislice CT angiography is an attractive technique for non-invasive detection of coronary artery stenosis, but its diagnostic accuracy is still uncertain. By definition, obstructive CHD is ultimately diagnosed by documenting flow-limiting coronary artery stenosis at angiography [2].

### Therapeutic Principles

The aims of treatment are to minimize or abolish symptoms and also improve prognosis by preventing myocardial infarction and death. Identifying and treating risk factors is a priority in patients with CHD. Interventions for secondary prevention include smoking cessation, dietary modification, and correction of

adiposity, as well as treatment of dyslipidemia (e.g. with statins), diabetes and hypertension. Drugs to improve outcomes in angina are antiplatelet agents such as acetyl salicylic acid and clopidogrel.  $\beta$ -adrenergic receptor antagonists reduce myocardial ischemia, improve exercise tolerance and provide symptomatic relieve in angina. ACE inhibitors are vasodilators and improve endothelial dysfunction and other properties that could translate into benefits in ischemic heart disease. Calcium antagonists have been shown to be effective in the treatment of coronary artery spasm. Also, they exhibit antianginal effect through reduction of myocardial oxygen demand secondary to decreased afterload and myocardial contractility. A new therapeutic class, called If inhibitor, has recently been made available: Ivabradine provides pure heart rate reduction, leading to major anti-ischemic and antianginal efficacy. All patients with angina pectoris and established CHD should be evaluated whether they might benefit from revascularization therapy by coronary bypass surgery or percutaneous coronary intervention. Criteria for prognostic indications have been developed. Moreover, patients with refractory angina pectoris despite optimal medical treatment should be evaluated for this option [2].

### ► Coronary Artery Disease

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## Angiodysplasia

### ► Lymphedema Syndromes

## Angiodysplasia of the Colon

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### Synonyms

Vascular ectasia of the colon; Colonic arteriovenous malformation; Colonic angioma

### Definition and Characteristics

Angiodysplasia is a degenerative lesion of previously healthy blood vessels found most commonly in the cecum and proximal ascending colon. Seventy-seven percent of angiodysplasias are located in the cecum and ascending colon, 15% are located in the jejunum and ileum, and the remainder are distributed throughout the alimentary tract. The lesions are small (less than 5 mm), impalpable and are not associated with skin or other visceral lesions [1]. Phillips, in a letter to the London Medical Gazette in 1839, first described a vascular abnormality causing bleeding from the large bowel. An association between colonic angiodysplasia and aortic stenosis was described by Heyde in 1958. In 1960, Margulis and colleagues identified a vascular malformation in the cecum of a 69-year-old woman who presented with massive bleeding. This diagnosis was accomplished by mesenteric arteriography. Galdabini first used the name angiodysplasia in 1974 [1]. Angiodysplasia occurs predominantly in those aged between 60 and 69 years although cases as young as 19 years have been reported. Patients with colonic angiodysplasia may present with hematochezia (0–60%), melena (0–26%), hemoccult-positive stool (4–47%) or iron deficiency anemia (0–51%). Bleeding is usually low grade but can be massive in approximately 15% of patients. Iron deficiency anemia and stools that are intermittently positive for occult blood can be the only manifestations of angiodysplasia in 10–15% of patients. Bleeding stops spontaneously in over 90% of cases but is often recurrent [1].

### Prevalence

The prevalence of angiodysplasia in the United States is 0.8% in healthy patients older than 50 years who are undergoing screening colonoscopy. Foutch et al. noted the prevalence of angiodysplasia to be 0.93% from three prospective studies in which screening colonoscopies were performed in 964 asymptomatic individuals (mean age, 61 years). Patients with von Willebrand's disease may have an increased incidence of gastrointestinal bleeding from colonic angiodysplasia [2].

### Genes

Sato et al. reported in 2004 a point mutation in the exon 28 of the von Willebrand's factor gene in some patients with von Willebrand's disease complicated with gastrointestinal angiodysplasia. Studies confirming the role of this gene defect have not been reported to date [2].

### Molecular and Systemic Pathophysiology

Angiodysplasias typically are irregularly shaped clusters of ectatic small arteries, small veins, and their capillary connections. Microscopically, angiodysplastic lesions are dilated, distorted, thin-walled vessels. The amount of smooth muscle in the vessel wall is variable. The vessel wall can become so thinned that it appears to be composed only of endothelium [1]. The exact mechanism of development of angiodysplasia is not known. One prominent hypothesis accounts for the high prevalence of these lesions in the right colon is based on the Laplace law. The Laplace law relates wall tension to luminal size and transmural pressure difference in a cylinder whereby the wall tension is equal to the pressure difference multiplied by the radius of the cylinder. In the case of the colon, wall tension refers to intramural tension, pressure difference is that between the bowel lumen and the peritoneal cavity, and cylinder radius is the radius of the right colon. Wall tension is highest in bowel segments with the greatest diameter, such as the right colon. This theory suggests that repeated episodes of colonic distention are associated with transient increases in lumen pressure and size. This results in multiple episodes of increasing wall tension with obstruction of submucosal venous outflow, especially where these vessels pierce the smooth muscle layers of the colon. Over many years, this process causes gradual dilation of the submucosal veins and, eventually, dilation of the venules and arteriolar capillary units feeding them. Ultimately, the capillary rings dilate, the precapillary sphincters lose their competency, and a small arteriovenous communication forms. This accounts for the characteristic early filling vein observed during mesenteric angiography. Of note, the aforementioned pathophysiological mechanisms responsible for the development of cecal lesions are unlikely to apply to lesions in the upper GI tract, despite being morphologically identical. Recently, a link between a deficiency of high molecular-weight multimers of von Willebrand factor, aortic stenosis, and colonic angiodysplasia has been proposed. Bleeding from angiodysplastic lesions in the upper and lower GI tract has been reported in patients with von Willebrand disease [2,3]. Because factor VIII complex is synthesized partly in vascular endothelial cells, patients with von Willebrand disease and angiodysplasia have been proposed to have an

underlying endothelial defect that may be related to the subsequent development of the two disorders (accelerated clearance of von Willebrand factor from plasma) [4]. However, as with renal failure, the coagulopathy more likely is responsible for bleeding than for the development of the lesions. Roskell et al. demonstrated a relative deficiency of collagen type IV in the mucosal vessels in angiodysplasia compared to controls. The authors propose that this deficiency may be related to the patients' susceptibility to ectasia and hemorrhage. In a small study, Junquera et al. noted an increased expression of angiogenic factors in human colonic angiodysplasia [5]. This study observed vascular immunoreactivity for basic fibroblast growth factor was observed in seven (39%) specimens from patients with colonic angiodysplasia, whereas either very limited or no immunostaining was found in sections from specimens of patients with colonic cancer and healthy margins.

### Diagnostic Principles

The diagnosis can be made radiologically, endoscopically, at operation or by the histopathologist. Selective mesenteric angiography is a useful diagnostic technique, especially in patients with massive bleeding in whom a colonoscopic diagnosis is difficult. Helical CT angiography can detect extravasation from angiodysplasia and potentially is an important noninvasive test in patients with obscure bleeding sites. Capsule endoscopy has been reported to detect cecal angiodysplasias in selected cases, but its role as a diagnostic test for the colon is still experimental. Endoscopy is the most common method of diagnosing angiodysplasia in both the upper and lower GI tract.

### Therapeutic Principles

Angiodysplasia of colonic origin has been managed by endoscopic obliteration. Argon plasma coagulation, heater probe and laser photocoagulation has been successful in controlling bleeding from colonic angiodysplasia. Endoclips have been used in anecdotal case reports for bleeding angiodysplasia of the cecum and right colon. Angiodysplasia that presents with acute hemorrhage can be controlled effectively with angiography, although it seldom is needed. Angiography is appropriate in severely ill patients who are not candidates for surgical intervention. In these patients, transcatheter embolization of selected mesenteric arteries has been quite effective. Surgical resection is the definitive treatment. Current data do not support the use of hormonal therapy or in patients with colonic angiodysplasia. Somatostatin analogs and thalidomide have been reported to decrease the rate of bleeding from intestinal angiodysplasia. Octreotide should be first choice in patients with portal hypertension.

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## Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced

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### Synonyms

Quincke edema; Kinine-induced angioedema; ACEi

### Definition and Characteristics

Sudden occurrence of subcutaneous or submucosal swelling (Fig. 1), so-called angioedema, is an established and – in case pharynx or larynx are involved – potentially life-threatening side effect of angiotensin-converting enzyme inhibitors (ACEi). The duration of ACE-inhibitor treatment at the onset of angioedema ranges from 1 day to 8 years with a median of 6 months [1].

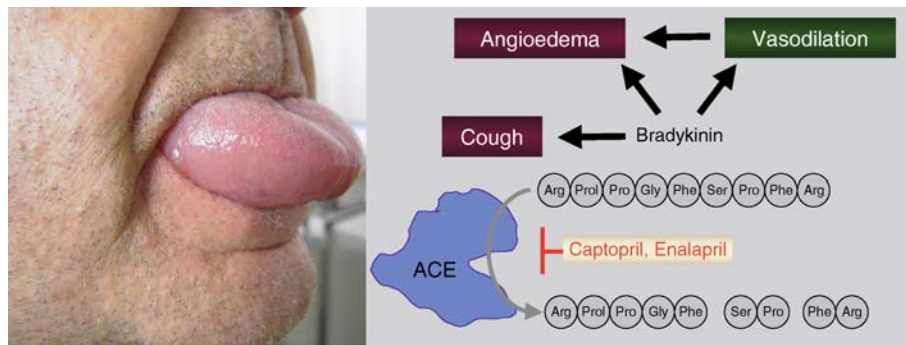
### Prevalence

The incidence of ACEi-induced angioedema is 0.4–0.7%. The mortality is world wide 0.1% of these cases. Black people may have an increased risk to develop an ACEi-induced angioedema [2].

### Molecular and Systemic Pathophysiology

ACE catalyses the generation of the important cardiovascular mediator angiotensin II from angiotensin I and substantially contributes to the inactivation of bradykinin (BK) (Fig. 1). Hence, inhibitors of ACE inevitably account for increased BK plasma levels. BK is a mediator of inflammation, activates nociceptors, increases vascular





**Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced. Figure 1** Clinical manifestation (right panel) and the possibly underlying pathophysiology (left panel) of ACEi induced pathophysiology of angioedema.

permeability, and causes endothelium-dependent vasodilatation. High levels of BK have been demonstrated ( $n = 4$ ) in plasma during an acute episode of angioedema [3] and both the amount and the activity of peptidases involved in the bradykinin metabolism such as aminopeptidase P [4] and dipeptidyl peptidase IV [5] are reduced.

These observations are consistent with the hypothesis that ACEi-induced angioedema is related to accumulation of bradykinin. However, the role of BK on angioedema is not completely understood. BK degradation is blocked in all patients treated with ACEi, but only a small percentage experience a single attack or recurrent angioedema [1]. Patients with ACE dysfunction are characterized clinically by low potassium serum concentrations, alkalosis, and high plasma levels of renin, angiotensin I, and BK, but the high plasma BK levels do not release an angioedema. Also, patients with the syndrome of idiopathic high levels of BK do not develop angioedema. Likewise, many patients experience ACEi-induced angioedema after many years of uneventful treatment with ACEi. Taken together, increased plasma bradykinin levels appear to play a role in the course of ACEi-induced angioedema but additional factors are likely involved in the underlying pathological process. For example, recent data suggest an involvement of acute phase proteins such as fibrinogen and C-reactive protein [1].

### Diagnostic Principles

Sudden swelling of lips, tongue, oropharynx, and larynx may be caused by a variety of pathophysiologic events. Most importantly, the diagnosis of ACEi-induced angioedema should be preceded by exclusion of other pathologies such as allergic reactions, deficiency of C1-esterase inhibitor, infection, inflammation, tumors, and diseases of large salivary glands. Furthermore, other drugs are known to induce angioedema with an incidence  $>1\%$  including rituximab, alteplase, fluoxetine, laronidase, lepirudin, and tacrolimus. It is

important to know that many patients can develop angioedema even after many years of uneventful ACEi treatment.

### Therapeutic Principles

Patients with acute angioedema should be hospitalized for at least 12–48 h. Any treatment with ACE inhibitors and other drugs known to induce angioedema (see above) must be discontinued. To maintain ventilation particularly in severe obstructive upper airway swelling, intubation and in rare cases tracheotomy has to be performed. In addition, oxygen may be necessary. In many cases of angioedema, emergency treatment includes intravenous corticosteroids, e.g., 250–500 mg prednisolone and inhalation of epinephrine before final diagnosis. It should be emphasized that none of these interventions are evidenced based strategies to treat ACEi-induced angioedema. A new option for pharmacologic treatment with a strong biologic rationale is the blockade of bradykinin B<sub>2</sub>-receptors, e.g., by icatibant.

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## Angioedema, Hereditary

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### Synonyms

Hereditary angioneurotic oedema; HAE

### Definition and Characteristics

It is an inherited, autosomal dominant disease of episodic, non-itching and non-inflammatory edema of the subcutaneous and submucosal tissue that completely resolves in 1–5 days. A major attack is frequently preceded by a prodromal rash, which consists of annular erythema and wheals. Edema of the skin can form monstrous deformities of the face; affected gastrointestinal mucosa leads to pain, vomiting and diarrhea and can be easily misdiagnosed as a surgical emergency. Involvement of oral mucosa, pharynx and larynx is common; larynx edema can lead to life threatening reactions resulting in death by asphyxia. The edema of the urinary tract mucosa leads to dysuria and the involvement of the ZNS to headache, dizziness and paralytic symptoms. The first symptoms of HAE occur in >50% of the patients before they are 10 years old, but the disease is mostly diagnosed in patients older than 20 years.

Quantitative or qualitative C1 esterase inhibitor (C1 INH) deficiency is the biochemical cause of HAE. Acute attacks of HAE can be related to dental treatments and surgical interventions. The therapy with corticosteroids is ineffective in the treatment of all types of HAE; the administration of C1 INH is the therapy of choice.

### Prevalence

The prevalence of HAE in the common population is two cases in 1,000–10,000; 85% suffer from type 1 HAE (quantitative deficiency of C1 INH) and 15% from type 2 HAE (dysfunctional C1 INH protein).

### Genes

The 17,159 kb long C1 inhibitor (C1 INH) gene (accession number X54486) is located on the chromosome 11 subregion q11.2–q13. Mutations were detected in all gene

regions; at present nearly 100 different mutations have been reported. In about 20% of the patients with HAE the mutations are spontaneous and therefore relatives are not affected.

### Molecular and Systemic Pathophysiology

C1 INH is a serine protease inhibitor central to the regulation of the complement system. It forms complexes with C1 and inhibits C1r and C1s in the complement system as kallikrein in the kinin-forming contact system. The defective inhibition of the target proteases (C1r, C1s, kallikrein) is clinically silent under normal circumstances but becomes clinically significant if triggering factors like trauma activate the complement components of the classical pathway. They cleave high-molecular-weight kininogen in the contact system and generate plasmin, leading to the release of peptides, increasing the vascular permeability responsible for edema.

### Diagnostic Principles

The diagnostic serologic parameters of the different types of HAE are given in Table 1.

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## Angiokeratoma Corporis Diffusum Universale

### ► Fabry Disease

**Angioedema, Hereditary. Table 1** Diagnostic serological parameters of the different types of HAE

HAE	C1-INH concentration	C1-INH function	C4	C1q
Type 1	↓ C1-INH	↓	↓	N
Type 2a	Inactive C1-INH	↓	↓	N
Type 2b	Protein-bound C1-INH	↓	↓	N

## Angioma Cavernosum

### ► Venous Malformation

## Angiomatous Hamartoma

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### Synonyms

Eccrine angiomatous hamartoma; EAH; Sudoriparous angiomatous hamartoma; Functioning sudoriparous angiomatous hamartoma; Nevus of the sweat gland; Cavernous angiomatosis of the sweat ducts

### Definition and Characteristics

Hamartoma is a non-neoplastic proliferation of cells and tissue components that occurs in an affected area. In its EAH form, there is an increased number of eccrine secretory and ductal elements within the angiomatous channels.

### Prevalence

Although adult onset has been reported, the disease is most commonly seen during early childhood. There is no apparent gender preference. EAH is a rare disorder with approximately 50 cases reported in the literature.

### Genes

The genetic characteristics have not been demonstrated.

### Molecular and Systemic Pathophysiology

EAH is a rare cutaneous hamartoma appearing histologically as a proliferation of eccrine sweat glands with angiomatous vascular elements that are of capillary origin. A deficiency between the mesenchyme and differentiating epithelium causes EAH. These layers cause the proliferation of the epithelial elements and an abnormal biochemical interaction is the main disturbance [1]. Histologic features of EAH are hyperplastic eccrine structures, increased proliferation of vascular structures, and variable presentations of increased lymphatic, smooth muscle, and pilar structures. An acanthotic epidermis is evident on hematoxylin and eosin-stained tissue sections. In the deeper part

of the dermis, mature eccrine sweat glands aggregate and numerous thin-walled blood vessels are detected. Unusual histological variants including the infiltration of adipose tissue, apocrine glands, hyperplastic nerve bundles and intercellular mucin deposits have been reported. Using immunohistochemical staining techniques, carcinoembryonic antigen, S100, and CD44 are stained in tissues derived from patients with EAH. CD34 is also strongly stained in the surrounding stroma, but not the pericytes or vascular endothelium. In other studies, the vascular elements have been shown to stain positively for anti-*Ulex europaeus* and anti-factor VIII antigens [2]. The secretory portions of the eccrine glands are positive for S100, carcinoembryonic antigen, epithelial membrane antigen, and Cam5.2. Characteristics of the tumor include tubular and glandular masses within a richly vascular stroma. Hamartoma occurs during early organogenesis which is thought to represent an abnormality of heterotypic dependency. According to this theory, the main problem rests with deficient biochemical interactions between differentiating epithelium and the underlying mesenchyme, which in turn causes malformation of adnexal and vascular structures.

### Diagnostic Principles

EAH lesions are characterized by solitary or multiple flesh-colored, blue-brown or pinkish-red slow growing nodules or plaques, and are mainly located on the limbs [3]. The disease manifests mainly at birth or in childhood. The lesions are often asymptomatic, but pain and hyperhidrosis are reported in one-third of the patients. Rapid growth of EAH has been reported during pregnancy and puberty, suggestive of hormonal influences. Osteolytic changes and destruction of the nail matrix with vestigial nails has been described (Fig. 1).



**Angiomatous Hamartoma. Figure 1** Eccrine angiomatous hamartoma lesions on the toes resulting in nail matrix destruction and vestigial nails.

Histological features including dermal proliferation of vascular channels, generally of capillary nature in close association with well-differentiated eccrine elements help to identify the disease. The main differential diagnosis is sudoriparous angioma, in which the angiomatous component with vessels of large calibre predominates and the eccrine elements show dilatation rather than proliferation.

### Therapeutic Principles

Surgical excision is curative and is reserved for painful or cosmetically unacceptable lesions. Occasionally, the pain may remit spontaneously without treatment after several years. Spontaneous regression of the disease is exceedingly rare [4].

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## Angiosarcoma

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### Synonyms

Hemangiosarcoma; Lymphangiosarcoma; Malignant hemangioendothelioma; Malignant angioendothelioma; Hemangioblastoma

### Definition and Characteristics

Angiosarcomas are rare malignant tumors with the tumor cells variably recapitulating the morphologic and functional features of normal endothelium. Consequently, the tumors present with varying degrees of differentiation (Fig. 1a, b).

Specifically undifferentiated tumors show high mitosis rates and high rates of metastasis. Reported tumor-related 5 year survival rates are below 20%.

### Prevalence

Angiosarcomas develop with similar frequency in females and males and constitute less than 1% of all sarcomas. One-third of the tumors occur in the skin, about one-fourth in soft tissue, and the remainder at other sites (e.g., breast, liver, bone, spleen). Approximately 50% of cutaneous angiosarcomas occur in the head and neck. Risk factors are radiation (angiosarcoma of the skin), exposure to vinyl chloride, arsenic, and thorium dioxide/thorotrast (angiosarcoma of the liver) as well as chronic lymphedema (Stewart-Treves-Syndrome) [1].

### Genes

TP53, MDM-2, p14ARF, VEGF, FGF2.

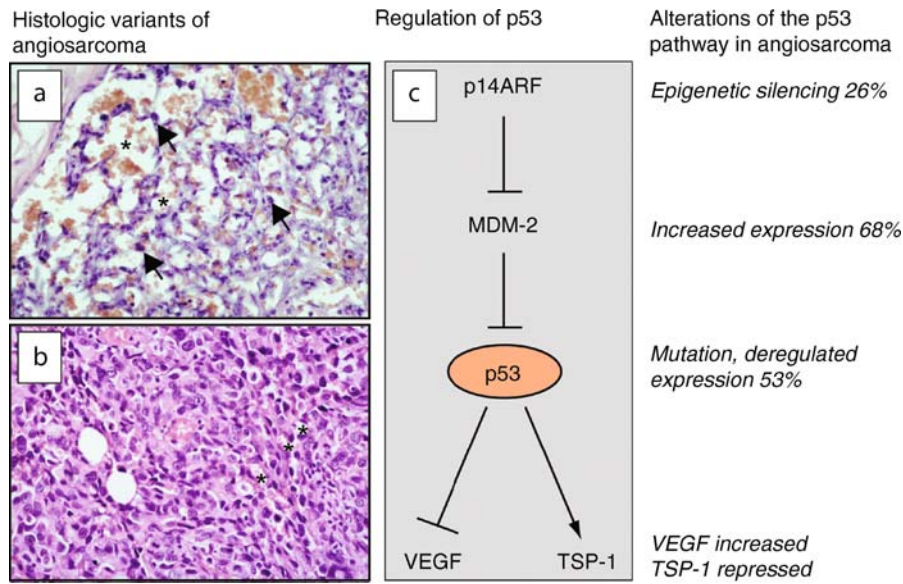
### Molecular and Systemic Pathophysiology

The tumor suppressor p53 plays a key role in the pathogenesis of angiosarcoma (Fig. 1c). P53 deficiency leads to development of angiosarcomas in mice. In humans mutations and deregulated expression of p53 have been detected in up to 53% of angiosarcomas. In addition, two major regulatory molecules of p53 activity, namely the murine double minus-2 protein (MDM-2) and p14ARF, are aberrantly expressed in many angiosarcomas. MDM-2, which inhibits p53 activity, is expressed in increased amounts in 68% of the tumors [2]. P14ARF, which inhibits MDM-2, has been found to be repressed by epigenetic silencing in 26% of the cases investigated [3]. In normal endothelial cells p53 inhibits angiogenic activation *via* suppression of pro-angiogenic vascular endothelial cell growth factor (VEGF) and activation of anti-angiogenic thrombospondin-1 (TSP-1) [4]. Impaired activity of p53 in angiosarcoma cells increases VEGF and represses TSP-1 expression. Both events activate the growth of the endothelial cell-derived tumor cells of angiosarcoma. In addition, a second pro-angiogenic factor, basic fibroblast growth factor (bFGF), and its receptor are upregulated in angiosarcoma cells and bFGF serum concentrations are increased in angiosarcoma patients. Altogether, a shift of the angiogenic balance in the course of deregulated p53 activity is a key event in the pathogenesis of angiosarcoma. Besides this, it may be of therapeutic relevance that the c-kit proto-oncogene, a tyrosin kinase receptor of stem cell factor, is expressed in more than 50% of angiosarcomas.

### Diagnostic Principles

Localization and extension of the primary tumor is commonly detected with magnetic resonance tomography.





**Angiosarcoma. Figure 1** Differentiation and molecular regulation of angiosarcoma. (a) Moderately differentiated angiosarcoma with numerous blood filled vessels with irregular size (\*) and atypical endothelial cells (arrows). (b) Low differentiated angiosarcoma with epithelioid structure and only few blood vessel channels (\*) between the neoplastic endothelial cells. (c) Schematic presentation of p53 regulation (left) and relative frequency of alterations of this pathway in angiosarcoma (right).

Distant metastases in the lung are commonly investigated with computer tomography. Histological staining of biopsies for CD31 and FLT1 demonstrates the endothelial cell origin of the tumor cells. In few morphologically questionable cases negativity of the human herpesvirus-8 latency associated nuclear antigen-1 (HHV8-LNA1) may be used to differentiate angiosarcoma from Kaposi's sarcoma.

### Therapeutic Principles

Gene directed molecular approaches for treatment of angiosarcoma are not available, as yet. The most widely used treatment at present is surgical resection with wide excision in combination with postoperative radiotherapy. The likelihood of local regional failure is high as is the risk of distant relapse. Chemotherapy may be used for short term medication [5].

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## Anhidrotic Ectodermal Dysplasia

### ► Hypohidrotic Ectodermal Dysplasias

## Anhidrotic Ectodermal Dysplasia with Immunodeficiency, Osteopetrosis and Lymphedema

### ► Hypohidrotic Ectodermal Dysplasias

## Aniridia

### ► Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome



## Ankylosing Spondylitis

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### Synonyms

Marie-Strumpell spondylitis; Bechterew syndrome; Rheumatoid spondylitis

### Definition and Characteristics

Ankylosing spondylitis (AS) [Online Mendelian Inheritance in Man (OMIM) #106300] literally means “fusion of the vertebrae due to inflammation.” AS is characterized by progressive back pain and stiffness, caused by recurring cycles of inflammation and new bone growth, resulting in fusion of vertebrae [1,2]. The process usually starts at the sacroiliac joints between the sacrum and pelvis. Progression can occur throughout the spine, however, there is considerable variation among individuals. Onset of AS usually occurs in the second or third decade of life. Other joints can also be affected and include the hips, knees, and ankles. The most serious complication is spinal fracture. Secondary features, outside the skeleton, may include inflammation of the eye (uveitis, iritis) and in the heart (around the aortic valve), psoriasis, and inflammatory bowel disease (Crohn’s disease and ulcerative colitis).

### Prevalence

AS is a common disorder, but the prevalence varies among ethnic groups and between males and females, with males having a higher incidence. The prevalence of AS is estimated at 0.5% in men and 0.2% in women in Britain, approximately 2% in men and 0.5% in women in Norway, and as high as 2.5% in the adult Eskimo population in Alaska, USA [1]. Conversely, the incidence of AS in Japan is very low (~0.01%). Worldwide, the prevalence of AS approaches 0.9% [1].

### Genes

The gene(s) responsible for AS has not yet been positively identified. AS is a complex genetic disorder with several genes (and corresponding genetic defects or polymorphisms) contributing to the disease. A variety of genetic studies have implicated the human leukocyte antigen B27 (HLA B27) to be directly involved in the disorder [3,4]. Additionally, other genes within the HLA genetic locus on chromosome 6p, are also likely involved, possibly tumor necrosis factor  $\alpha$  (TNF $\alpha$ ). Other genes, near the HLA locus, are also

likely involved. Recurrence risk modeling suggests a total of 5 genes will probably account for AS. Genome-wide scans have identified additional candidate loci on chromosomes 1p, 2q, 6p, 9q, 10q, 16q, and 19q [3,4]. Candidate genes include interleukin 1 (IL-1 on chromosome 2) and the cytochrome P450 2D6 gene (debrisoquine hydroxylase, CYP2D6) on chromosome 22q [3,4]. Defects in CYP2D6 may disrupt metabolism of a natural toxin or antigen, increasing susceptibility to AS.

### Molecular and Systemic Pathophysiology

The pathogenesis of AS is not completely understood, but will likely turn out to be a complex disorder with genetic, immunological, and environmental components [1,2]. AS is caused by recurring cycles of inflammation and new bone growth that eventually lead to fusion of the spine. The process starts with inflammation at the site of attachment of tendons to bone (enthesitis) and progresses with deterioration of the bone at these sites (enthesopathy). This inflammatory process is promoted by HLA B27, which has a direct role in antigen presentation. Likewise, defects or polymorphic variants in CYP2D6 may have an effect on normal processing of antigens. Further, polymorphic variants in the cytokines TNF $\alpha$  and IL-1, also modulate the inflammatory process. As the inflammation subsides, new bone growth occurs. TNF $\alpha$ , IL-1 and other cytokines involved in inflammation also stimulate normal bone turnover (osteoclastogenesis and coupled osteoblastogenesis). Hence, cytokines appear to have a dual role in AS, inflammation and bone turnover—both processes that contribute to the pathophysiology of AS. Only when the additional genetic factors are identified, will the precise pathogenesis of AS be elucidated.

### Diagnostic Principles

Symptoms usually start in late adolescence or early adulthood, and include low back pain and stiffness, commonly occurring in the morning and improving with exercise. There is also loss of spinal mobility. Laboratory testing for HLA-B27 is positive in most cases of AS. Diagnosis is confirmed when there is inflammatory back pain with radiological evidence of sacroiliitis (either grade II bilaterally or grade III unilaterally) [1].

### Therapeutic Principles

Non-steroidal anti-inflammatory drugs (NSAID) are commonly used to reduce the pain and stiffness associated with AS, although they are ineffective at retarding the progression of the disease. NSAID use is often associated with gastrointestinal side effects, which may limit its use [5]. These may be avoided by use of NSAIDs that inhibit cyclo-oxygenase-2 (COX-2

inhibitors). Some of the disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine, are the secondary approach to AS, although controlled studies are limited [5]. Two new anti-TNF $\alpha$  agents (infliximab, a TNF $\alpha$  monoclonal antibody, and etanercept, a TNF $\alpha$  receptor fusion protein) are in clinical trials and show promise in treating AS [5]. Regular exercise and physical therapy are also important components in treatment of AS [2].

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## Annular Pancreas

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## Synonyms

Pancreas annulare

## Definition and Characteristics

Annular pancreas is an embryologic malformation characterized by the presence of a ring of pancreatic tissue completely or partially surrounding the second part of the duodenum. Its major clinical symptom is complete or partial duodenal obstruction. Several anatomic classifications have been proposed according to the fusion pattern of ventral and dorsal pancreatic duct, the intra- or extramural position of pancreatic tissue in the duodenal wall, the place of drainage of the annular duct and the origin of the annulus from the different biliopancreatic ducts [1,2] (Fig. 1a).

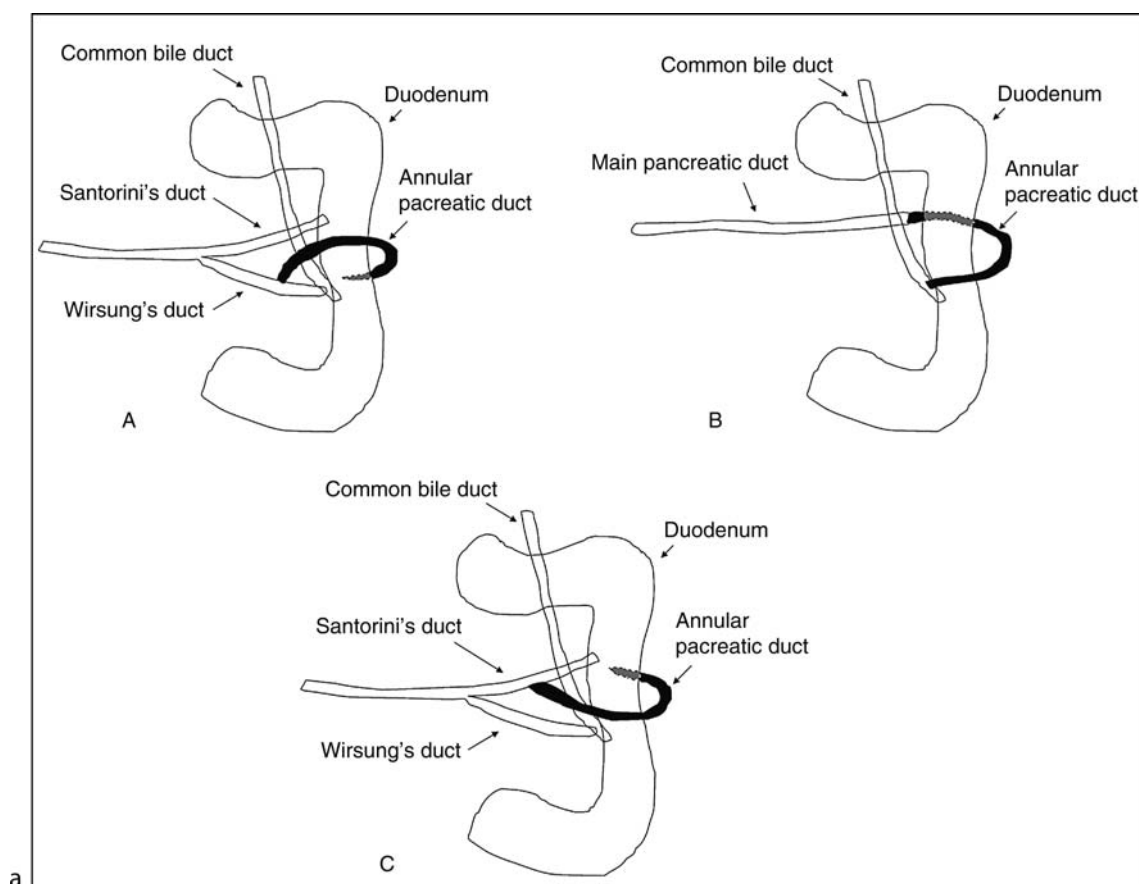
The disease was diagnosed during childhood in 51.5% and in adults in 48.5% of all published cases. In up to 70% of newborn children annular pancreas is associated with other congenital anomalies like duodenal atresia, Down's syndrome, esophageal atresia, congenital heart defects, imperforate anus, chromosome 1p36 deletion syndrome and other structural birth defects. In patients with Down syndrome the risk for annular pancreas is increased 430 times [3]. The spectrum of symptoms and clinical presentations varies with the degree of duodenal obstruction due to annular pancreas. In children, duodenal obstruction is the most common presenting complaint which makes vomiting the leading clinical symptom. Annular pancreas often does not become symptomatic until later in life, mainly in the third and fourth decade. In adults the major clinical though unspecific symptoms suggestive of annular pancreas are abdominal pain (70%) and nausea and vomiting (60%). Peptic ulcer disease, obstructive jaundice and pancreatitis are less common.

## Prevalence

No exact data exist on the prevalence. In surgical and autopsy series the incidence was three cases in 24,519 and three cases in 20,000 respectively. In different ERCP series the incidence was between 1 in 160 and 1 in 250 cases. It appears to be more frequent in males than in females with a ratio of about 2:1. The occurrence of annular pancreas in successive generations of a family argues for an autosomal dominant or X-linked inheritance.

## Molecular and Systemic Pathophysiology

The ectopic tissue of annular pancreas is a remnant of the developing head of the pancreas during embryonic development. In pancreatic organogenesis two members of the hedgehog family of cell signals – Indian hedgehog (Ihh) and Sonic hedgehog (Shh) – regulate crucial developmental processes. In an experimental model in mice the inactivation of Ihh or Shh caused overgrowth of ventral pancreatic tissue resulting in an annulus around the duodenum [4]. The results from this study demonstrated that the annulus is derived from the ventral pancreas by asymmetric lateral branching of the ventral duct and symmetric branching of the ventral bud. This experimental phenotype is strikingly similar to the annular pancreas in humans. Different other hypotheses were mainly descriptive but were not supported by experimental evidence [1]. They include both dorsal and ventral bud hypertrophy resulting in a complete ring. Another theory suggests that the ventral bud of pancreatic anlage adheres to the duodenal wall and stretches to form a ring during rotation.



a



b

**Annular Pancreas. Figure 1** (a) Scheme of three types of annular pancreas. (A) annular duct develops from the Wirsung duct, (B) main pancreatic duct surrounds the duodenum, (C) annular duct develops from Santorini duct or common bile duct (Ref. [2], with permission). (b) Ct scan from a 26 year old female. Pancreatic tissue (arrowheads) surrounds the duodenum (arrow) (by courtesy of A. Aschoff, Dep Radiology, University Hospital Ulm, Germany).

### Diagnostic Principles

Different imaging techniques are available to demonstrate an annular pancreas. Nevertheless in up to 40% final diagnosis requires surgery for confirmation. A complete duodenal obstruction causing dilated

stomach and proximal duodenum may result in the “double bubble” sign on an abdominal radiograph. Transabdominal ultrasound may demonstrate a fluid filled dilated descending duodenum encircled by pancreatic tissue and is increasingly used to make

prenatal diagnosis. Pancreatic parenchyma surrounding the duodenum can be visualized by CT or MR imaging (Fig. 1b).

Endosonography, ERCP and MRCP can demonstrate the typical circular structure of pancreatic duct.

### Therapeutic Principles

Symptomatic annular pancreas should be treated operatively. There is no single operative procedure of choice. Published experience clearly argues against direct intervention on the offending annulus. Resection of the annulus has been associated with numerous complications including persistent duodenal obstruction, pancreatitis and pancreatic fistula. In pediatric and adult patients side-to-side duodenoduodenostomy, gastrojejunostomy or duodenojejunostomy are the treatments of choice. In adults a further variety of surgical, laparoscopic and interventional endoscopic procedures have been mentioned to be effective [5].

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## Anorexia

### ► Anorexia Nervosa

## Anorexia Nervosa

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### Synonyms

Anorexia; Eating disorder; Self-starvation

### Definition and Characteristics

Anorexia nervosa is a psychiatric disorder that according to the Diagnostic and Statistical Manual for Mental

Disorders, Fourth Edition (DSM-IV), is defined as “the refusal to maintain body weight about 85% of predicted, an intense fear of gaining weight, undue influence of body shape or weight on self image, and missing at least three consecutive menstrual periods.” Individuals with anorexia nervosa aim to control body weight and or shape by voluntary starvation, alongside this starvation there is often inappropriate compensatory behaviors such as vomiting, excessive exercise, abuse of diet pills, diuretic drugs, laxative pills, and thyroid hormone abuse. Anorexia nervosa is a complex condition involving psychological, neurobiological, physiological, sociological and genetic components.

### Prevalence

The group with highest prevalence of Anorexia nervosa are young females between the ages of 15 and 25 from social classes one and two. In this group the prevalence is about 1%. Males also develop anorexia nervosa with estimates of 1:10, male: female ratio. It is estimated that about 10% of females in the general population are affected by some form of eating disorder (including those that just fail to meet the full diagnostic criteria, eating disorders not otherwise specified, EDNOS).

### Genes

Theander [1] first considered the possibility of a genetic influence in AN in 1970. He noted an increased prevalence of AN in the sisters of sufferers, prevalence rates of 3–7% and 1–6% have been observed in siblings of affected individuals and first-degree relatives respectively, and the propensity for a particular illness to group within relatives is in general a characteristic of intergenerational family transmission. More recent studies have suggested that the prevalence of AN in relatives of sufferers is more than 11 times greater than that in the general population.

AN is unlikely to be caused by a defect in a single gene. It is more likely that subtle variation in several genes and their interaction with the environment will result in increased susceptibility to AN. A candidate gene approach has been employed to attempt to identify genes which may be associated with AN. Genes are selected on the basis of their believed roles in traits such as perfectionism, obsessive behaviors, maturity fears, low self-esteem overall anxiety, mood and eating behavior. To date analyses on 16 different candidate genes association studies with AN have been published. Of these six of the genes are related to the serotonergic system. The most promising of these is the HTR2A receptor polymorphism (–1,438G > A), however there is mixed evidence of this association [2]. A further area that has received a great deal of attention is the catecholamine system, three genes have been investigated in this system these are DRD3, DRD4 and COMT. These genes have been shown to be associated

with other psychiatric disorders (schizophrenia and substance abuse). However, the published reports failed to show any evidence of association with AN. The final group of genes that has received attention are the neuroendocrine genes, these are involved in appetite regulation and energy metabolism. The genes investigated within this group include DRD3, DRD4, COMT, AGRP, LEP, MCH4, UCP [1–3] ESR and HLA-A. Of these some evidence of association has been shown with UCP, ESR1 and HLA-A. Currently the most promising associations appear to be with OPRD1 and HTR1D, these associations were first identified through a genome scan which identified 1p33–36 as a hot spot. Both these genes were identified within this region and were reported to be associated with AN [3]. This finding has since been confirmed in a second cohort [4].

### Molecular and Systemic Pathophysiology

AN has one of the highest morbidity and mortality rates of any psychiatric disorder. The health consequences of long term maintenance of extreme body weight are many and varied, ranging from an increased risk of premature death to several non-fatal but debilitating complaints that impact on the immediate quality of life [5]. Macro and micro-nutrient deficiencies and disruption of multiple organ systems is brought about through starvation. In addition to hypoglycemia and vitamin deficiencies, starvation results in the suppression of thyroid function, in hypercortisolemia, and in release of endogenous opioids, which may contribute to reduction in hunger described by patients with AN.

Starvation results in many biochemical changes such as hypercortisolemia, nonsuppression of dexamethasone, suppression of thyroid function and amenorrhea. Computerized tomographic (CT) studies of the brain have revealed enlarged sulci and ventricles in underweight patients, which return to normal size with weight gain.

Neuroendocrine disturbances are responsible for delayed puberty, amenorrhea, anovulation, decreased oestrogen levels, increased growth hormone, decreased antidiuretic hormone, hypercarotenemia, and hypothermia.

Self-induced vomiting can lead to swelling of salivary glands, electrolyte and mineral disturbances, and enamel erosion in teeth. Laxative abuse can lead to long lasting disruptions of normal bowel functioning. Complications such as tearing the esophagus, rupturing the stomach, and developing life-threatening irregularities of the heart rhythm may also result.

### Diagnostic Principles

Physical signs and symptoms can include constipation, abnormally low heart rate, dizziness, disturbances of

vision, abdominal pain, hypotension, lanugo and disruption of menstrual cycle.

### Therapeutic Principles

Psychosocial problems abound both within the individual sufferer and also in their families. The complexity of this disorder underpins the problems of devising the best treatment plan for patients. The first stage of treatment will often involve treating medical complications in order to stabilise a patient. Following this, the major aims of treatment are to restore patients nutritional status and establish healthy eating patterns, address dysfunctional thoughts related to the eating disorder. These treatment aims are best achieved through psychotherapy. There is limited use of pharmacotherapy whilst weight is still low. Drugs are more commonly administered after weight has been restored in order to help maintain weight and normal eating behaviors as well as treat associated psychiatric symptoms. These include: Antidepressants: Serotonin-specific reuptake inhibitors are commonly administered to treat depressive, obsessive or compulsive symptoms that persist in spite of or in the absence of weight gain. Antipsychotics may also be used to treat agitation and psychotic thinking. In some cases anti-anxiety medications may be used to reduce anticipatory anxiety.

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## Anthraxis

► Coal Workers' Pneumoconiosis



## Anthrax

### ► Pulmonary Anthrax

## Anthrax Pneumonia

### ► Pulmonary Anthrax

## Antibody Deficiency with Normal Immunoglobulins

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### Synonyms

Antibody deficiency with normal serum immunoglobulins; Selective antibody deficiency; IgG subclass deficiency

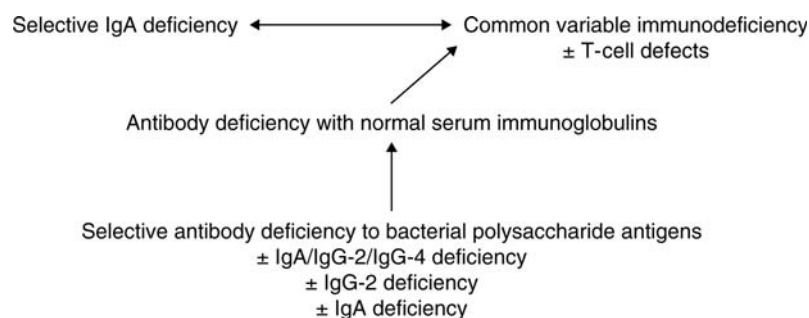
### Definition and Characteristics

Antibody deficiencies are the most common of primary immunodeficiency disorders. The spectrum of B-cell deficits range from profound hypogammaglobulinemia and antibody deficiency, such as in the B negative

agammaglobulinemia states, common variable immunodeficiency (CVID), and hyper-IgM deficiency syndrome (HIGM def) to antibody deficiency disorders with normal and/or near normal serum immunoglobulin levels. The later antibody deficiency disorders are comprised of a spectrum: [1] antibody deficiency with normal or elevated immunoglobulins, [2] selective antibody deficiency to bacterial polysaccharide antigens, and [3] IgG subclass deficiency (Fig. 1).

The hallmark of antibody deficiency with normal immunoglobulins is a profound antibody deficiency to multiple protein and polysaccharide antigens with normal or elevated serum immunoglobulin IgG, IgA, and IgM, and normal T-cell numbers and function. However, with the exception of immunoglobulin levels, this B cell immune deficiency clinically- and laboratory-wise is similar to CVID. Thus, it is speculated that some patients with antibody deficiency may evolve into CVID. In addition, some of these patients may be diagnosed as having an IgG subclass deficiency. Though in the later, antibody responses to protein antigens are typically normal and have a selective antibody deficiency to polysaccharide antigens. If there is a profound T-cell immune deficiency associated with the antibody deficiency, these patients are categorized as a combined T- and B- cell immunodeficiency (CID), Nezelof syndrome or thymic dysplasia.

Antibody deficiency with normal immunoglobulins needs to be differentiated from [1] selective antibody deficiency to bacterial polysaccharide antigens, [2] IgG subclass deficiency, and [3] antibody deficiency with associated T-cell deficiency (Fig. 1). In selective antibody deficiency, there is a deficiency of antibody responses to bacterial polysaccharide antigens, such as to *Streptococcus pneumoniae*, but antibody responses to protein antigens, serum IgG, IgA, IgM, and IgG-subclasses are normal. In IgG subclass deficiency, there is usually decreased IgG-2 levels, sometimes associated with IgG-4 and/or IgA deficiency, IgG-2, IgG-2/IgG-4, IgA/IgG-2/IgG-4 deficiencies, and these are associated



**Antibody Deficiency with Normal Immunoglobulins. Figure 1** Proposed relationship of IgG subclass deficiency, selective antibody deficiency, antibody deficiency with normal immunoglobulins with common variable immunodeficiency and selective IgA deficiency.

with defective antibody responses to bacterial polysaccharide antigens. In antibody deficiency with normal immunoglobulins associated with defects of T-cell numbers and function, this is categorized as a combined immunodeficiency (CID) or Nezelof syndrome.

### Prevalence

The spectrum of disorders of antibody deficiency with normal immunoglobulins include selective antibody deficiency and IgG subclass deficiency. In studies examining patient populations with increased susceptibility to infections, IgG subclass deficiency is a common finding. Aucouturier et al reported an IgG subclass deficiency frequency of 24%, with a predominance of IgG2 deficiency, in a group of 229 patients with abnormally frequent and/or prolonged or severe infections recruited from three departments of clinical immunology between 1983 and 1987. This same group screened a similar population of 254 patients in a subsequent study, this time recruited from departments of pediatrics or infectious diseases throughout France between 1988 and 1990. Using similar laboratory techniques and diagnostic criteria, the frequency of IgG subclass deficiency was 18% though IgG3 isotype deficiency predominated rather than IgG2. The IgG3 deficiency predominance remained a highly significant finding when both studies were analyzed as a whole series of 483 patients. The findings of these studies correlated with the results of a preceding large series of patients by Oxelius et al in which IgG3 was also found to be the most frequently defective isotype. The frequency of IgG subclass deficiency may also vary by age and sex. Studies carried out in Scandinavia suggested that children were more likely to have IgG2 subclass deficiency whereas adults were more likely to have IgG3 deficiency.

The prevalence of selective antibody deficiency is unknown; however, it is more common in younger children compared to older children and adults. Selective antibody deficiency in children <6 years old may be akin to transient hypogammaglobulinemia of infancy (THI) representing a maturational delay in which the children “outgrow”. The exact frequency of THI is unknown; although it has been estimated at 1 per 10,000. In this author's experience, THI and selective antibody deficiency are relatively common diagnoses in young children referred for evaluation of recurrent infections. On the other hand, antibody deficiency with normal immunoglobulins appears to be a rare immunodeficiency.

### Genes

No specific gene defects have been identified in antibody deficiency with normal immunoglobulins, selective antibody deficiency, and IgG subclass deficiency. However, a number of genetic defects have been reported in

CVID: CD19 deficiency, inducible costimulator (ICOS), transmembrane activator & calcium-modulator and cyto-philin ligand interactor (TACI), B cell activating factor receptor (BAFFR) deficiency. These have not been studied in antibody deficiency with normal immunoglobulins, selective antibody deficiency, and IgG subclass deficiency.

### Molecular and Systemic Pathophysiology

The immunopathogenesis of antibody deficiency with normal immunoglobulins is unknown. However, it appears to be an intrinsic B cell defect, similar to common variable immunodeficiency (CVID). We have observed that memory B cells, CD27<sup>+</sup> B cells, may be decreased in selective antibody deficiency and CVID and may precede the development of CVID (personal observation). Similar to CVID, inadequate T helper cell activity for B-cell immunoglobulin synthesis and increased T-suppressor activity have been described. Decreased CD4<sup>+</sup> CD45RA<sup>+</sup> naïve T helper cells have also been observed. We have observed decreased IL-2 synthesis, similar to that seen in some patients with CVID; this has not been evaluated in antibody deficiency with normal immunoglobulins.

### Diagnostic Principles

**Infections:** The susceptibility to infections in antibody deficiency with normal immunoglobulins is similar to that of patients with CVID. These include primarily respiratory infections with polysaccharide encapsulated bacteria. Thus, these patients have recurrent/chronic sinusitis, otitis media, pneumonia, and pharyngitis. Recurrent pulmonary infections may lead to bronchiectasis. These patients are also susceptible to bacterial sepsis and meningitis. The microorganisms responsible are similar to those seen in CVID, namely *Streptococcus pneumoniae*, non-typable *Hemophilus influenzae*, *Moraxilla catarrhalis*, and *Staphylococcus aureus*. Indeed, Higuchi et al [4] reported two brothers with recurrent infections resembling toxic shock syndrome with absent antibody response to *S. aureus* toxic shock syndrome toxins.

**Other features:** Allergic diseases, usually asthma and allergic rhinitis, occur in approximately 55% of children with selective antibody deficiency. As seen in patients with CVID, persistent lymphadenopathy may also be present. In addition, Knutsen et al described intestinal lymphoid nodular hyperplasia (ILNH) in a girl with this syndrome. ILNH has been reported in CVID and selective IgA deficiency.

### Therapeutic Principles

The treatment of antibody deficiency with normal immunoglobulins is similar to that with patients with CVID, namely antibody replacement therapy with

intravenous immunoglobulin (IVIG) infusions [5]. Since IgG levels remain elevated, IVIG dose depends upon clinical improvement. In addition, there appears to be increased catabolism of IgG with IVIG therapy, which may necessitate using higher and/or more frequent doses of IVIG. Alternatively, subcutaneous gammaglobulin (SCGG) therapy may be used on a weekly basis that maintains steady state IgG levels. Both IVIG and SCGG therapy result in reduction of sinopulmonary infections.

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## Anti-glomerular Basement Membrane Antibody Disease with Pulmonary Hemorrhage

### ► Goodpasture Syndrome

## Antiphospholipid Syndrome

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### Definition and Characteristics

A systemic syndrome characterized by presence of antiphospholipid antibodies (aPLA) (lupus anticoagulant,

antibodies against cardiolipin or/and  $\beta$ 2-glycoprotein I ( $\beta$ 2-GPI)), and recurrent vascular thrombosis, causing complications in pregnancy, deep venous thrombosis, pulmonary emboli, livedo reticularis, and thrombocytopenia. In primary antiphospholipid syndrome (APS), there is no evidence of underlying disease, whereas the frequent association with systemic lupus erythematosus or less commonly with other disorders is referred to as secondary APS.

### Prevalence

aPLA are found among young subjects at a prevalence of 1–5%. There is a rise in elderly patients with chronic diseases. Among the patients with systemic lupus erythematosus, prevalence of antibodies ranges between 12 and 34%. There are no sufficient data to determine what percentage of persons with aPLA develop complications consistent with APS. However, 50–70% of patients with systemic lupus erythematosus and aPLA will develop the syndrome. About 20–30% of all deep vein thromboses are also due to APS (reviewed in [1]).

### Molecular and Systemic Pathophysiology

*Formation of aPLA:* These heterogeneous antibodies show simultaneous reactivity against several  $\beta$ 2-GPI peptides. Recent studies identified a hexapeptide (TLRVYK) as one epitope on  $\beta$ 2-GPI antibodies and showed that microbial pathogens (*Haemophilus influenzae*, *Neisseria gonorrhoeae*, and tetanus toxoid) carried sequences related to this hexapeptide and that they could induce formation of corresponding antibodies and disease symptoms in mice [2]. Similarly, aPLA were formed after immunization of mice with peptides from Cytomegalievirus that had structural similarity to one binding site on  $\beta$ 2-GPI. Thus, molecular mimicry between infecting agents and autoantigens could be an underlying mechanism.

*Thrombotic disease:* three major molecular mechanisms are proposed:

1. aPLA may act in vivo by disrupting the kinetics of the normal procoagulant and anticoagulant reactions of phospholipids on cell membranes: upregulation of tissue factor, inhibition of protein C pathway,  $\beta$ 2-GPI anticoagulant activity, antithrombin III activity, or annexin V anticoagulant activity. The membrane protein annexin V (formerly called lipocortin) has anticoagulant activity as it impairs via crystallization the formation of the coagulatory complex of enzyme, substrate and cofactor on anionic surfaces. Binding of aPLA to annexin counteracts this impairment [3].
2. aPLA may enhance platelet aggregation and they may activate endothelial cells and neutrophils resulting in increased adherence and release of damaging or proinflammatory agents. In mouse experiments,

aPLA-induced damage of cells, especially in the placenta, was dependent on activation of complement and C5a–C5aR-mediated recruitment of neutrophils [4].

3. For thromboembolic events to be induced by aPLA, alterations leading to damage of endothelial cells may be additionally required, e.g., via oxidized LDL (“second hit” hypothesis).

On histology, there is thrombotic microangiopathy involving the venous and arterial vascular beds, but no vasculitis.

### Diagnostic Principles

According to international consensus [1], at least one of the clinical criterion (vascular thrombosis, pregnancy complications) and one laboratory criterion (lupus anticoagulant, by at least two phospholipid-dependent coagulation assays, and/or moderate or high levels of antibodies against cardiolipin or  $\beta$ 2-GPI) should be present on at least two occasions, 6 weeks apart for diagnosis of APS. Almost any organ and tissue may be involved in the disease, including the brain, the heart, the placenta, the skin, the endocrine system, the blood, or the kidneys (refer to ► [Sneddon syndrome](#) for further diagnostic measures).

### Therapeutic Principles

Prophylactic anticoagulation is not mandatory in patients with high titer anticardiolipin antibodies, but no history of thrombosis. As however may be justified. General measures to prevent thrombosis and other vasoprotective actions should be taken.

When a history of recurrent deep vein thrombosis or pulmonary embolism is established, long-term anticoagulant therapy is needed with international normalized ratio (INR) of ~2.0–3.0 [5]. Treatment for pregnant patients with APS includes low molecular weight heparin (LMWH) and low dose aspirin (325 mg). Women with previous thromboses may receive doses for full anticoagulation. Warfarin can also be used from 14 to 34 weeks for the patients with previous stroke or severe arterial thromboses. The use of intravenous immunoglobulin (IVIG) seems to be restricted to the patients with pregnancy losses despite conventional treatment. For contraception, oral oestrogens should not be used.

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## Antisocial Personality/Psychopathy Disorder

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### Synonyms

ASPD

### Definition and Characteristics

According to the DSM-IV, antisocial personality disorder (ASPD) is characterized by a pervasive pattern of disregard for social norms and violation of the rights of others [1]. The ASPD criteria are broad and encompass a heterogeneous population of antisocial individuals. Psychopaths form a particularly severe subgroup of ASPD. Psychopathy is most commonly assessed using the Psychopathy Checklist - Revised (PCL-R) [2]. The PCL-R defines psychopathy with a cluster of interpersonal and affective characteristics in addition to overt antisocial behavior. These include superficial charm, deceitfulness and callousness. The overlap between ASPD and psychopathy is asymmetric; that is individuals identified as psychopathic most often receive a diagnosis of ASPD, but the reverse is not true [2].

### Prevalence

Approximately 3% of men and 1% of women in the general population meet the DSM-IV criteria for ASPD [1]. There is no information available on the prevalence



of psychopathy in the general population. Data from prison samples suggest that only approximately 25% of ASPD diagnosed men meet the PCL-R criteria for psychopathy [2].

### Genes

Genes regulating serotonergic neurotransmission, in particular monoamine oxidase A (MAOA), have been associated with antisocial behavior. These may interact with environmental risk factors to increase risk for antisocial behavior [3]. The affective-interpersonal dimension of psychopathy has received little attention in molecular genetic studies. Twin and adoption studies confirm that this core psychopathic dimension is heritable. The possibility of different genetic bases for antisocial behavior and the affective-interpersonal dimension of psychopathy have not been investigated in molecular genetic studies, even though results from twin studies indicate a substantial genetic overlap [2].

### Molecular and Systemic Pathophysiology

So far no monocausal pathophysiological origin is known for ASPD or psychopathy. Several brain areas and cognitive functions associated with perception and regulation of emotions have been found to correlate with antisocial behavior. Most studies concentrate on frontal and temporal abnormalities in antisocial behavior. Neuropsychological functions associated with these brain regions, such as perception of threat and modulation of affective response are compromised in antisocial individuals. Toxic environments may contribute to this association by inducing hyperreactivity of the brain's emotional circuitry in ASPD in general. Psychopathic individuals show the opposite pattern at the neural level [4]. Data indicate that psychopaths show hyporeactivity to emotional stimuli. At the neurochemical level there is some data suggesting a relationship between reduced central serotonergic activity and increased levels of aggressive antisocial behavior. Unfortunately, none of these studies have differentiated between psychopathic and non-psychopathic antisocial behavior. Psychophysiological data suggest that electrodermal reactivity is positively associated with aggressive antisocial behavior and negatively related with psychopathy. Low resting heart rate and high heart rate reactivity are associated with aggressive antisocial behavior, but not with psychopathy [2].

### Diagnostic Principles

Diagnosis of ASPD is based on detailed psychiatric exploration and classification according to DSM-IV diagnostic criteria. Individuals diagnosed with ASPD must be at least 18 years old and have had a history of

conduct disorder before age fifteen. Three or more of the following criteria are required: failure to conform to social norms with respect to lawful behaviors, deceitfulness, impulsivity or failure to plan ahead, irritability and aggressiveness, reckless disregard for the safety of self or others, consistent irresponsibility or lack of remorse [1]. The PCL-R consists of 20 items. Each item is scored on a 3-point scale (0, 1, 2) according to the extent to which the rater judges that it applies to a given individual. Total scores can range from 0 to 40, reflecting the degree to which the individual matches the prototypical psychopath. A score of 30 or above is typically used as a cut score for diagnosis of psychopathy, but other cut scores have been used, depending on the purpose of the assessments and the context in which they are made. The actual diagnosis is made based on a semi-structured interview, file and collateral information and specific scoring criteria [2].

### Therapeutic Principles

Some efforts have been made to identify medications that effectively treat behavioral correlates of psychopathy, such as aggression and impulsivity or comorbid disorders such as substance abuse. For example, selective serotonin reuptake inhibitors have shown efficacy in impulsive aggression [2]. Very little research has examined the pharmacological treatment of psychopathy per se. In addition, there is no evidence that any non-pharmacological treatments yet applied are successful for use with psychopaths. Nevertheless, recently developed guidelines for treatment of institutional psychopathy, suggest that a cognitive-behavioral program that incorporates relapse prevention to combat substance abuse, anger management to control aggression, prosocial modeling to break down antisocial thinking and values and motivation interviewing to enhance commitment to treatment may be effective if implemented systematically [5]. The literature supporting this approach is still scarce [2].

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## Antithrombin III/AT3

### ► Antithrombin Deficiency

## Antithrombin Deficiency

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### Synonyms

Deficiency of AT-III SERPINC1; Antithrombin III; AT3

### Definition and Characteristics

First described by Egeberg in a pedigree in which persons in three generations had thrombophlebitis and other thrombotic disease associated with about half-normal levels of antithrombin III [1]. The molecule is presently described as “antithrombin” (AT). Subsequent, numerous publications, including several large kindreds have been described, establishing AT deficiency as a risk factor for venous thrombosis. The mature AT molecule has a molecular weight of 58,200 with 432 amino acids. AT is a member of the serine protease inhibitor (SERPIN) superfamily. It is the principal inhibitor of a number of coagulation proteases including thrombin, factors Xa and IXa. It forms a covalent 1:1 complex with the serine protease, called suicide substrate inhibition. About 10% of the AT molecules have a high affinity for heparin, and possibly also for some of the natural anticoagulant glycosaminoglycans.

### Prevalence

AT deficiency is rare, in a recent review of literature data the population estimates range from 0.2/1,000 to 11/1,000 [2]. In patients with venous thrombosis the prevalence ranges from 1–8%.

### Genes

The gene spans 13.4 kb and has seven exons. Males and females are equally affected. Heterozygous deficiency is associated with an increased risk of venous thrombosis; homozygous deficiency is extremely rare and thought to be incompatible with life [2].

*Gene Map Locus:* 1Q23–Q25.

## Molecular and Systemic Pathophysiology

The first mutation linked to antithrombin deficiency was described in 1983. Since then an array of mutations have been identified. AT deficiency is divided into:

*Type I:* low plasma levels of both functional and immunological AT.

*Type II:* variant AT in plasma, further divided in RS (defective reactive site), HBS (defective heparin-binding site) and PE (pleiotropic, i.e. multiple functional effects). The most recent updated database of AT mutations contains 256 entries [3].

A reduced plasma concentration (of about 50% of normal) is associated with an increased level of thrombin generation, which may explain the greater risk of thrombosis. In specific young individuals AT deficiency has been associated with either venous thrombosis at specific sites such as mesenteric veins, or with arterial thromboembolism. In the majority of congenital AT deficient individuals there is a risk of venous thromboembolism; this predisposition is similar in individuals with an *acquired* AT deficiency (see below).

*Clinical Features:* The risk of venous thromboembolism is increased by an estimated fivefold in patients with a heterozygous deficiency, while mortality is not increased [2].

### Diagnostic Principles

In individuals with (an increased risk of) venous thromboembolism AT deficiency is usually identified by a functional, amidolytic assay. The normal range in adult individuals is quite high (83–128%). In the case of a deficiency, verification of antigen levels is obtained to determine the type of deficiency [4]. It is imperative to rule out any acquired types of AT deficiency such as those associated with DIC or nephrotic syndrome. Thus, information of overall clotting times, platelet count, routine chemistry and urine may be required for proper interpretation.

### Therapeutic Principles

In individuals with a congenital AT deficiency, adequate thrombosis prophylaxis is warranted in high risk for thrombosis conditions such as following surgery. In specific situations such as pregnancy, the use of low molecular weight heparin prophylaxis throughout pregnancy and postpartum is presently indicated. Replacement with purified or recombinant AT preparations is usually not indicated, except for high risk for thrombosis situations such as may occur in pregnant women who suffer pre-eclampsia or sepsis.

In patients with an *acquired* AT deficiency due to protein loss or depletion in the course of DIC, incidental reports have mentioned the application of AT replacement therapy. In general, the high costs and doubtful benefit should restrict the general use of replacement

therapy. A recent large randomized controlled trial in patients with sepsis did not show any benefit from AT administration over placebo on mortality [5].

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## $\alpha$ -1 Antitrypsin Deficiency

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## Synonyms

Alpha-1 antiprotease deficiency; “Genetic emphysema”; AAT

## Definition and Characteristics

Clinical features of alpha-1 antitrypsin (AAT) deficiency may involve several organs (lung, liver, skin, and blood vessels) and include emphysema, hepatitis, cirrhosis, panniculitis, and an association with C-anticytoplasmic antibody positive (C-ANCA) vasculitis. Different pathophysiologic mechanisms underlie these various manifestations. Specifically, emphysema results from inflammation and unopposed proteolytic damage to alveolar walls when serum and lung levels of AAT fall below a “protective threshold value” (11  $\mu$ M in the serum). Individuals with severe deficiency of AAT (i.e., serum levels below this protective threshold value) are at risk for developing accelerated airflow obstruction; other known risk factors for airflow obstruction include cigarette smoking and dusty occupational exposure.

Liver disease associated with AAT deficiency (AATD) may occur in individuals with variants associated with intra-hepatocyte accumulation of AAT, which has been called “loop-sheet polymerization.” Such variants include Z, Mmalton, and Siiyama in which structural instability of the protein allows polymerization within the hepatocyte and accumulation of the unsecreted protein within the endoplasmic reticulum of the cell. While the pathophysiologic mechanism of liver disease remains unclear, it appears that inadequate protein trafficking and clearance of the abnormal unsecreted AAT protein causes liver inflammation, cirrhosis, and the possibility of hepatoma.

Panniculitis in AATD results from unopposed proteolytic damage, manifesting histologically as lobular panniculitis. Panniculitis is uncommon in AATD.

Though the association of AATD with vasculitis is perhaps least well-characterized, the prevalence of abnormal AAT phenotypes among individuals with C-ANCA positive vasculitis is clearly higher than in the general population.

## Prevalence

PI\*ZZ homozygotes – 1/1639 to 1/5097; PI\*MZ – 1.9 to 5.2%.

## Genes

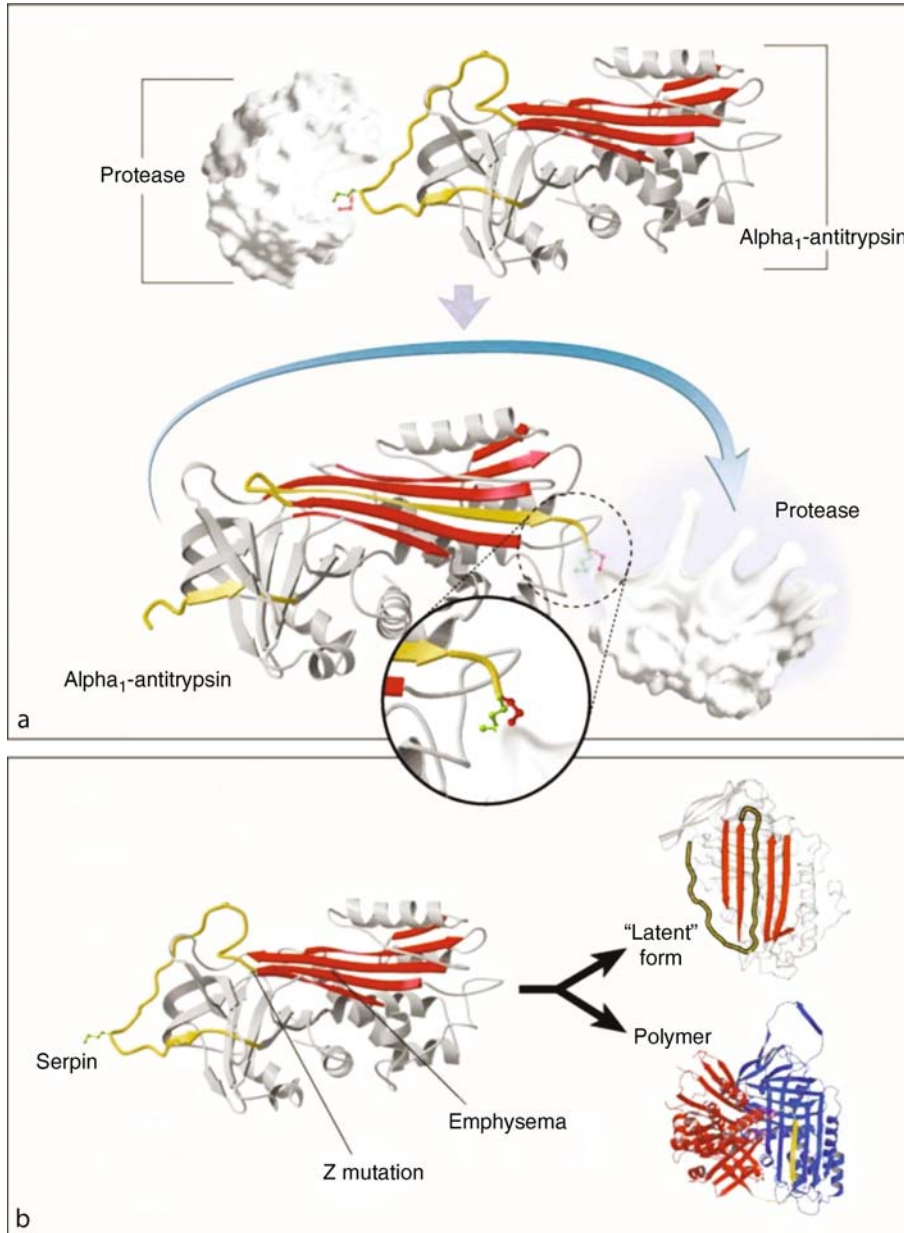
AAT is encoded by the 12.2-kb, 7-exon SERPINA1 gene on the long arm of chromosome 14 (14q32.1). Over 100 allelic variants have been classified using the PI (protease inhibitor) nomenclature that assesses AAT mobility in isoelectric focusing analysis. Normal AAT migrates in the middle (M) and variants are designated A (anodal) to L, if they migrate faster than M, and N to Z, if they migrate more slowly. The most common variants are the Z (Glu342Lys) and S alleles (Glu264Val). Point mutations are inherited as a simple Mendelian trait; the normal genotype is designated PI MM or PI M, a heterozygote for the Z gene is PI MZ, and a homozygote is PI ZZ or PI Z. AAT alleles are co-dominantly expressed; each allele contributes to the plasma level of protein. Thus, each of the deficiency alleles causes a characteristic decrease in the plasma concentration of AAT; the S variant forms 60% of the normal M concentration and the Z variant 10–15%. Null alleles produce no AAT. Thus, combinations of alleles have predictable effects, the MZ heterozygote has an AAT plasma level of 60% (50% from the normal M allele and 10% from the Z allele), the MS heterozygote 80% and the SZ heterozygote 40%.

## Molecular and Systemic Pathophysiology

**Liver Disease:** The Z mutation (Glu342Lys) results in normal translation of the gene, but 85% of the Z AAT is

retained within the endoplasmic reticulum with only 10–15% entering the circulation. The Z mutation distorts the relationship between the reactive-center loop (that binds to the target proteinase) and  $\beta$ -pleated sheet A that forms the major feature of the molecule.

The consequent perturbation in structure allows the reactive-center loop of one AAT molecule to lock into the A sheet of a second molecule to form a dimer which then extends to form chains of loop-sheet polymers (Fig. 1).



**$\alpha$ -1 Antitrypsin Deficiency. Figure 1** Mechanism of inhibition of proteases by  $\alpha_1$ -antitrypsin and of polymerization in serpinopathies. (a) (*Upper*) Docking of the protease to the reactive centre loop of  $\alpha_1$  antitrypsin. (*Lower*) The protease has cleaved the reactive centre loop, releasing it from its metastable high energy state. The reactive loop swings with the protease in tow into a more stable conformation within the main  $\beta$ -sheet. The process distorts and alters the structure of the protease. (b) Mutations of serpins can result in several diseases. In the case of  $\alpha_1$ -antitrypsin deficiency caused by a Z mutation, a substitution of lysine for glutamic acid at position 342 widens the  $\beta$ -sheet A. The gap in the  $\beta$ -sheet A can either accept its own loop to form a latent conformation or proceed to polymerization in an irreversible process. Adapted from Carrell RW, Lomas DA (2002)  $\alpha_1$ -antitrypsin deficiency: a model for conformational diseases. *N Engl J Med* 346:45–53.

These polymer chains become interwoven to form the insoluble PAS-positive aggregates that are the hallmark of AAT liver disease. The process of intra-hepatic polymerization also underlies the severe plasma deficiency of the rare Siiyama (Ser53Phe) and Mmalton (deletion of residue 52) deficiency alleles and the mild plasma deficiency of the S (Glu264Val) and I (Arg39Cys) variants.

There is a strong genotype-phenotype correlation that can be explained by the molecular instability caused by the mutation and, in particular, the rate at which the mutant forms polymers. Those mutants that cause the most rapid polymerization cause the most retention of AAT within the liver. This in turn correlates with the greatest risk of liver damage and cirrhosis, and the most severe plasma deficiency.

**Lung Disease:** The quantitative deficiency of AAT in the serum is compounded by a fivefold reduction in association rate kinetics with neutrophil elastase caused by the Z mutation and the polymerization of secreted Z AAT within the airways and alveoli. The formation of polymers inactivates AAT (thereby further reducing the protein available to inhibit neutrophil elastase) and the polymers themselves may be chemotactic and drive excessive inflammation.

### Diagnostic Principles

AATD is clearly under-recognized by clinicians, with evidence of long diagnostic delays (3–7 years) between patients' initial symptom and the initial diagnosis. Furthermore, available evidence suggests many patients may see multiple healthcare providers with attributable symptoms before the initial diagnosis is made.

Once suspicion is established, diagnostic tests include measuring the serum level (often by nephelometry) and determining the phenotype, often by isoelectric focusing after using allele-specific probes in polymerase chain reaction assays, particularly for the Z and S alleles.

Pulmonary function testing, including spirometry with bronchodilators and diffusing capacity measurements, are important in assessing the presence of obstructive lung disease and in monitoring disease progression.

### Therapeutic Principles

Therapy of lung-affected individuals with AATD includes all of the standard treatments for chronic obstructive pulmonary disease, e.g., including bronchodilators, preventive vaccinations, supplemental oxygen when indicated, pulmonary rehabilitation, and lung transplantation, when indicated. Available data suggest that lung volume reduction surgery is a relatively unappealing option for individuals with emphysema due to AATD.

Specific therapy for AATD currently consists of the infusion of purified pooled, human plasma AAT, for which three preparations are currently available in the United States. Many therapies are currently under investigation and include gene therapy for transfecting the normal human AAT gene (e.g., using an adeno-associated virus vector system), administration of purified or recombinant AAT by inhalation, administration of small molecular elastase inhibitors, and development of small molecules to prevent polymerization of aberrant AAT protein.

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## $\alpha$ -1 Antitrypsin Deficiency Panniculitis

### ► Panniculitis at Alpha-1 Antitrypsin Deficiency

## Anxiety Disorders

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### Definition and Characteristics

Anxiety disorders are frequent and disabling disorders with great socioeconomic impact. They are most frequently seen in primary care and there is a great degree of underdiagnosis and even more undertreatment. According to ICD-10 [1] and DSM-IV [2] generalized anxiety disorder (GAD), panic disorder with and without



agoraphobia, social anxiety disorder, specific phobias and posttraumatic stress disorder (PTSD) are classified as anxiety disorders. Panic disorder is characterized by suddenly occurring panic attacks, which are accompanied by an intense vegetative reaction. The leading symptom of generalized anxiety disorder is continuous worry together with inner tension. The predominant symptom of social anxiety disorder is anxiety in social situations where subjects are observed by others. Specific phobias are strictly related to a specific situation or a specific object. PTSD is a later occurring reaction to a trauma or a severe life event. The exact diagnostic criteria are given in the ICD-10 [1] or the DSM-IV [2], respectively.

### Prevalence

Panic disorder 2.7%, specific phobia, 8.7%, social anxiety disorder 6.8%, GAD 3.1%, PTSD 3.5%.

### Genes

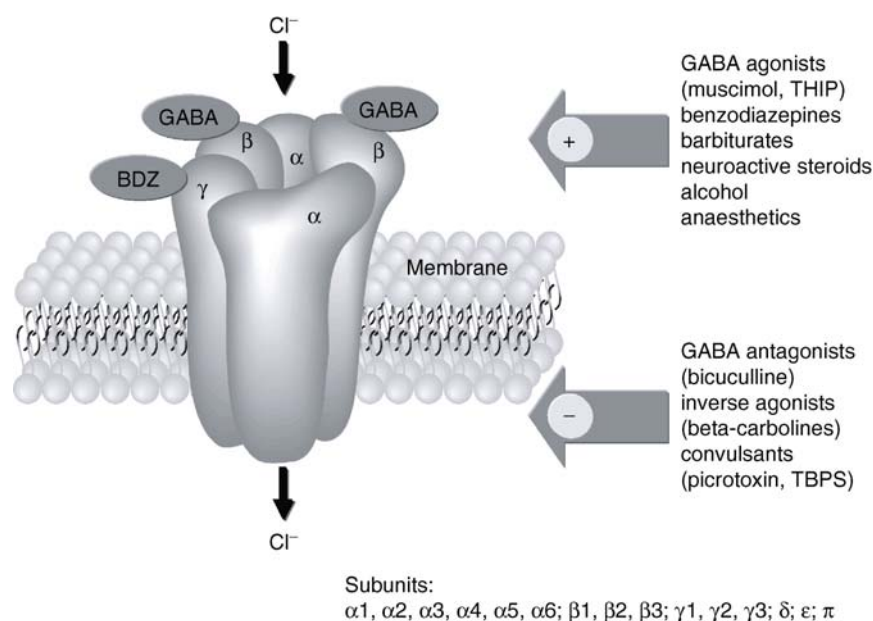
Although various genetic association studies have been published for anxiety disorders such as panic disorder, so far no specific anxiety gene has been identified.

### Molecular and Systemic Pathophysiology

So far no monocausal pathophysiological origin is known for any of the anxiety disorders. Most pathophysiological studies have been performed in panic disorder and

suggest that there is a dysfunction of the GABAergic system. There is evidence from spectroscopy studies that GABA levels are decreased in the cortex of patients with panic disorders. This is in line with neurophysiological studies suggesting changes in the control of saccadic eye velocity and alterations in the equilibrium of GABAergic neuroactive steroids. Moreover, benzodiazepines, which target GABA<sub>A</sub> receptors, are powerful anxiolytic agents. GABA<sub>A</sub> receptors belong to the family of ligand-gated ion channels with four transmembrane spanning domains and share considerable homology with nicotinic acetylcholine, serotonin type 3 and glycine receptors. They consist of various subunits, which usually form a pentamer containing  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits [3] (Fig. 1).

Besides the most abundant  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, other subunits ( $\delta$ ,  $\epsilon$ ,  $\pi$ , and  $\theta$ ) are known [4] which are important for tissue specific receptor expression. A variety of different compounds act at GABA<sub>A</sub> receptors, e.g., agonists for the GABA binding site and allosteric modulators such as benzodiazepines. The differential pharmacology of benzodiazepines is largely determined by variations in the expression of  $\alpha$  subunits [3]. Currently, six  $\alpha$  subunits ( $\alpha 1$ – $\alpha 6$ ) are known. For the development of novel anxiolytic compounds it is intriguing that the various  $\alpha$  subunits confer distinct pharmacological properties on benzodiazepines with regard to their anxiolytic, anticonvulsant, sedative or muscle relaxant effects. Such differential effects of benzodiazepines are in part determined by



**Anxiety Disorders. Figure 1** Pharmacology of the GABA<sub>A</sub> receptor complex. The GABA<sub>A</sub> receptor consists of various subunits, which usually form a pentamer containing  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits. Besides the most abundant  $\alpha$ ,  $\beta$  and  $\gamma$  subunits, other subunits ( $\delta$ ,  $\epsilon$ ,  $\pi$ , and  $\theta$ ) are known [3]. A variety of different compounds act at GABA<sub>A</sub> receptors, e.g. agonists for the GABA binding site and allosteric modulators such as benzodiazepines. TBPS: t-butylbicyclophosphorothionate.



a single amino acid. For example, a histidine at position 101 in the  $\alpha 1$  subunit is crucial for the GABA enhancing effects of benzodiazepines, whereas an arginine at position 101 as present in  $\alpha 6$  leads to a decrease in the GABA response to benzodiazepines [3]. Moreover, transgenic mouse models have suggested that the sedative effects of benzodiazepines are conferred via the  $\alpha 1$  subunit, whereas their anxiolytic effects are mediated through  $\alpha 2$  and  $\alpha 1$  subunits [3]. The GABA binding site can be labeled by muscimol and is located within subunits of the  $\beta$  type. In spite of the importance of  $\alpha$  subunits for benzodiazepine pharmacology the presence of a  $\gamma$  subunit appears to be important for the binding of benzodiazepines to GABA<sub>A</sub> receptors [3].

### Diagnostic Principles

Anxiety disorders have to undergo thorough physical and neurological examination to exclude a somatic cause of the disorder. This is usually accompanied by routine laboratory screening, electrocardiogram (ECG), electroencephalography (EEG) and neuroimaging methods such as cranial computer tomography or magnetic resonance tomography (MRT). Diagnosis is based on detailed psychiatric exploration and classification according to accepted diagnostic criteria such as the International Classification of Diseases (ICD-10) [1] or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2] after exclusion of a somatic disorder.

### Therapeutic Principles

Anxiety disorders are treated by pharmacotherapy, psychotherapy or a combination of both. Specific phobias are usually treated by cognitive behavioral therapy (CBT). CBT is also the best-studied psychotherapy for the treatment of other anxiety disorders. With regard to pharmacotherapy, antidepressants, especially selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors, represent first line treatment options. However, due to their slow onset of action, the addition of benzodiazepines is frequently required during treatment initiation. Benzodiazepines should not constitute a long-term treatment option in view of their abuse liability and withdrawal problems. Novel treatment developments focus on GABA-analogues, subtype specific benzodiazepines, modulators of neuroactive steroids, drugs targeting the GABA binding site of the GABA<sub>A</sub> receptor and on neuropeptides. Detailed guidelines for the treatment of anxiety disorders have been provided recently [4,5]. It has to be emphasized that every pharmacotherapy of anxiety disorders has to be accompanied by at least psychoeducation, even if a systematic psychotherapy is not provided.

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## AOM

► Otitis Media, Acute

## Aortic Aneurysm

► Aneurysm, Aortic and Arterial

## Aortic Coarctation

► Coarctation of the Aorta

## Aortic Dissection

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### Synonyms

Dissecting aneurysm of the aorta

## Definition and Characteristics

Aortic aneurysms and dissections are the major diseases affecting the aorta, and a leading cause of morbidity and mortality in industrialized countries. The most common locations for aneurysms are the ascending thoracic aorta and the infrarenal abdominal aorta. Aortic dissections are closely associated with aortic aneurysms and typically begin with a tear in the aortic inner layer, the intima; blood then penetrates the diseased medial layer and dissects along the plane of the aortic wall. The dissection usually proceeds antegrade from the site of the intimal tear, but can also proceed retrograde. More than 95% of aortic dissections originate either in the ascending aorta within several centimeters of the aortic valve or in the descending aorta just distal to the origin of the left subclavian artery. Thoracic aortic aneurysms and aortic dissections are related conditions as indicated by the fact that progressive enlargement of the aorta leads to dissections in the absence of prophylactic surgical repair of the aneurysm.

## Prevalence

For a very long time, this pathology was considered uncommon and carried such a hopeless prognosis that it received little attention except as a medical curiosity. However, the incidence of the pathology had been underestimated since there are 5–30 cases per million population of aortic dissections per year.

The average age of patients with a thoracic aortic aneurysm is 65 years, and men are at a slightly increased risk compared to women (1.7:1). However, every fourth dissection affects patients younger than 40 years of age. The reason for this discrepancy is the different pathomechanism of the aortic disease in younger and older subjects. While genetic syndromes with connective tissue disorders lead to aortic aneurysms and dissection early in some patients, most aortic aneurysms in older subjects are caused by slow degenerative processes explained in detail below.

## Genes

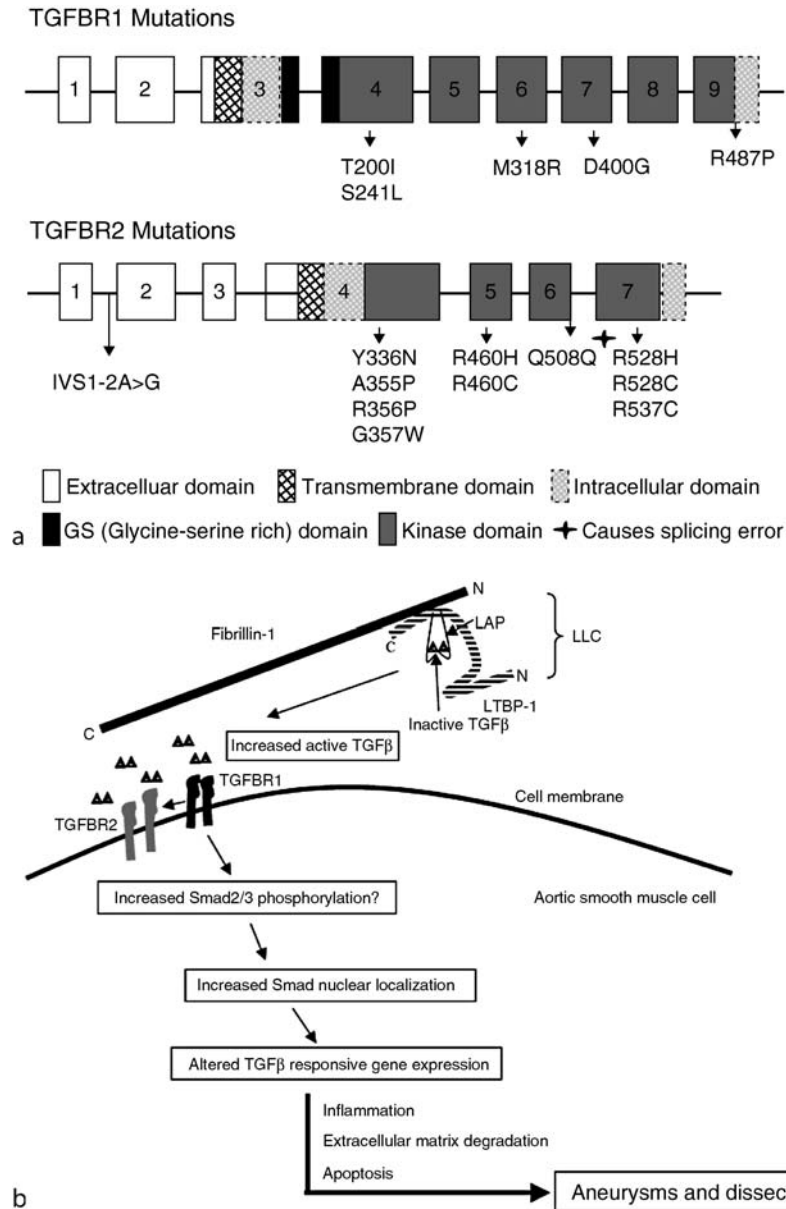
The genetic basis of aortic aneurysms and aortic dissections is being investigated only relatively recently. It has been recognized for some years that aortic dissections occur in conjunction with several genetic syndromes, in particular Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), and research initially focused on the genetic basis of syndromic aortic dissections. More recently, research has focused on defining the genetic component for non-syndromic dissections, and identifying genes for this condition. The identification of disease genes causing both syndromic and non-syndromic aortic dissections have advanced rapidly and facilitated the progress in understanding the disease.

Thoracic aortic dissections are the major cardiovascular complication associated with the well-known genetic syndrome known as Marfan syndrome (MFS), a disorder with skeletal, ocular, and cardiovascular manifestations that is inherited in an autosomal dominant manner. The progressive dilation of the aortic root terminating in dissection is a major cause of mortality and morbidity in Marfan patients. As described mainly by the group of Dietz in 1991, aortic disease in MFS is the result of defects in the fibrillin-1 (FBN1) gene that localizes to chromosome 15q15–31 [1]. FBN1 is a major component of the microfibrils that build the elastic fiber and has a repetitive domain structure containing calcium-binding epidermal growth factor precursor-like and transforming growth factor- $\beta$ -binding motifs. More than 700 mutations in the FBN1 gene have been identified to date. In addition to MFS, FBN1 mutations can also result in other clinical manifestations, including isolated ocular or skeletal defects on the one hand or cardiovascular features of MFS without fulfilling the diagnostic Gent criteria described by de Paepe et al. [2] on the other hand. Metabolic labeling and immunohistochemical studies have shown that the majority of fibroblasts explanted from MFS patients have a decrease in fibrillin-1-containing microfibrils in the extracellular matrix far below the 50% level. The analysis of the FBN1-deficient mouse models of MFS has provided a linking pathway between decreased formation of microfibrils and the manifestations of MFS. Fibrillin-1-deficient mice demonstrated increased active transforming growth factor- $\beta$  (TGF- $\beta$ ) in tissues when compared with wild-type mice, suggesting that reduced microfibrils increased the bioavailability of active TGF- $\beta$  in tissues. Furthermore, antagonism of TGF- $\beta$  signaling prohibited the pulmonary parenchymal abnormalities, mitral valve anomalies, and aortic dilatation observed in the transgenic mouse models of MFS, suggesting a crucial role for TGF- $\beta$  signaling in MFS.

Recently, DNA from nine MFS families with no identified mutations in FBN1 was also sequenced, and TGF- $\beta$  receptor 2 (TGFB2) missense mutations were identified in three of these families. These TGFB2 mutations in MFS patients involved the intracellular serine-threonine kinase domain of the receptor, and have been determined to reduce receptor signaling induced by TGF- $\beta$  when co-expressed with a TGF- $\beta$  responsive promoter in an *in vitro* assay system.

TGFB1 and TGFB2 mutations have also been described in a syndrome associated with cleft palate, craniosynostosis, congenital heart disease, arterial aneurysms, and mental retardation as part of the phenotype, termed Loeys-Dietz syndrome (LDS) [3] (Fig. 1a).

Most mutations observed were germline heterozygous missense mutations that affect amino acids in the functionally important intracellular kinase domain



**Aortic Dissection. Figure 1** (a) Heterozygous germline TGFR1 and TGFR2 mutations in syndromic and nonsyndromic aortic disease. Genomic and protein structure of the TGFR1 and TGFR2 genes showing known mutations previously identified in MFS, LDS, and others. (b) Dysregulated TGF- $\beta$  signaling leading to aneurysms and dissections. TGF- $\beta$  is secreted in an inactive form and stored in the extracellular matrix in a complex termed the large latent TGF- $\beta$  complex (LLC), consisting of a latency-associated peptide (LAP) and a latent TGF- $\beta$ -binding protein-1 (LTBP-1). Dysregulation of TGF- $\beta$  signaling results from fibrillin-1, TGFR1, or TGFR2 mutations, leading to altered transcription of TGF- $\beta$ -responsive genes, resulting in the clinically relevant medial degeneration leading to aneurysms and dissections (Figs. 1a and b are obtained from Pannu H et al. Ann NY Acad Sci 2006 with permission of Blackwell Publishing).

of the proteins. Surprisingly, tissues from affected patients showed increased expression of collagen and connective tissue growth factor in addition to nuclear enrichment of phosphorylated Smad2, both observations suggesting enhanced TGF- $\beta$  signaling in these

tissues. This suggests a common pathway of dysregulated TGF- $\beta$  signaling in the pathogenesis of aortic disease, either due to the presence of amplified active TGF- $\beta$  as observed in Marfan or by disruptions in signaling due to TGF- $\beta$  receptor mutations (Fig. 1b).

The bioavailability of active TGF- $\beta$  is recognized to be strongly regulated and dependent on its release from a large latent complex to which TGF- $\beta$  is non-covalently associated with its propeptide fragment, labeled the latency-associated peptide, and covalently linked to latent TGF- $\beta$ -binding protein (LTBP) (Fig. 1b). This complex associates with fibrillin-1-containing extracellular microfibrils and fibrillin-1 mutations lead to impaired amounts of microfibrils in the extracellular matrix, and thereby to enlarged amounts of bioavailable TGF- $\beta$  in the patients' tissues with relevant FBN1 mutations. This mechanism of increased TGF- $\beta$  signaling caused by relevant FBN1 mutations, while difficult to resolve with the putatively kinase-inactivating TGFBR1 and TGFBR2 mutations identified in Loays-Dietz syndrome, appears to be the origin of aortic disease in both these syndromes as enhanced TGF- $\beta$  signaling is observed in aortic tissue from LDS patients as well. These observations are remarkably similar to previous investigations demonstrating fibroblast-specific expression of a kinase-deficient TGFBR2 in a transgenic mouse model, causing paradoxical upregulation of the TGF- $\beta$  signaling pathway. The biological mechanism following the TGF- $\beta$  signaling upregulation observed in aortic disease remains to be clarified. Interestingly, the angiotensin-1 antagonist losartan known for TGF- $\beta$  antagonism was able to reverse the clinical manifestations of Marfan, including the aortic manifestation when administered in a transgenic mouse model of MFS. Moreover the TGF- $\beta$ -induced failure of muscle regeneration is attenuated in disease-related myopathy using Losartan in the mouse model. Possibly, the use of losartan can replace beta-blockers in the first line as preventive and antihypertensive treatment of genetically disposed patients in the future.

Familial aggregation studies of patients referred for surgery of ascending aneurysms or dissections, who did not have an associated genetic syndrome, have shown that 11–20% of these patients have a first-degree relative with a history of aortic dissections, providing evidence that genetic predisposition plays a key role in the etiology of this disease. Screening for aortic aneurysms of individuals at risk for inheriting the defective gene often identifies individuals with asymptomatic ascending aortic aneurysms and supports the confirmation of autosomal dominant inheritance of the disorder. Families with inherited forms of aortic dissections display a wide range of first onset of the familial disease (variable expression); the age of acute dissections has ranged from adolescence to octogenarians within a single family. In families with inherited forms of aortic dissections, the pathology in the aortic wall of aneurysms and dissection is mainly medial degeneration.

Several families were genetically studied in detail. Interestingly one identified defect (MYH11) involved

the smooth muscle cells. In the family, there was a co-existing risk of persistent ductus arteriosus (PDA) due to failing smooth muscle cell action. In addition to the isolated aortic dissections in families, there are aortic dissection families described with associated features such as bicuspid aortic valve, cervicocephalic arterial dissections, cerebral aneurysms, and coarctation of the aorta, suggesting that these malformations result from a single developmental disposition and are potentially due to different genes for each noted familial form of aortic dissection associated with a specific gene defect (Fig. 1). The successful identification of MYH11 as the gene responsible for PDA in conjunction with aortic dissections lends support to this hypothesis. In addition, familial aggregation studies have established the co-existence of aortic dissections and bicuspid aortic valve. Additionally, an increased prevalence of aortic root enlargement has been noted in patients with bicuspid aortic valve, suggesting another common genetic basis for aortic dissections and bicuspid aortic valve.

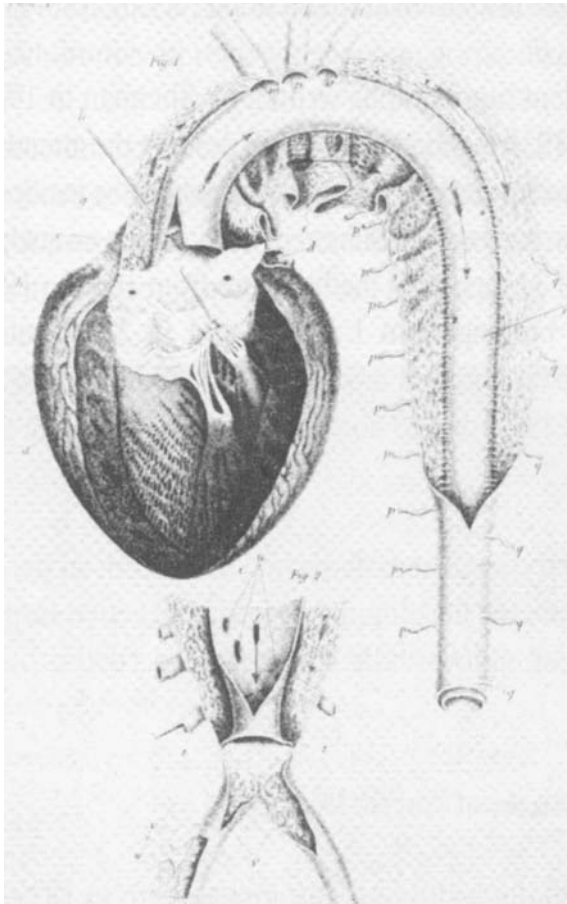
## Molecular and Systemic Pathophysiology

Dissecting aneurysms have neither a common etiology nor a common pathology. The most common pathology associated with thoracic aortic aneurysms is medial degeneration, a poorly understood pathologic process previously termed *cystic medial necrosis* by Erdheim [4], which will be dealt with in greater detail later. It might be caused by an irregular reconstruction of the aortic wall in response to stressors like hypertension.

Aortic dissection has been recognized as a clinical and pathologic entity for 250 years. F. Nicholls was the first to describe an aortic dissection after his autopsy on King George II in October, 1760. The king's surgeon tried everything to save His Majesty's life, but in vain. At necropsy the next day, Nichols, physician to his Majesty, described the lesion as a blood collection under the external coat together with a rupture of the right ventricle. Forty years later, in 1802, Jean-Pierre Maunoir from Geneva termed the phenomenon of the infiltration of blood in the arterial wall "dissection" and introduced the term *anévrisme disséqué* (dissected aneurysm). Around 1840, Pennock identified that the dissections take place in the laminae of the media. At that time, J. Hope published the first precise illustration of an acute dissection of the entire aorta (see Fig. 2).

At the end of the nineteenth century, B. Paacock revealed the cough mechanism in a review of 80 cases from multiple centers around the world and divided the dynamics of the disease into three still valid stages: rupture of the internal coat, dissection and possible external rupture, and recanalization. He also noted the high mortality of the disease within the first day.



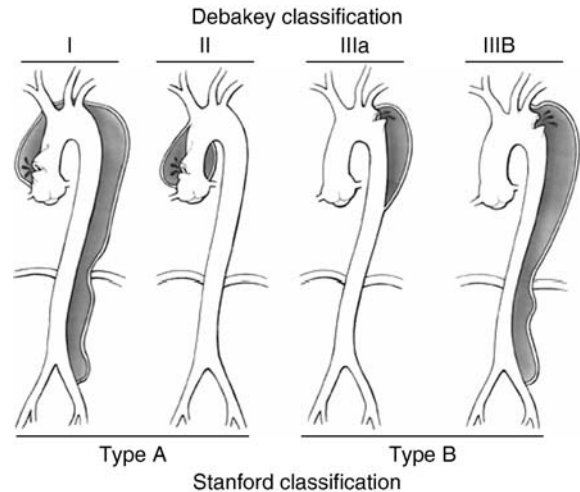


**Aortic Dissection. Figure 2** First illustration of dissection from the aortic valve to the bifurcation. From J. Hope (1842) with permission of J. B. Lippincott.

In the beginning of the twentieth century, Krukenberg and others speculated that an involvement of a rupture of the vasa vasorum in the media and consecutive media weakening by intramural hematoma would cause the intimal tear as the starting point of the dissection. More recently, the interest in dissecting aneurysms of the aorta was stimulated by the development of reconstructive surgery in the 1960s and endovascular surgery in the 1990s. Indications for surgery are based on the symptomatology and the morphology of the dissection. Several morphological classifications have been proposed; the DeBakey classification from 1961 and the Stanford classification from 1970 are commonly used.

DeBakey and colleagues classified aortic dissections according to their origin and extent (Fig. 3).

A dissection beginning in the proximal aorta that involves most of the entire aorta was classified as type I (12% of the cases). Type II (6%) involves only the ascending aorta and is the most common type in Marfan syndrome. In type III (60%), the dissecting process



**Aortic Dissection. Figure 3** DeBakey's classification and Stanford classification of aortic dissection.

originates immediately distal to the left subclavian artery and continues well below the diaphragm. Type IV (22%) is similar to type III, except that the dissection remains confined to the descending thoracic aorta.

In 1970, Daily et al. [5] from Stanford University Medical School introduced the Stanford classification (Fig. 3): dissections involving the ascending aorta, regardless of the site of primary intimal tear and extent of distal propagation of the dissection are type A; those without involvement of the ascending aorta are type B. This classification is based on the difference in management: any type A dissections were (and still are) considered an indication for emergency surgery, while medical treatment should be the preferred treatment for a large subset of patients with type B dissections. This Stanford-classification is still the most common nomenclature for dissections around the world.

In his initial description of aortic dissection in 1819, Laennec comments on the cause of dissection. In addition to "high impetus of blood," he listed bony incrustations within the arterial wall, tears and ulcerations in the intimal membrane, and, occasionally, tubercles and small abscesses within the fibrinous membrane. It appeared much later that this speculation was right. Nicholls demonstrated in 1728 that experimental over-distension of an artery at the autopsy table results in the bursting of the intima with the formation of an aneurismal outpouching of the external layer. He had already interpreted the observation that high intravascular blood pressure might lead to distention without rupture or a rupture of the internal coat. This internal layer was less resistant and is more likely to give way because of the anatomic disposition of fibers, he believed. This concept is still valid almost 300 years later.



Atherosclerosis is the next major cause of aortic dissection. In 1893, the pathologist Joseph Coats concluded that atheromas were of critical importance in the pathogenesis of aneurysms and consecutive dissection. He performed several autopsies and found small aneurysms commencing in 6 cases and, in all of them, atheromatous thickening of the intima and wasting of the media with atrophy and even wasting of the elastic fibers in the sections of the commencing aneurysms. The elastic lamina ended fairly abruptly. According to Coats, the atrophy of the media was the most important causative factor in aneurysmal formation. To include the causative effect of hypertension he postulated that the atheromatous patch was projected by the pressure of blood against the media in every systole of the heart.

More specifically, and modern concepts expand the previous description of the atherosclerotic aorta, the thickened intima shows massive fibrosis and calcification and increased amounts of intracellular fatty acids. The extracellular matrix is degraded by histiocytic cells and can compromise the integrity of the intima. Additionally, degenerative changes might develop within fibrous tissue with reduced cellularity and collagen-fiber hyalinization. Both mechanisms may result in intimal rupture, most often at the onset of the plaque (see Fig. 4).

Degeneration of the media is a predisposing factor for aortic dissection. The microscopic aspects of the typical lesions of dystrophy within the media were first described by Otto Gsell in 1928. He described necrosis

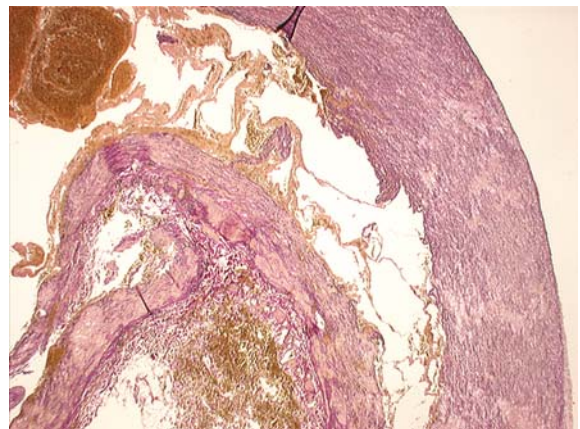
of muscle cells in the wall of dissected aortas, followed by degeneration of elastic tissue and production of collagen, which finally resulted in cleft formation. The clefts were filled with mucoid ground substances. A year later, Jakob Erdheim called this alteration “medionecrosis aortae idiopathica cystica” emphasizing the predominant role of mucoid changes within the media [4]. The loss of muscular cells combined with mucoid degeneration is very frequent in elderly people and might be induced by sclerosis of the vasa vasorum with resulting ischemia within the arterial wall. In 1970, Carlson et al. reported the histological findings in 250 autopsies of human ascending aortas. This study revealed that the incidence of mucoid degeneration increases progressively with age: from 10% in the first two decades (genetic syndromic patients were excluded) to 60 and 64% in the seventh and eighth decade, respectively. Among patients with hypertension the incidence of cystic mucoid necrosis is consistently higher than in normotensive patients of the same age.

Histologically, aortic aneurysms are characterized by the degradation of elastin in the media and adventitia, smooth muscle cell loss with thinning of the medial wall, infiltration of lymphocytes and macrophages, and revascularization (see Fig. 5).

The pathogenesis of aneurysms is, therefore, complex and multifactorial. There appear to be environmental, genetic, inflammatory, and structural factors. It seems to be not a specific disease process but rather the metabolic end-effect to which age and hypertension may strongly contribute.



**Aortic Dissection. Figure 4** Macroscopic view of a post mortem aorta. Aortic dissection is located near the aortic arch (formalin fixed) showing the real lumen (forceps) and the false lumen filled with thrombotic material. Note that the false lumen has a wider appearance than the original one.



**Aortic Dissection. Figure 5** Microscopic specimen of a recent case (from Pathological Institute of the University Medical Centre Freiburg, EvG, 25×). Aortic dissection seen in the outer third of the media with interposed thrombus and fibrin exudation. There is a clear disruption of the wall texture, with interruptions of the elastic lamellae in the media, which leads to instability of the aortic wall from shear stress and pressure.

Aortic dissection is not exclusively observed in older subjects. Schnikter and Bayer reviewed the literature in 1944 and found that 141 of 580 (24%) cases of proven aortic dissections occurred in patients less than 40 years of age. The high incidence of elastic tissue lesions in the younger age group suggests a relationship to hereditary defects, which have been discussed earlier. Other predisposing factors to aortic dissections were pregnancy, bicuspid aortic valve, and coarctation of the aortic isthmus.

The first isolated case of aortic dissection during pregnancy was reported in 1832. Later studies showed that the frequency of dissections in pregnancy is highest in the third trimester and occurs seldom during labor or shortly afterwards. In 2003, Immer et al. reviewed the recent literature (1983–2002) on this topic and collected 57 cases of pregnancy and aortic dissection. As reasons for the number of dissections during pregnancy multiple factors are discussed, especially, that the coexisting hemodynamic alteration during the third trimester plus the physiologic changes in extracellular matrix architecture by hormonal factors may predispose to dissections. Additionally, Marfan syndrome meeting the Gent criteria was diagnosed in 40% of the cases, and 10% of the Type-A dissections had a bicuspid aortic valve – another predisposing factor.

Indeed, a bicuspid aortic valve appears to be related in some way to a structurally weaker aorta. The abnormal elastic properties, similar to the findings in Marfan syndrome, have been described in the aortic wall of patients with bicuspid aortic valves.

Aortic coarctation is also clearly associated with a higher frequency of aortic dissections. In the series of Schnikter and Bayer, 32% of the 141 young patients with aortic dissection presented aortic coarctation. This high frequency is related to the often developed systemic hypertension and also to the frequent association of aortic coarctation with a bicuspid aortic valve. In the autopsy series of Reifstein, in the 104 patients who died from the complication of aortic coarctation, the bicuspid aortic valve accounted for the most common associated anomaly (42% of the cases).

Blunt trauma has occasionally been reported as a cause of aortic dissection. Traumatic dissection is lined typically between the intact adventitia and the media, and not within the media as commonly seen in patients with spontaneous dissection of other etiology. Often, the dissection starts at the level of the ligamentum arteriosum, where most traumatic ruptures are localized as well. Wilson and Hutchins found 3 out of 204 aortic dissections caused by trauma. The dissection rarely progresses retrograde to the ascending aorta and more frequently involves the distal parts of the aorta. This is often complicated by thrombosis within the false or true lumen, followed by malperfusion injury like paraplegia.

## Diagnostic Principles

In patients at risk for aortic dissection, routine imaging of the aortic anatomy is warranted to identify situations with the need for prophylactic surgical treatment (see Therapeutic Principles).

The typical presentation of a patient suffering from an acute aortic dissection is severe chest pain and pain in the back. Some compare their pain with a knife in the back. Only a few patients recognize a caudal moving pain which is likely to be linked to the proceeding dissection. Patients suffering from malperfusion might present with the respective symptomatology. These reach from obstruction of a peripheral artery with acute leg ischemia or abdominal pain from mesenteric ischemia to severe neurological dysfunction from carotid occlusion. The notion of a chronic aortic dissection without the history of pain as an incidental finding is rare.

In physical examination on presentation of the patients, special care is warranted to realize malperfusion and distinguish it from other diagnoses with chest pain, especially myocardial infarction. In the era of widespread distribution of 24 h catheter laboratories for emergency coronary angiograms, it is not unusual that patients with aortic dissections are transferred to the catheter lab first and the features of normal coronaries and an intimal flap in the aorta are found.

In the first minutes after presentation of the patient, a powerful monitoring should be implemented as soon as possible, without losing time in transportation to an emergency CT scan. Whenever the patient needs to be transported to a facility with CT scan, the hospital with the ability to treat all entities of aortic dissection will be the best choice. The CT scan with contrast medium represents the Gold-Standard diagnostic feature for aortic dissection. To identify an involvement of the ascending aorta and omit misinterpretations from movements with the heart rhythms, an ECG-triggered CT of the thoracic aorta should be performed. As alternative investigations in circumstances when CT-scans are impossible (e.g., broken machine or pregnant women), the MRI is the next best choice. However, in most hospitals an emergency MRI is not easy to obtain.

Additionally, the involvement of the ascending aorta might be diagnosed by transesophageal echocardiography.

## Therapeutic Principles

Treating patients with aneurysms needs to be discussed separately for the group of patients at risk for an aortic dissection presenting with genetic syndromes or non-syndromic aortic aneurysms and for the other group of patients with concrete dissection.

In general, prophylactic surgical treatment of aortic aneurysms should be performed when the risk for dissection or rupture is higher than the risk for prophylactic

surgery. In patients with connective tissue disorders and a history of aortic dissection in their families, many centers operate aneurysms of the aorta with a diameter of between 40 and 45 mm prophylactically. In patients without genetic disorders, 50 mm diameter is the most common threshold for prophylactic aortic surgery of an aneurysm. Patients known to be at risk or with existing aneurysms below the threshold for surgery need to be reevaluated in accurate time intervals and optimal blood pressure management including  $\beta$ -Blocker therapy is needed.

The main principle in the treatment of an acute (and chronic) dissection is that type A dissections need an emergency operation and prosthetic treatment of the ascending aorta and most of the type B dissection can be managed without operations. The reason to treat dissected ascending aortas surgically is the high fatal complication rate within the first hours after onset of symptoms. Within the first hours after the initial event, 5% mortality per hour was observed. This notion explains that a delay of treatment is no option in type A dissections. Causal factors for the high complication rate in type A dissections are hemorrhagic pericardial tamponade or severe aortic valve incompetence from proximal ascending aortic lesions together with malperfusion events of the aortic arch's branches, with subsequent brain damage or aortic rupture.

Originally, these patients with type A dissections were operated in deep hypothermic circulatory arrest with arterial cannulation of the femoral artery and vein. Recently, most centers use selective cerebral perfusion with moderate cooling during arch or distal ascending aorta repair to protect the patients from brain damage from deep hypothermia. For the selective cerebral perfusion, it is possible to cannulate the right subclavian artery (and perfuse the brain through the brachiocephalic trunk and right carotid artery) or one or both carotid arteries. The aortic resection can include resection of only the ascending aorta or concomitant resection of the aortic valve with valve replacement and reconstruction and reinsertion of the coronaries in the artificial graft. Concomitant arch repair or replacement is needed in some cases as well. Importantly, the entry of the dissection needs to be resected during the operation. In most cases, the distal portion of the dissected aorta will be treated with a glue to allow only antegrade flow in the true lumen and close the false lumen.

Patients with type B dissection are typically treated without the need for urgent operations. The important component in the first week of treatment is proper control of pain and hypertension, with regular physical and CT-scan control of possible malperfusion of organs or body parts. Arterial pressure control, especially, might be challenging and sometimes multiple intravenous antihypertensive drugs are necessary within the

first weeks. Monitoring in an intensive care unit for the first few days is needed for most patients.

For some patients, a surgical treatment is mandatory. Indications for surgery are impossible control of pain or hypertension, rapid growth of the dissected aorta and occlusion of arteries from the dissection membrane. Recent technological developments have made endovascular treatment possible in the majority of patients using stent-grafts to enlarge the true lumen and occlude the false lumen and fenestration of the dissection membrane in malperfusion events. Using a hybrid approach in some cases, surgical revascularization of stent-graft occluded arteries is needed. Endovascular treatment is not recommended in patients with connective tissue disorders, which should preferentially be treated with open surgery.

In all patients suffering from dissections, strict follow-up investigations are needed to identify pathological changes such as enlargement, beginning penetration and others.

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## Aortic (Valve) Insufficiency

### ► Aortic Valve Regurgitation

## Aortic Regurgitation

### ► Aortic Valve Regurgitation

## Aortic Root to Right Heart Shunts

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### Synonyms

ARHS

### Definition and Characteristics

The three most common causes of aortic root to right heart shunts (ARHS) are sinus of Valsalva aneurysm with fistula (SVAF), coronary arterial venous fistula (CAF), and anomalous pulmonary origin of the left coronary arteries (APOCA). SVAF consists of a separation or lack of fusion between the media of the aorta (Ao) and the annulus of the aortic valve (AV). Approximately 90–95% of congenital aneurysms originate in the right or noncoronary sinus, and project into the right ventricle (RV) or right atrium (RA), respectively. Rupture usually occurs in the third or fourth decade of life. An abrupt sizable rupture causes chest pain, bounding pulse, elevated jugular venous pressure with prominent tall A and V waves, a continuous thrill and murmur accentuated in diastole, aortic regurgitation murmur, pulmonary arterial hypertension (PAH) and volume overload of the heart. A small perforation that progresses slowly may at first go unnoticed, and congestive heart failure (CHF) may occur after months or years. The natural history of APOCA is characterized by the origin of the coronary artery arising from the pulmonary artery (PA). The most common variant is an anomalous origin of the left coronary artery (LCA) from the PA. APOCA has three general patterns: (i) 80–90% suffer from acute progression to myocardial infarction (MI) or CHF in early infancy, with death before the first year of life; (ii) early illness followed by improvement in childhood; and (iii) asymptomatic. Clinically, the symptomatic patient is usually an acutely ill infant with pulsus alternans, elevated jugular venous pulse, or a third heart sound, and mitral regurgitation (MR) murmur. The characteristic cardiac murmur across the shunt that connects the right and left coronary artery can be systolic, diastolic, continuous or absent. CAF consists of a communication between a coronary artery and another cardiac chamber: the coronary sinus, right atrium (RA) or right ventricle (RV). The shunt is usually of small magnitude, and myocardial blood flow is not

usually compromised. Potential complications include infective endocarditis, thrombus formation with occlusion or distal embolization of the fistula, rupture of an aneurysmal fistula, and rarely PAH and CHF. A loud superficial continuous murmur usually occurs at the lower or midsternal border.

### Prevalence

APOCA occurs approximately 1 in 300,000 life births. SVAF and CAF are both very rare.

### Molecular and Systemic Pathophysiology

The pathophysiological consequence of ARHS depends chiefly on three factors: the amount of blood flowing through the abnormal communication from the aortic root, the rapidity through which the shunt develops, and the chamber that receives the shunted blood: RA, coronary sinus (CS), RV or the pulmonary artery (PA). Shunted blood must flow through the pulmonary bed, left atrium (LA) and left ventricle (LV) on its way back to the Ao. Hence, volume overload occurs in the left heart chambers and the lungs, and causes PAH and CHF. The recipient cardiac chambers of the shunt as well as the downstream cardiac structures are all dilated secondary to volume overload. In SVAF, an acute rupture gives the heart little chance to adapt and acute progression to CHF occurs; whereas a small perforation is much better tolerated and the progression to CHF is much more gradual. In patients with APOCA, high pressure in the pulmonary trunk (PT) in the fetal and early neonatal provides a perfusion gradient for flow into the anomalous coronary artery. The Ao perfuses the normally originating coronary artery, e.g. right coronary artery (RCA). The subsequent fall in neonatal PA pressure is accompanied by a parallel fall in flow through the LCA. When the pressure in the anomalous LCA falls below the pressure in the RCA, blood then flows from the RCA to LCA via intercoronary anastomosis. The LCA drains into the PA and does not receive blood from it. This causes severe myocardial ischemia, infarction, extensive LV scarring and dilatation. The ischemic cardiomyopathy and the presence of ischemic MR would result in CHF and arrhythmic sudden death.

### Diagnostic Principles

When present, a continuous murmur and its location trigger the suspicion of ARHS. In ARHS, the electrocardiogram (ECG), chest x-ray, transthoracic Doppler echocardiogram (TTE), transoesophageal echocardiogram (TEE), and cardiac magnetic resonance (CMR) may reveal chamber dilatation of the left heart as well as the recipient (and downstream) right-sided heart chambers or structures of a significant shunt. TTE, TEE and CMR may locate the shunt as well as ventricular wall motion abnormalities. EKG may locate the site of MI



and ischemia, especially in APOCA. Cardiac catheterization (CC) with retrograde thoracic aortography and selective coronary angiography locate and quantify the left to right shunt and confirm the diagnosis.

### Therapeutic Principles

Medical management in ARHS consists of measures to relieve CHF, and to treat coexistent arrhythmias and endocarditis. In SVAf, corrective surgery with cardiopulmonary bypass consists of direct closure of the defect and repair of the aneurysm. All efforts should be made to preserve the aortic valve in children because aortic valve replacement greatly increases the operative risk in small patients. Rarely, device closure of the ruptured aneurysm is successful [1]. Small CAF have an excellent long-term prognosis, whereas untreated larger CAF may cause premature coronary artery disease. Hence, for large CAF, coil embolization at the time of CC is the treatment of choice [2] but surgical treatment is still needed in selective cases [3]. Once diagnosed, coronary artery bypass surgery is indicated in APOCA because of the likely progression to malignant arrhythmias, cardiomyopathy and sudden death [4].

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## Aortic Septal Defect

### ►Aortopulmonary Septal Defects

## Aortic Stenosis

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### Synonyms

Calcific aortic stenosis

### Definition and Characteristics

Calcific aortic valve disease is a slowly progressive disorder ranging from fibro-calcific valvular thickening without obstruction of blood flow (aortic sclerosis) to severe calcification of the aortic valve cusps with impaired leaflet motion (aortic stenosis).

### Prevalence

Calcific aortic valve stenosis is the most common heart valve disorder in the elderly in developed countries. The prevalence of this condition increases with age, and is reported for American populations aged  $\geq 65$  years to exceed 2%, and for American/Finnish populations aged  $\geq 75$  years to range from 2.6 to 12.4%.

### Genes

The following genes have been proposed to predispose for the development of calcific aortic stenosis: the B allele of the vitamin D receptor; interleukin ten polymorphisms –1082, –819, and –592; connective tissue growth factor polymorphism –447, and 32-bp deletion polymorphism of the chemokine receptor 5, respectively. Furthermore, a shorter leukocyte telomere length is associated with the development of calcific aortic stenosis.

### Molecular and Systemic Pathophysiology

The aetiologies of calcific aortic stenosis include degeneration, bicuspid aortic valves, familial hypercholesterolemia, hyperuricaemia, hyperparathyroidism, Paget's disease, ochronosis, Fabry's disease, systemic lupus erythematosus, and drug induced valve disease.

For decades, degenerative calcific aortic stenosis was believed to be a primarily age-dependent disease of the valve tissue with passive calcium deposition. Newer studies have pointed out, however, that the pathologic changes in calcific aortic stenosis are based on an actively regulated cellular process of valvular matrix remodelling and biomineralization. On the basis of histopathological, experimental and clinical studies, pathogenesis of the disease is considered as follows: Underlying genetic and cardiovascular risk factors as well as mechanical stress are likely to contribute to the histopathologically demonstrated valvular macrophage and lymphocyte infiltration. An "early lesion" with deposition of lipids that has much in common with the early lesion in atherosclerotic plaques has been described. The leukocytes induce a chronic inflammatory tissue milieu followed by an activation of myofibroblasts and increased cell proliferation by release of pro-inflammatory cytokines, such as interleukin-1 $\beta$  and tumour necrosis factor (TNF)- $\alpha$ . TNF- $\alpha$  mediates the formation of an osteoblast phenotype of local myofibroblasts in stenotic aortic valves. The concomitant expression and activation of



matrix metalloproteinases promotes the profound conversion of the valvular tissue. Tissue calcification and bone formation is further promoted by the release of bone-associated cytokines such as bone-morphogenetic protein-2 and -4, and the activation of osteoblast-specific transcription factors such as Cbfa-1, respectively. Recent studies also suggest neoangiogenesis to be involved in the pathogenesis of aortic valve stenosis (for reference, see also 1).

Valve leaflet thickening, calcific nodule formation, and bone formation might be the end stage of the active disease process described above, and eventually lead to aortic stenosis with an obstruction to left ventricular outflow and an increase in left ventricular afterload. With severe aortic stenosis, left ventricular hypertrophy occurs leading to a loss of myocardial cells, subendocardial ischemia, and fibrosis. Initial symptoms are often due to diastolic left ventricular dysfunction. Eventually, the classical symptoms of angina, non-Q wave myocardial infarction, exertional syncope, and heart failure occur. However, many patients present with more subtle symptoms, typically decreased exercise tolerance, or dyspnoea on exertion.

### Diagnostic Principles

The standard diagnostic evaluation of aortic stenosis includes echocardiographic assessment of leaflet anatomy and the extent of valvular calcification. The severity of aortic stenosis can be graded on the basis of antegrade velocity, mean pressure gradient, and continuity equation valve area [1] (Table 1).

Cardiac catheterization for measurement of the transvalvular gradient is recommended for the rare patient in whom noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of aortic stenosis. However, coronary angiography is recommended before valve surgery in patients with aortic sclerosis at risk for coronary artery disease to determine whether concurrent coronary artery bypass surgery is needed [2]. Exercise testing in asymptomatic patients with aortic stenosis can elicit exercise-induced symptoms

and abnormal blood pressure responses [2]. Additionally, serum neurohormone levels, such as brain natriuretic peptide (BNP), show an association of increased levels with disease severity.

### Therapeutic Principles

Current guidelines recommend surgical aortic valve replacement in patients with severe aortic stenosis once cardiac symptoms (e.g. angina, congestive heart failure, and syncope) are present [3]. The age-corrected survival postoperatively is nearly normalized [4]. The percutaneous implantation of a self-expanding aortic valve bioprosthesis as an alternative to valve surgery is currently subject to research. A future possibility to delay timing of surgical aortic valve replacement may be slowing the disease progression with medical therapy (e.g. statins, [5]).

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**Aortic Stenosis. Table 1** Degrees of severity in aortic valve stenosis

	Transvalvular maximal flow velocity, m/sec	Aortic valve area, cm <sup>2</sup>
Mild aortic stenosis	2.5–3.0	>1.5
Moderate aortic stenosis	3.0–4.0	1.0–1.5
Severe aortic stenosis	>4.0	<1.0

## Aortic Valve Regurgitation

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### Synonyms

Aortic regurgitation; Aortic (valve) insufficiency

### Definition and Characteristics

Aortic valve regurgitation is defined as diastolic reflux of blood from the aorta into the left ventricle due to malcoaptation of the aortic cusps. The regurgitant blood leads to volume overload of the left ventricle. Depending on the acuity of onset, severity of regurgitant volume, etiology of cusp malcoaptation and concomitant cardiac diseases, clinical presentation may vary from absence of symptoms to rapid death [1].

### Prevalence

The exact prevalence of aortic regurgitation is not known. It is estimated that chronic aortic regurgitation has a prevalence of up to 10% in the adult population.

### Genes

In most cases aortic regurgitation is currently considered to be an acquired disease. However, several inherited connective tissue disorders are associated with aortic regurgitation, including Marfan syndrome (mutations of the fibrillin gene), Ehlers-Danlos syndrome (mutations in collagen and procollagen genes), as well as osteogenesis imperfecta (mutations in procollagen genes). More recently, a link between specific genes regulating aortic valve development and aortic regurgitation has been unraveled: Mutations of the transcriptional regulator NOTCH1 have been identified in families with aortic valve diseases, such as bicuspid valves, which facilitate valvular degeneration and subsequent regurgitation [2].

### Molecular and Systemic Pathophysiology

Two major pathophysiologic entities can be distinguished in aortic regurgitation: dilation of the aortic root vs. genuine diseases of the aortic valve.

Clinically, it is critical to differentiate acute and chronic onset of aortic valve regurgitation. *Acute* aortic regurgitation is commonly caused by acute infectious endocarditis, aortic dissection, or blunt chest trauma. Due to the rapid onset and the typically severe degree of regurgitation, the myocardium cannot adapt to the massive volume overload of the left ventricle. Therefore, acute aortic regurgitation often leads to rapid

cardiac decompensation and – if not treated in time – death due to cardiogenic shock. In contrast, *chronic* aortic regurgitation may be asymptomatic for many decades. The most common causes for chronic aortic regurgitation include aortic valve calcification/degeneration (correlating with age), aortic root dilation (often accompanied by arterial hypertension), congenital abnormalities (i.e., bicuspid aortic valves), as well as (subacute) infectious endocarditis. While valve calcification/degeneration has been considered to be purely an age-dependent process, it is increasingly recognized that it is also influenced by genetic factors. Mutations of the NOTCH1 gene impair embryonic aortic valve development and have been shown to cause aortic valve calcification in patients [2]. Activation of osteoblast-specific genes seems to be a key mechanism by which NOTCH1 mutations facilitate aortic valve calcification.

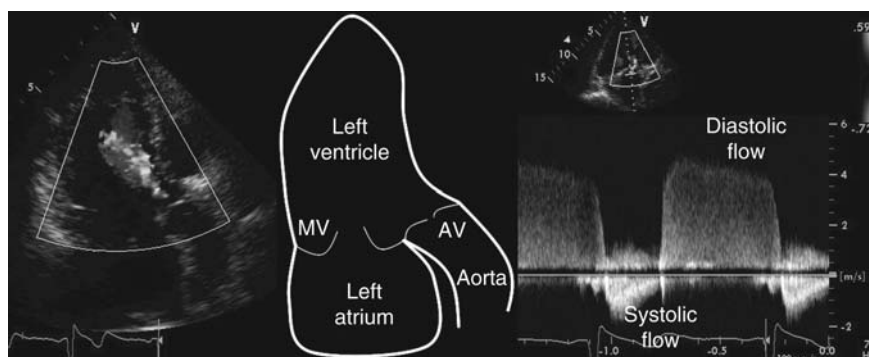
In chronic aortic regurgitation, compensatory mechanisms such as eccentric hypertrophy result in preservation of diastolic compliance and ejection fraction, thereby delaying the onset of clinical symptoms. However, in chronic severe regurgitation, left ventricular dilation and hypertension may further increase wall stress and volume/mass ratio, eventually resulting in decompensation with systolic and diastolic heart failure.

### Diagnostic Principles

On physical examination several signs may indicate aortic regurgitation such as a diastolic decrescendo murmur and high blood pressure amplitudes. The most important diagnostic tool is echocardiography, allowing for measurements of left ventricular dimensions, determination of systolic and diastolic function, morphologic evaluation of the aortic valve and visualization of diastolic regurgitation in Doppler color flow mapping and continuous wave Doppler imaging (Fig. 1). Cardiac catheterization should be applied if preoperative evaluation of the coronaries is mandated and additionally permits grading of aortic regurgitation by supravalvular aortography as well as direct cardiac pressure measurements. More recently, cine magnetic resonance imaging has been introduced to visualize and grade aortic regurgitation noninvasively.

### Therapeutic Principles

In acute aortic regurgitation, rapid aortic valve replacement is the only treatment option for the patient. In chronic aortic regurgitation, a more conservative strategy may be applied. As long as aortic regurgitation is quantified as mild to moderate and ventricular function is not impaired, surgical treatment can be postponed. Pharmacologic treatment does not influence outcome of chronic aortic regurgitation [3]. If severe aortic valve regurgitation is symptomatic and/or left



**Aortic Valve Regurgitation. Figure 1** *Left:* echocardiographic color flow image of a heart with aortic valve regurgitation, showing a regurgitation jet into the left ventricle. *Middle:* schematic representing the anatomy of the echocardiographic image on the left (MV = mitral valve; AV = aortic valve). *Right:* Continuous wave Doppler of the diastolic regurgitation.

ventricular function is impaired, the patient should be referred for aortic valve replacement [4].

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or over. Isolated aortitis (IA) contributing to the fever of unknown origin (FUO) syndrome. It is not evident, GCA and IA are two separate entities, but their clinical courses differ substantially. Other similar aortitis are assumed to be secondary.

## Prevalence

The prevalence is unknown; its incidence is low, with geomorphic, racial, age, and gender affiliation. For TA, the incidence is 0.26/100,000/year, with the male/female ratio (1:8) higher among persons of Asian origin. For GCA, the incidence is 0.17/100,000/year, with the male/female ratio 1:3, in patients aged 50 or over, the incidence is approximately ten times higher. The incidence is higher in Caucasians, in Northern Europeans is more frequently associated with polymyalgia rheumatica. The incidence of IA has not been traced.

## Genes

The effect of any single gene is modest. A risk of GCA was proven in association with different HLA-DRB1 genes, while the risk of TA was associated with HLA-B genes. HLA-B52, B54, HLA-B51, B52, HLA-B52, B39 and HLA- B52, A31. In identical twins, concordance for aortitis is lower than 100%, so the pathogenetic factors must be both genetic and environmental [1]. An environmental impact on the incidence of GCA indicates the proven seasonal fluctuation.

## Aortitis

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## Definition and Characteristics

Aortitis comprises rare disorders of unknown primary cause. Based on clinical features, the primary, non-infectious, granulomatous inflammation of the aortic wall splits into three types: aortitis in Takayasu arteritis (TA), vasculitis of younger patients. Aortitis in giant cell arteritis (GCA), vasculitis of older patients aged 40

## Molecular and Systemic Pathophysiology

It is not evident that the molecular pathophysiology differs between individual granulomatous inflammations of the aortic wall. For the chronic stage, it is evident that the histological patterns of primary and secondary aortitis are similar.

The recent theory of the formation of GCA in noninfectious medium-sized arteries clarifying documented observations is limited because some parts remain unexplained [2]. Information concerning the pathophysiology of aortitis is less comprehensive, based only on the examination of the specimens of surgically treated aortic aneurysms. In contrast to arteritis, the chronic stage of the granulomatous inflammation of the aortic wall is not associated with medial hyperplasia, but with weakening due to medial degeneration and laminar medial necrosis, followed by the dilatation of the diameter of the aorta.

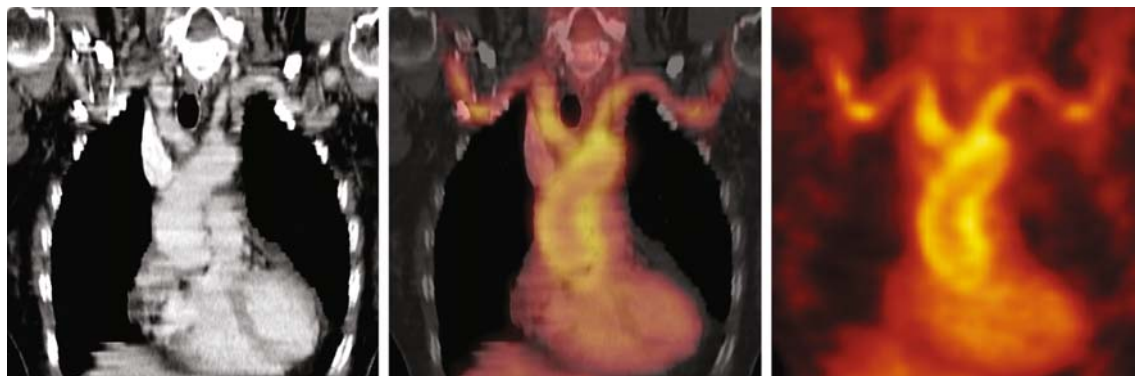
The granulomatous inflammation of the vessel wall is the result of two different immunopathogenetic processes. The inflammation is ignited by the activation of innate immunity and develops into a loss of self-tolerance in the artery wall [2].

The innate immune system is represented by immature and quiescent myeloid dendritic cells (mDCs) in the adventitia. The cells express Toll Like Receptors (TLR) TLR2 and TLR4, ready to bind to PAMPs (pathogen-associated molecular patterns); when triggered by PAMPs, undergo maturation, turn into chemokine-producing cells. Acute-phase responses are generated via a cascade of signals with Interleukin-1 (IL-1) and IL-6 as a main stimulator of acute-phase proteins. Matured mDCs bridge innate and adaptive

immunity, developing into professional antigen presenting cells (APC), activating CD4+ T cells. CD4+ T cells release IL-2 and IF- $\gamma$ , and regulate the differentiation and function of tissue-infiltrating macrophages. Macrophages residing in the adventitia stimulate T-cell production by pro-inflammatory cytokines IL-1 $\beta$ , IL-6, and TGF- $\beta$  (transforming growth factor). Macrophages in the smooth-muscle cell layer are responsible for oxidative stress and the production of matrix metalloproteinase, the principal instruments evident in the lipid per-oxidation, injury of the smooth-muscle cells, the fragmentation of the internal elastic lamina, and the thinning of the media. The role of the nitric oxide synthetase-2 released by macrophages residing in the adventitia is not understood. As a result of the immune impairment of the vessel wall, macrophages release mediators (e.g., growth- and angiogenic-factors, endothelial growth factor), inducing the angiogenesis, the proliferation, and migration of myofibroblasts, accompanied by a deposition of intracellular matrix [2].

### Diagnostic Principles

The acute phase of aortitis is clinically not characterized by any disease-specific symptom (headaches, malaise, fatigue, weight loss, anorexia, night sweat, and fever). Laboratory tests commonly show an



**Aortitis. Figure 1** FDG-PET/CT imaging of ascending aorta, aortic arch and its branches. CT imaging on the left, PET imaging on the right, fused imaging PET/CT in the middle. No systemic or local infection was found in a 60-year-old woman who had been complaining of fever for 6 weeks. Elevated CRP, erythrocyte sedimentation ratio, malaise, and fatigue were observed. The complaint diminished spontaneously during the last 2 weeks before the FDG-PET/CT investigation without any therapy. A slightly wider, hypodense aortic wall was detected on CT scan. PET revealed a significantly increased FDG uptake in the wall of aorta and its main branches as a sign of inflammation. The spontaneous decrease of clinical symptoms with the gradual normalization of laboratory tests makes isolated aortitis the obvious cause of FUO in this patient. The main advantage of FDG information is the *in vivo* imaging of glucose metabolism, the main disadvantage is its inability to translate the signs of hypermetabolism into proper histopathology. It is difficult to differentiate high consumption of glucose in malignant and inflammation processes. Furthermore, in the diagnostics of aorta wall inflammation, the primarily noninflammation hypermetabolic processes (e.g., high metabolic activity of macrophages in vulnerable atherosclerotic plaques or higher uptake of FDG in lamina muscularis in patients with arterial hypertension) are potential pitfalls.



abnormally elevated erythrocyte sedimentation ratio, a high white cell count, elevated alkaline phosphatase levels, and anemia. The chronic phase of aortitis is clinically silent until the dilatation of the aorta, or aortic valve regurgitation. In the histological differential diagnosis, it is still unclear whether histological features exist to separate clinically distinguishable types of aortitis [3]. CT images correctly the lumen of the aorta. MRI proves the inflammation changes by an enhancement in the aorta wall. To the diagnosis of inflammation, the in vivo imaging of glucose metabolism (Fig. 1) by FDG-PET or FDG-PET/CT contributes substantially [4,5]. But, in the diagnostics of aorta wall inflammation, the primarily non-inflammation hypermetabolic processes (e.g., high metabolic activity of macrophages in vulnerable atherosclerotic plaques or higher uptake of FDG in lamina muscularis in patients with arterial hypertension) are able to cause pitfalls.

### Therapeutic Principles

In the acute phase, almost all patients respond to initial doses of prednisone. Depending on residual clinical activity, the dose is titrated to lower levels. In an unknown number of patients with FUO, the symptoms of aortitis can subside spontaneously, without prednisone therapy. The use of the immunosuppressive agent methotrexate is not superior to prednisone. The chronic stage of aortitis manifested by dilatation or aneurysm of the aorta, or aortic valve regurgitation, has to be treated surgically.

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## Aortopulmonary Septal Defects

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### Synonyms

Aortopulmonary window; Aortopulmonary fenestration or fistula; Aortic septal defect; Partial persistent truncus arteriosus; APSD

### Definition and Characteristics

Aortopulmonary septal defect (APSD) is a rare congenital cardiac abnormality defined as a communication between adjacent portions of the ascending aorta (AAo) and the pulmonary artery (PA), with the presence of separate semilunar valves. APSD may exist as an isolated lesion, the rest (47–77%) are found in conjunction with other congenital heart disease, including patent ductus arteriosus, ventricular septal defects (20%) tetralogy of Fallot (6%), right aortic arch (5–20%), transposition of the great arteries (10%), interrupted aortic arch (8%), coarctation of the aorta (13–20%) and coronary artery anomalies (23%) [1]. APSD is subdivided into three subtypes. Type I occurs between the origin of the main PA and the posteromedial wall of AAo immediately above the sinus of Valsalva. Type II describes a communication between the AAo and the origin of the right PA. It involves the anomalous origin of the right PA from the aorta. Type III is a defect between the PA and the majority of the AAo together with a Type II defect; here the right PA arises from the posterior or posterolateral AAo, and is completely separate from the main PA trunk. Most APSD is large and the blood flow is from left to right after birth. The common presentation is that of early congestive heart failure (CHF), irreversible pulmonary hypertension (PH), acute decompensation from intercurrent infections and death. Only a minority of patients with uncorrected APSD reaches their teens or young adulthood. The patients with smaller APSD are underdeveloped, tachypnoeic and have a tendency toward recurrent respiratory infections. Physical signs include bounding arterial pulse with wide pulse pressure, cardiac enlargement with a prominent apical impulse. The murmur of APSD is loud and harsh, and can be holosystolic or early systolic. Alternatively it can

## Aortopulmonary Fenestration or Fistula



be continuous in restrictive APSD which accounts for 20% of all APSD cases. The murmur is usually loudest in the third left intercostal space. Other murmurs include Graham Steell murmur resulting from a dilated pulmonary trunk, and an apical mild diastolic mitral murmur caused by increased flow. When the flow across the APSD shunt is reversed from the development of suprasystolic PH, patients would develop increasing generalized cyanosis, a loud pulmonic ejection murmur, a loud single second beat, the stigmata of the Eisenmenger complex, and the disappearance of the systolic murmur across the defect.

### Prevalence

APSD is a rare defect consisting of about 0.1–0.6% of congenital heart disease. The male to female ratio is about 1.8:1 and no racial trend exists.

### Molecular and Systemic Pathophysiology

The aberrant embryogenesis of APSD originates from the incomplete fusion and/or malalignment of the right and left conotruncal ridges which may cause defective and unequal partitioning of the aortopulmonary (AP) trunk (Type I) and a more posterior and dorsal aorta. The abnormally positioned aorta may then connect to the right sixth aortic arch, which is the precursor of the right PA. Hence, the right PA may connect to the main PA as well as having an orifice into the aorta (Type II), giving rise to the anomalous origin of the right PA from the AAo. The pathophysiology of APSD is closely related to the size of the defect, the direction of blood flow across the shunt and the development of pulmonary hypertension. Regardless of the size, APSD does not affect the fetus. After birth, the fall in pulmonary vascular resistance (PVR) causes progressive shunting of blood from the systemic to the pulmonary circuit across the APSD. This results in PH, CHF and the development of pulmonary vascular obstructive disease which eventually would progress to shunt reversal and the Eisenmenger complex. The above progression is also highly dependant on the nature of the other congenital heart lesions if present.

### Diagnostic Principles

The diagnostic features of APSD are dependant on the size and direction of the shunt, the presence of PH and associated congenital abnormalities. Differential diagnosis includes coronary artery anomalies, large patent ductus arteriosus, truncus arteriosus, pulmonary arteriovenous fistula, ruptured sinus of Valsalva aneurysm, and ventricular septal defect. Echocardiogram is usually the method of choice for the diagnosis of APSD [2]. It shows enlarged cardiac chambers and measures PA pressure; the APSD can best be delineated with color flow Doppler. Cardiac magnetic resonance angiography can accurately visualize and measure the size of the

APSD. Cardiac catheterization performed before surgery can identify a shunt at the level of the PA and assess the extent of PH and related congenital abnormalities. Selective aortography and manipulation of the catheter from the main PA directly to the AAo confirm the diagnosis.

### Therapeutic Principles

As most APSD are large, irreversible PH occurs early. Hence, surgical closure is ideally performed in the first few months of life [3]. Currently, the procedure of choice involves transaortic closure of the APSD by direct suture (small defects) or by using a prosthetic patch (large defects) while providing cardiopulmonary bypass [4,5]. Stenosis of grafts or surgical sites of the APSD repair are the most common long term complications. Patients should also receive bacterial endocarditis prophylaxis for life.

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## Aortopulmonary Window

### ► Aortopulmonary Septal Defects

## APC Resistance

### ► Thrombosis, Venous, Factor V Leiden, Resistance against Activated Protein C

## APECED

### ► Polyendocrinopathy Ectodermal Dystrophy, Auto-immune

## APECED Syndrome

### ► Multiple Endocrine Abnormalities

## Aperistalsis

### ► Achalasia

## Apert Syndrome

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### Synonyms

Acrocephalosyndactyly

### Definition and Characteristics

Apert syndrome (AS) represents one of the most common and severe syndromic forms of craniosynostosis (premature fusion of one or more cranial sutures). Unlike other craniosynostosis syndromes, AS is additionally characterized by syndactyly (fusion of one or more digits) and dermatological manifestations. Central nervous system, cardiovascular, respiratory, urogenital, and other visceral defects occur less frequently.

### Prevalence

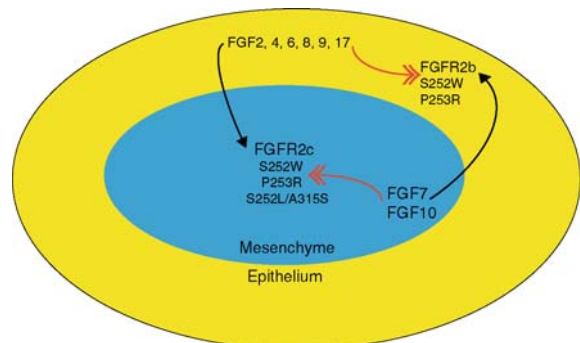
Apert syndrome (AS) is inherited in an autosomal dominant fashion with a prevalence of about 1 in 70,000 births [1]. The incidence of AS increases with advanced paternal age and is believed to result from mutations arising in the male germ cells that confer a selective survival advantage on sperm cells [2].

### Genes

AS results from mutations in the gene encoding fibroblast growth factor receptor 2 (FGFR2), located on chromosome 10q26 [3]. Mutations in FGFR2 are also responsible for other craniosynostosis syndromes

including Crouzon syndrome (CS), Pfeiffer syndrome (PS), and Jackson-Weiss syndrome (JWS). FGFR2 is one of four members of the FGFR family (FGFR1–4) of receptor tyrosine kinases and consists of an extracellular portion composed of three immunoglobulin-like domains (D1–D3), a single transmembrane helix, and an intracellular portion with tyrosine kinase activity. A tissue-specific alternative splicing event in D3 creates epithelial FGFR2b and mesenchymal FGFR2c, each of which binds selectively to a unique subset of the eighteen human FGFs that are expressed in the opposite tissue as their respective FGFR2 isoform [4]. This leads to the establishment of a paracrine signaling circuit between mesenchyme and epithelium that is fundamental for organogenesis and tissue homeostasis (Fig. 1). Both crystallographic and biochemical data demonstrate that FGFs interact with D2, D3 and the short interconnecting D2–D3 linker region.

Two canonical missense mutations, S252W and P253R, which map to the D2–D3 linker region of FGFR2, account for 67 and 32% of AS cases, respectively [3]. Rare cases of AS result from a S252F mutation and Alu-element insertions in the intron preceding or within the “c” isoform specific exon of the FGFR2 gene. A S252L/A315S double mutation in FGFR2 results in an atypical form of AS, characterized by syndactyly in the absence of craniosynostosis. Consistent with the location of the canonical AS mutations, which precede the alternatively spliced region of FGFR2, the AS mutations have been detected in both FGFR2c and FGFR2b splice isoforms. However, because many of the related craniosynostosis syndromes, including CS and PS, are caused by mutations in the “c” specific exon of FGFR2, it is likely that the AS mutations predominantly act by affecting FGFR2c, and not FGFR2b [5].



**Apert Syndrome. Figure 1** Schematic of the FGFR2 epithelial-mesenchymal paracrine signaling loop in normal human development (black arrows). AS mutations short circuit normal signaling mechanisms (red double headed arrows) by creating autocrine signaling loops.

## Molecular and Systemic Pathophysiology

Biochemical analysis of several CS mutations demonstrates that these mutations activate FGFR2c constitutively (in the absence of FGF) by inducing the formation of intermolecular disulfide-bridged FGFR2c dimers. In contrast, *in vitro* binding and cellular studies showed that FGFR2c harboring the AS mutation retained FGF-dependency. Interestingly, AS patients with the S252W mutation have a more severe craniofacial phenotype, whereas AS patients with the P253R mutation present with more severe syndactyly. This, taken together with the observation that craniosynostosis and syndactyly can either occur in combination or individually, has led to the hypothesis that distinct pathophysiological mechanisms give rise to craniofacial and limb abnormalities in AS. Indeed, recent structural and biochemical studies have shed light onto how the dissociation of craniofacial and limb phenotypes occurs in AS [4,5].

The crystal structures of S252W FGFR2c and P253R FGFR2c bound to FGF2 have revealed the molecular basis by which these AS mutations lead to FGF-dependent FGFR2c gain-of-function. Each AS mutation is shown to create additional but distinct ligand-receptor interactions, thereby leading to enhanced FGFR2c-FGF binding affinity. Ser252Trp FGFR2c makes additional hydrophobic contacts with the N-terminal region of FGF2 [4]. In contrast, Pro253Arg FGFR2c makes additional hydrogen bonds with the core loop region of FGF2 [4]. Analysis of the effect of the AS mutations on ligand binding affinity/specificity of FGFR2c revealed that the two canonical AS mutations increase the binding affinity of FGFR2c to all FGFs, including FGF10, an FGF ligand that normally does not bind to wild-type FGFR2c [5]. In contrast, the atypical S252L/A315S double mutation leads to an increase in binding to FGF10 mainly [5]. Based on these data, the syndactyly phenotype in AS is proposed to manifest from illegitimate autocrine FGFR2c-FGF10 binding and signaling in the mesenchyme (Fig. 1) [1,5].

This hypothesis also accounts for the more severe syndactyly in P253R AS patients than in S252W patients, as P253R FGFR2c binds with greater affinity to FGF10 than S252W FGFR2c does. This model of syndactyly is also consistent with the finding that Alu-insertions (responsible for rare cases of AS) lead to the ectopic mesenchymal expression of FGFR2b, and thus also permit illegitimate autocrine FGF10 signaling in the mesenchymal tissue of these patients [1,5].

These binding studies also reveal a direct correlation between the severity of craniosynostosis phenotype in AS and the differential ability of the AS mutations to cause an overall increase in FGFR2c binding affinity towards multiple FGFs. The S252W mutation, which is associated with more a severe craniofacial phenotype,

results in greater enhancement in FGFR2c binding to most FGF ligands, relative to the P253R mutation. Moreover, the inability of the S252L/A315S double mutation to confer a widespread increase in FGFR2c-FGF binding explains the lack of craniosynostosis in patients harboring the S252L/A315S double mutation. The widespread enhancement of FGF binding by the AS mutations will lead to a global elevation of mutant FGFR2c signaling that is parallel to the FGF-independent increase in FGFR signaling causing CS and nearly all cases of PS [5].

## Diagnostic Principles

The diagnosis is suggested by craniosynostosis in the presence of syndactyly patient and confirmed by mutational analysis.

## Therapeutic Principles

AS and other craniosynostosis syndromes are currently managed using a multidisciplinary approach relying primarily upon multiple surgical interventions to repair craniofacial and hand/foot anomalies. With the recent advances in our understanding of the molecular basis for FGFR2 gain-of-function in AS, the non-surgical management of AS with inhibitors of FGFR signaling may soon be an exciting possibility [5].

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## Aphthous Ulcers

### ► Recurrent Aphthous Ulcers

## Aplasia Pilonum Intermittens

### ► Monilethrix

## Apo B Deficiency

### ► Abetalipoproteinemia

## Apo C-II Deficiency

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### Synonyms

APOC2 deficiency; Hyperlipoproteinemia type Ib; C-II anapolipoproteinemia

### Definition and Characteristics

Autosomal recessive defect of apolipoprotein C-II (apo C-II), the cofactor of lipoprotein lipase (LPL), leading to excessive fasting hypertriglyceridemia and chylomicronemia.

As a result of the hypertriglyceridemia the patients may suffer from pancreatitis, eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. Heterozygous carriers are typically normolipidemic. Clinically and biochemically, apo C-II deficiency closely mimics LPL deficiency.

### Prevalence

Extremely rare, <1:10<sup>6</sup>.

### Genes

APOC2, localized on chromosome 19q13.2, contains four exons, overall length 3,570 bp, a single transcript of 717 bp. An overview of published mutations is shown in [Table 1](#).

### Molecular and Systemic Pathophysiology

The mature apo C-II is a 79 amino acid exchangeable apolipoprotein. In humans, the major site of expression is the liver, a minor site is the intestine. Apo C-II is always lipid-bound and can be found on the surface of chylomicrons, chylomicron remnants, very low density (VLDL), intermediate density (IDL) and high density lipoproteins (HDL). Amphipathic helices, responsible

**Apo C-II Deficiency. Table 1** Mutations in the APOC2 gene

Position	Molecular defect	Synonym	Lipoprotein disorder
Promoter and Exon 1	Deletion	ApoCII-CIV Nijmegen	Familial chylomicronemia
Promoter -86A > G	No expression		Familial chylomicronemia
Met-22Val	No initiation	Paris-1	Familial chylomicronemia
Arg-19STOP	Truncation	Paris-2, Barcelona	Familial chylomicronemia
Gln2	Deletion, followed by premature STOP	Venezuela	Familial chylomicronemia
Intron 2 + 1G > C	Donor splice defect	Hamburg, Tokyo	Familial chylomicronemia
Gln17	Deletion, followed by premature STOP	Nijmegen	Familial chylomicronemia
Lys19Tyr			Hyperlipidemia
Trp26Arg		Wakayama	Familial chylomicronemia
Tyr37STOP	Truncation	Bari, Padova	Familial chylomicronemia
Glu38Lys		San Francisco	Hyperlipidemia
Lys55Gln		African	–
Tyr63STOP	Truncation	Auckland	Chylomicronemia
Thr68	Deletion, followed by premature STOP	Toronto	Familial chylomicronemia
Gln70Pro	Insertion, followed by altered 26 aminoacids	St Michael	Familial chylomicronemia
Leu72Pro			Familial chylomicronemia

for lipid binding, were predicted for residues 14–39 and 43–55 [1].

Apo C-II is the requisite cofactor of LPL (EC 3.1.1.34), an enzyme catalyzing the hydrolysis of triglycerides on lipoproteins, and therefore plays an essential role in plasma triglyceride metabolism. The structures needed for activation of LPL reside within the C-terminal one-third of apo C-II, concentrated in a third helix [2,3]. Activation of LPL by apoC-II depends on the ability of apoC-II to bind LPL and stabilize a ternary complex with the lipoprotein substrate. In addition to this bridging function apo C-II binding may also induce a change in LPL conformation to expose the active site of the enzyme, normally covered by a lid-domain.

Interestingly transgenic mice overexpressing the human apo C-II gene are hypertriglyceridemic, suggesting that apo C-II has functions in the metabolism of plasma triglycerides beyond activating LPL [4].

### Diagnostic Principles

Absence of apo C-II in serum/plasma; missing or extremely low activity of LPL in post heparin plasma, which can be restored by exogenous heat inactivated plasma as a source of apo C-II.

### Therapeutic Principles

There is no gene therapy and no pharmacological therapy available. Fibrates upregulate LPL but there exist no data whether enhanced LPL mass may improve the condition. Dietary therapy exists in the form of a low fat diet, supplemented with medium chain fatty acids. Other treatments include infusion of plasma as apo C-II source [5].

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## APOC2 Deficiency

### ► Apo C-II Deficiency

## Apolipoprotein B Deficiency

### ► Bassen-Kornzweig Syndrome

## Apoptosis

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### Synonyms

Programmed cell death type 1

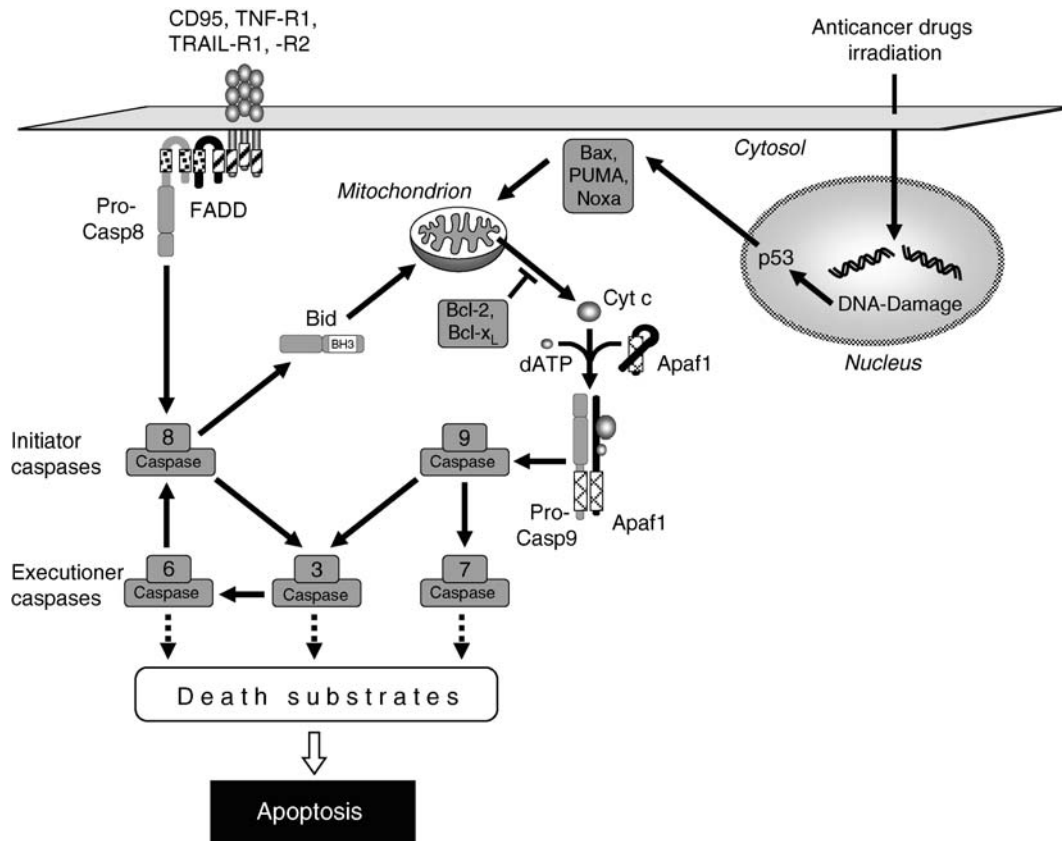
### Definition and Characteristics

Apoptosis plays a major role during embryonic morphogenesis and in tissue homeostasis in the adult organism. The major executioners of the endogenous suicide program are cysteine proteases of the caspase family that are activated upon partial proteolysis. Usually initiator-caspases are activated in high molecular weight complexes and activate downstream located effector-caspases. There exist two major apoptosis signaling pathways – the extrinsic death receptor pathway that enables cytotoxic T lymphocytes to eliminate virus-infected cells and tumor cells and the intrinsic mitochondrial death pathway that is activated upon cellular stress and is the major executioner of DNA damage-induced cell death in tumor cells upon radio- and chemotherapy (Fig. 1) [1].

### Prevalence

Embryonic morphogenesis. In the adult organism: elimination of autoreactive thymocytes, downregulation of the immune response, elimination of tumor cells and virus-infected cells. As an antagonist of mitosis responsible for cell homeostasis.





**Apoptosis. Figure 1** The two major signaling pathways of apoptosis. The death receptor pathway (*left*) is initiated upon receptor ligation, resulting in the recruitment of the adapter protein FADD. FADD in turn recruits the initiator-caspase-8 which undergoes autoproteolytic activation at the receptor complex. The mitochondrial death pathway (*right*), could be activated by many apoptotic stimuli, such as DNA-damaging agents (anticancer drugs or irradiation). DNA-damage can activate the tumor suppressor p53 that in turn induces the expression of pro-apoptotic Bcl-2 members (Bax, Puma and Noxa) which induce the release of cytochrome c into the cytosol. Cytochrome c, after hydrolysis of (d)ATP, binds to the adaptor Apaf-1 and in turn activates the initiator-caspase-9. Expression of anti-apoptotic Bcl-2 proteins (Bcl-2 or Bcl-xL) inhibits the release of cytochrome c from the mitochondrion and thus the activation of the mitochondrial death pathway. Activation of both pathways via initiator caspase-8 or -9 leads to the activation of effector-caspases (caspase-3, -6 and -7) that after cleavage of vital death substrates induce the final demise of the cell. Because caspase-8 cleaves the Bcl-2 protein Bid and generates a truncated, pro-apoptotic BH3-containing fragment that induces cytochrome c release, both pathways are interconnected.

## Genes

See [Table 1](#).

## Molecular and Systemic Pathophysiology

Defects in apoptosis signaling can affect cell homeostasis. Thus, tumors tend to inhibit the apoptotic machinery (e.g., by inactivation of p53, Apaf-1, Bax, Bak or overexpression of Bcl-2, Bcl-xL, Mcl1) and thereby develop resistance to radio- and chemotherapy. Defects in apoptosis signaling are also associated with autoimmune diseases (e.g., rheumatoid arthritis). Defective elimination of apoptotic cells (defects in C1q, C4) can also contribute to autoimmune diseases,

such as lupus erythematosus [2]. An excess of apoptosis occurs during hepatitis, neurodegeneration (multiple sclerosis, Alzheimer disease, Parkinson disease), apoplexy and cardiac infarction.

## Diagnostic Principles

So far, parameters in apoptosis signaling have not entered routine diagnosis. However, since tumors with a defective mitochondrial death pathway comprise resistance to radio- and chemotherapy, the function and expression levels of pro-apoptotic Bcl-2 members (such as Bax, Bak, Bim, Puma, Noxa) and anti-apoptotic Bcl-2 members (such as Bcl-2, Bcl-xL,

**Apoptosis. Table 1**

Pro-apoptotic factors	Description
CD95L, TNF $\alpha$ , TRAIL	Death ligands
CD95/Apo-1/Fas, TNF-R1, TRAIL-R1, TRAIL-R2	Death receptors
Bax, Bak, Puma, Noxa, Bid, Bim, Bad	Bcl-2 members
Caspase-3, caspase-6, caspase-7	Executioner caspases
Caspase-8, caspase-9	Initiator caspases
p53	Tumor suppressor
Cytochrome c, Smac, Diablo	Activators of the mitochondrial death pathway
Apaf-1	Adapter protein in mitochondrial apoptosis pathway
FADD	Adapter protein in death receptor pathway
Anti-apoptotic factors	
Bcl-2, Bcl-xL, Mcl-1	Bcl-2 members
XIAP	Inhibitor of caspase-3, -7, -9
FLIP	Inhibitor of death receptor pathway

Mcl-1) or Apaf-1 might serve as valuable diagnostic parameters for tumor therapy in the future. In addition, annexin V is used as a tracer for molecular imaging of tumor apoptosis in preliminary clinical studies in order to evaluate the response to radio- and chemotherapy.

### Therapeutic Principles

Commonly, chemo- and radiotherapy eliminate tumors by induction of apoptosis. Death receptor ligands (TRAIL, TRAIL-receptor agonists (mapatumumab, lexatimumab), TNF $\alpha$ ), and activators of the mitochondrial apoptosis pathway like BH3-mimetic inhibitors of Bcl-2 proteins (ABT-737) are used in first clinical trials [3].

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### APS1

► Polyendocrinopathy      Ectodermal      Dystrophy, Autoimmune

### ARCL1

► Cutis Laxa

### ARCL2

► Cutis Laxa

### APRT Deficiency

► Adenine Phosphoribosyltransferase Deficiency

### Arctic-Type

► Cerebral Amyloid Angiopathies, Hereditary

## ARF

### ► Rheumatic Fever, Acute

## Arginine-Glycine Amidinotransferase Deficiency

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### Synonyms

AGAT deficiency; Creatine deficiency syndrome

### Definition and Characteristics

Autosomal recessive deficiency of creatine synthesis [1]. Main clinical manifestations include mental retardation and epilepsy. Affected patients appear normal at birth and develop first symptoms within the first months or years of life [2,3].

### Prevalence

The true prevalence is unknown. Since its first description in 2001, only four patients from two different families have been diagnosed. Three cases have been published [1–3].

### Genes

The human AGAT gene (OMIM#602360) has been mapped to chromosome 15q15.3. The AGAT genomic DNA is 16,858 bp long (genomic DNA: GenBank accession no. 1432573), and consists of nine exons (mRNA: GenBank accession no. S68805). AGAT [2.1.4.1] is localized in the mitochondrial intermembrane space and has also been found in the cytosol. AGAT is expressed at high levels in kidney, liver, and pancreas and is detectable also in other organs such as muscle, brain, and testis.

### Molecular and Systemic Pathophysiology

Creatine is synthesized mainly in liver, kidney, and pancreas by two enzymatic reactions catalyzed by arginine:glycine amidinotransferase (AGAT) and by

guanidinoacetate methyltransferase (GAMT). Creatine is transported via the blood stream to tissues including skeletal muscle and brain and taken up against a large concentration gradient via an active sodium dependent creatine transport system (CRTR). AGAT catalyzes the first of the two reactions in creatine biosynthesis, effecting the transfer of the amidino group from arginine to glycine and formation of ornithine and guanidinoacetate, the immediate precursor of creatine.

Deficiency of AGAT activity results in deficiency of both, creatine and guanidinoacetate, mainly in brain and body fluids. In humans with AGAT deficiency, no substrate accumulation (glycine and arginine) could be demonstrated [2,3]. This points to the fact that only minor amounts of both amino acids are substrates for creatine synthesis, while major amounts are utilized in other metabolic pathways. Deficiency of creatine in the brain results in loss of capacity of the creatine/creatine-phosphate system to store and transmit phosphate bound energy. In the three cases published so far, a point mutation resulting in a stop codon on exon 3 (T149X) has been found [1,3]. AGAT deficiency is a model of brain creatine deficiency. Animal models for AGAT deficiency do not exist so far, but as soon as available, they will provide an ideal tool for the investigation of the potential neuroprotective effects of creatine.

### Diagnostic Principles

Lower than normal levels of guanidinoacetate in body fluids is characteristic of AGAT deficiency. Therefore determination of this compound in urine, plasma, and/or CSF is the first diagnostic hint. Methods for determination of guanidinoacetate are mainly based on gas chromatography–mass spectrometry and tandem mass spectrometry. For diagnosis of AGAT deficiency, these methods must be sensitive enough to detect lower than normal levels. Additional diagnostic clues are deficiency of creatine/creatine phosphate in the brain as determined by in vivo proton magnetic resonance spectroscopy, and abnormally low urinary creatinine excretion, which is directly proportional to the intracellular body creatine pool. Diagnosis is confirmed by mutation analysis. Determination of AGAT activity is possible in fibroblasts and virus transformed lymphoblasts. So far, no experience is available with prenatal diagnosis.

### Therapeutic Principles

Oral substitution of creatine corrects brain creatine deficiency and leads to considerable but incomplete clinical improvement [2,5]. It is not known so far, if early recognition (e.g., by newborn screening) and presymptomatic treatment might lead to a better outcome.

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## Argininosuccinic Acid Lyase and Arginase Deficiency

- Hyperammonemia

## Argininosuccinic Acid Synthetase Deficiency

- Hyperammonemia

## ARHS

- Aortic Root to Right Heart Shunts

## Arias Syndrome

- Crigler-Najjar Syndrome

## Arndt-Gottron Scleromyxedema

- Scleromyxedema

## Aromatic L-Amino Acid Decarboxylase Deficiency

- Catecholamine Deficiency

## AROS

- Okiihiro Syndrome

## ARPKD

- Polycystic Disease (Kidney)

## Arrhythmia, Cardiac in Adults with Congenital Heart Disease

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### Synonyms

Atrial flutter; Atrial fibrillation; Atrial tachycardia; AV accessory pathways; Ventricular tachycardia; Atrioventricular nodal reentrant tachycardia; AVNRT

### Definition and Characteristics

Due to the success of corrective surgical procedures for congenital heart disease (CHD), many more patients

**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Table 1** Arrhythmias associated with surgically corrected congenital heart defects

Atrial septal defect (ASD)
• Atrial flutter
• Atrial fibrillation
Ebstein's anomaly
• Atrial tachycardia
• AV Accessory pathways
• Atrial flutter
• Atrial fibrillation
• Ventricular tachycardia
Post Fontan operation
• Atrial flutter
Tetralogy of Fallot
• Atrial flutter
• Atrial fibrillation
• Ventricular tachycardia
Transposition of the great arteries
• Atrial flutter
• Atrial tachycardia
• Atrioventricular nodal reentrant tachycardia (AVNRT)
• Ventricular tachycardia

are now reaching adulthood. Increased survival of these patients has been associated with an increasing number of arrhythmic problems (Table 1). Atrial arrhythmias are most common, but ventricular arrhythmias may also be seen. Arrhythmias may occur as a result of structural changes, due to the effects of pressure or volume overload, or may be a result of reentrant circuits created by suture lines and/or patches placed. Atrial stretch as a result of pressure or volume overload affects atrial refractoriness potentiating the vulnerability to induction of atrial arrhythmias such as atrial flutter or fibrillation. Progressive fibrosis of the right ventricle with areas of slow conduction, coupled with the presence of scars and patches from corrective surgical procedures leads to anatomic substrates required for sustaining ventricular tachycardia (VT). Right ventricular dilatation and stretch with areas of slowed ventricular activation may contribute to the creation of reentrant circuits within the right ventricle.

### Prevalence

*Atrial Septal Defect (ASD):* The most common arrhythmias seen in adults who have had surgical repair

of atrial septal defects are atrial flutter and atrial fibrillation [1]. Approximately 60% of these patients will develop atrial flutter or atrial fibrillation, particularly those older than 40 years of age.

*Ebstein's Anomaly:* About one third of patients with Ebstein's anomaly have an arrhythmia, most commonly AV reentrant tachycardia, Wolff-Parkinson-White Syndrome related tachycardias and to a lesser extent, atrial tachycardia, atrial flutter, atrial fibrillation, and VT. Atrial arrhythmias are encountered more frequently with increasing age and duration of follow-up [2].

*Tetralogy of Fallot:* Sustained VT has a prevalence of 4–7% and usually has left bundle branch block-like morphology secondary to a reentrant rhythm originating from the right ventricular outflow tract. Non-sustained ventricular arrhythmias detected by Holter monitoring is present in up to 60% of patients. It has low predictive value for subsequent sustained VT or sudden cardiac death (SCD) in these patients. There is a small, but persistent risk of late SCD in patients following Tetralogy of Fallot surgery, with an estimated incidence of 0.5–6%. Older age at initial repair, moderate or severe pulmonary regurgitation, a history of sustained VT, moderate or severe left ventricular dysfunction, a QRS duration of 180 ms or greater and a rapid increase in QRS duration are predictive of risk for sudden cardiac death [4].

Risk factors for sudden cardiac death in patients with repair of Tetralogy of Fallot:

- Older age at initial repair
- Moderate or severe pulmonary regurgitation
- History of sustained ventricular tachycardia
- Moderate or severe left ventricular dysfunction
- QRS duration of 180 ms or greater
- Rapid increase in QRS duration

*Transposition of the Great Arteries (TGA):* In the adult patient post Mustard repair, there is a high incidence of systemic right ventricular dysfunction associated with late atrial arrhythmias. Also present, is a higher risk of SCD, reported at 7% on long-term follow-up, attributed to ventricular arrhythmias or atrial flutter with 1:1 AV conduction degenerating into ventricular fibrillation, and asystole. An increased QT dispersion is a marker for the presence of heterogeneity of ventricular repolarization, with rapid heart rates due to physical stress, atrial flutter and ectopic ventricular beats serving as triggers for reentrant ventricular arrhythmias. Increased QT dispersion and the loss of sinus rhythm have been associated with SCD in these patients. At long-term follow-up of adult patients post Mustard repair, only one-third remained arrhythmia-free. A progressive loss of sinus rhythm has been observed at a rate of 2.4%/year with sinus rhythm present in 77% at 5 years and 40% at 20 years. Loss of sinus rhythm has been associated with previous septectomy,



postoperative bradycardia, late atrial flutter, and preoperative arrhythmias. The loss of sinus rhythm in patients after Mustard repair is in contrast to the long-term maintenance of sinus rhythm in 95–98% of patients who have undergone an arterial switch operation.

A large population based study has estimated the incidence of late *sudden cardiac death* (SCD) in patients with congenital heart disease who have undergone surgery to be 0.9/1,000 patient-years. There is an increased incidence of SCD in patients with tetralogy of Fallot, transposition of the great arteries (TGA), coarctation of the aorta and congenital aortic stenosis. The event rate for the group of patients with obstructive left heart lesions and cyanotic defects is 2.2/1,000 patient-years compared to a rate of 0.14/1,000 patient-years in those with left to right intra-cardiac shunt lesions or pulmonic stenosis. While the most common cause of SCD is arrhythmic in origin, embolic events, aneurysm rupture, and acute ventricular failure have been reported as well. The risk of SCD after repair of transposition of the great arteries starts early after repair and remains high thereafter. The rate of SCD is approximately 4% at 10 years and 9% at 20 years. In contrast, the risk of SCD after repair of tetralogy of Fallot is 2.2% at 20 years, 4% at 25 years and 6% at 30 years.

### Molecular and Systemic Pathophysiology

**Atrial Septal Defect (ASD):** Early closure of an ASD has been shown to reduce long-term occurrence of atrial arrhythmias. Predictors of late post-operative atrial arrhythmias include older age at repair, pre-operative atrial flutter or fibrillation and the presence of atrial fibrillation, atrial flutter or junctional rhythm post-operatively. Atrial flutter following surgical ASD repair is usually due to macro-reentry. The re-entrant circuit may be right sided involving the common flutter isthmus (caval-tricuspid isthmus), may involve an atriotomy scar or both. The former is seen more frequently. Occasionally, circuits with a “figure of eight” configuration may be present. Atrial flutter circuits may also be left atrial in origin.

**Ebstein's Anomaly:** In Ebstein's anomaly, there is apical displacement of one or more tricuspid valve leaflets from the atrioventricular (AV) ring into the right ventricle. This is associated with a diminution in size of the functioning right ventricle. The deformity with displacement of the tricuspid valve can result in tricuspid insufficiency and right atrial dilatation. These abnormalities, along with the frequent coexistence of an ASD, predispose to the development of atrial arrhythmias. In addition, there is a high prevalence of accessory pathways in these patients. Accessory pathways may be present anywhere along the right

sided-AV ring or in the postero-septal region and often multiple pathways are present. This is presumed to be a consequence of the discontinuity of the central fibrous body and septal AV ring, resulting in persistence of fetal accessory AV pathways. Accessory pathway variants, such as Mahaim fibers, are also more common in this condition.

**Fontan Operation:** The Fontan operation is a palliative surgical procedure employed in patients with tricuspid atresia, pulmonary atresia, complex single ventricle and double-inlet ventricle. Older variants such as the right atrium-pulmonary artery connection have given way to newer modifications that reduce the distention of the right atrium, such as the lateral tunnel and external conduit. In response to chronic stretching secondary to persistent pressure overload, the Fontan right atrium remodels and dilates. This is associated with a change in the electrophysiological properties of the right atrium manifest by atrial conduction delay and an increase in conduction heterogeneity in the atrium. Risk factors for early postoperative arrhythmias (Table 3) include preoperative AV valve regurgitation and an anatomically abnormal AV valve.

Risk factors for the development of arrhythmias after the Fontan operation:

- Preoperative atrioventricular valve regurgitation
- Older age at operation
- Poor functional status preoperatively
- Previous atrial septectomy
- Atrial tachyarrhythmias preoperatively
- Pulmonary artery reconstruction
- Atriopulmonary anastomosis
- Postoperative sinus node dysfunction
- Length of follow-up

Older age at the time of repair is a risk factor for the development of arrhythmias as these patients will have experienced long periods of hypoxia, volume overload, ventricular hypertrophy and often have abnormal diastolic filling prior to surgery. Risk factors for development of late atrial arrhythmias include poor preoperative functional status, previous atrial septectomy, preoperative atrial tachyarrhythmias, older age at operation, need for AV valve replacement, pulmonary artery reconstruction, atriopulmonary anastomosis, early postoperative atrial tachyarrhythmias, postoperative sinus node dysfunction, and length of follow-up [3].

**Tetralogy of Fallot:** This condition is composed of four features: subpulmonary infundibular stenosis, Ventricular septal defect (VSD), overriding aorta and right ventricular hypertrophy. These patients are predisposed to both atrial and ventricular arrhythmias. The combination of moderate or severe left ventricular systolic dysfunction and QRS duration greater than 180 ms has a positive predictive value of 66% and negative predictive value of 93% for sudden cardiac death. QRS duration

greater than 180 ms has been shown to have 100% sensitivity and 95% specificity for sustained VT and SCD in tetralogy of Fallot patients. QRS prolongation reflects damage to the right bundle branch during surgical repair and late progressive QRS prolongation, secondary to RV dilatation, the result of chronic pulmonary regurgitation. Moderate to severe pulmonary regurgitation and aneurysmal dilatation of the RV outflow tract are observed with a greater frequency in patients with sustained VT. Programmed electrical stimulation is often used to risk stratify patients, as patients with inducible arrhythmias are probably at the highest risk. One-third of tetralogy of Fallot patients manifest atrial arrhythmias, with both congestive heart failure and recurrent atrial arrhythmias observed on follow-up. Risk factors for development of atrial arrhythmias include older age at operation, increased atrial size, tricuspid or pulmonary regurgitation and ventricular dysfunction. Atrial flutter and atrial fibrillation is more common in patients with long-lasting pulmonary artery shunts, early operations for residual hemodynamic lesions, older age at repair and moderate to severe tricuspid regurgitation. Tricuspid regurgitation leads to right atrial dilatation from volume and/or pressure overload that prolongs atrial refractoriness and creates the substrate for atrial arrhythmias. Patients usually present with palpitations, though occasionally atrial arrhythmias may manifest as syncope or presyncope.

**Transposition of the Great Arteries (TGA):** This malformation occurs when the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. At birth, a patent foramen ovale and a patent ductus arteriosus allow for mixing of blood to sustain life. The Mustard and Senning operations were developed to correct the physiologic abnormality by forming a baffle within the atria to switch the flow of blood at the inflow level. The Mustard repair requires extensive incisions and suture lines in the atria. This results in intra-atrial conduction delay and abnormalities in atrial refractoriness, creating the substrate for atrial flutter. The arterial switch operation was subsequently created to enable the left ventricle to become the systemic ventricle.

## Diagnostic Principles

Cardiac arrhythmias are diagnosed by ECG. In patients with paroxysmal arrhythmias, Holter monitoring or Event monitoring is often required. The diagnosis may also be confirmed by electrophysiologic studies.

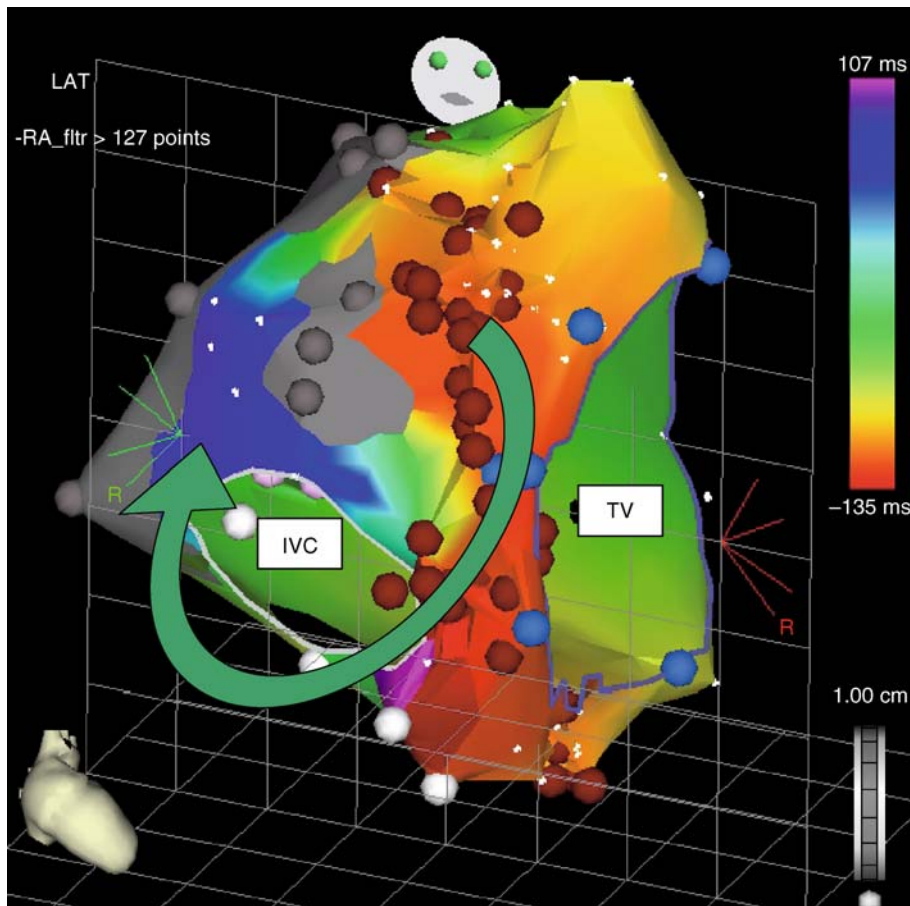
## Therapeutic Principles

**Atrial Septal Defect (ASD):** Catheter mapping techniques can be used to definitively determine the location of the reentrant circuit. Activation mapping, entrainment

mapping, and 3D electro-anatomical mapping techniques are essential for localizing the reentrant circuits and areas of slow conduction. Employing entrainment techniques as well as mapping with three-dimensional electro-anatomic systems is essential when treating atrial arrhythmias in the setting of surgical repair of an ASD. Catheter ablation of critical isthmuses and regions of slow conduction necessary for maintenance of the reentrant rhythm is then feasible (Fig. 1). Success rates of radiofrequency ablation of these circuits vary, but approach 80% and ablation is considered the treatment of choice in these patients. Occasionally, patients are referred for ASD closure as an adult. If the patient has a prior history of atrial fibrillation, a MAZE procedure can be performed at the time of ASD closure with excellent results. When the standard MAZE procedure has been performed at the time of ASD closure, results are excellent with no recurrence of atrial fibrillation. Long-term incidence of arrhythmias after catheter-based techniques of ASD is unclear as these are relatively new but is expected to be low.

Radiofrequency ablation is the treatment of choice for all arrhythmias in patients with *Ebstein's anomaly*, however success rate is lower (76%) compared to rates of 95% in patients without the anomaly. Factors that contribute to decreased success include the complex geometry of the accessory pathway due to the anomalous AV ring anatomy, location of the pathway along the atrialized portion of the right ventricle, abnormal endocardial activation potentials confounding identification of the accessory pathway, distorted anatomy of the AV ring, and the presence of multiple pathways (Fig. 2). In addition to a low success rate, radiofrequency ablation in Ebstein's anomaly is associated with a 25% risk of recurrence. Refractory arrhythmias are an indication for surgical repair in these patients. In patients undergoing tricuspid valve repair or replacement surgical cryoablation for accessory pathways, as well as right atrial or biatrial MAZE may be performed for atrial flutter or atrial fibrillation. Surgical intervention for accessory pathway-mediated tachycardia and atrioventricular node reentrant tachycardia (AVNRT) has had excellent long-term results. In contrast, surgical intervention for atrial flutter or atrial fibrillation has been less effective, with a recurrence rate of 40%.

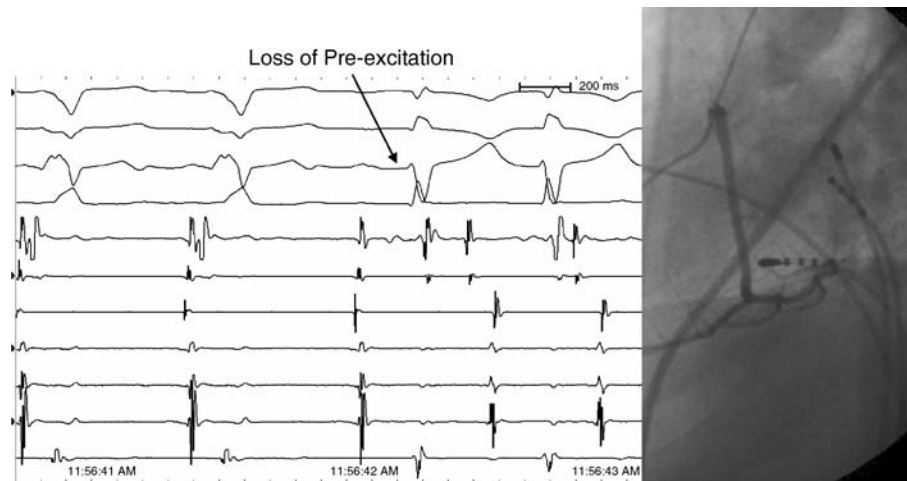
Atrial arrhythmias develop in 41–61% of post-Fontan procedure patients [3]. Management of the atrial arrhythmias in patient population after the Fontan Operation generally entails a combination of antiarrhythmic drugs, permanent pacemakers, radiofrequency ablation, and reoperation. Antiarrhythmic drugs must be used cautiously, as many patients have underlying sinus node disease and are at risk of developing severe bradycardia. Furthermore, antiarrhythmic drugs may cause slowing of atrial rates during tachycardia facilitating 1:1 conduction. Finally, proarrhythmia is always



**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 1** Electro-anatomical mapping of a right atrial flutter in a patient 20 years after surgical correction of an atrial septal defect. Grey areas represent areas of scar. The arrow represents the circuit for the scar related atrial flutter. A line of radiofrequency lesions (red dots) from scar to IVC resulted in termination of atrial flutter. A line of radiofrequency lesions was also given along the TV to IVC isthmus. IVC inferior vena cava; TV tricuspid valve.

a concern when prescribing anti-arrhythmic agents, especially in the setting of ventricular dysfunction. Permanent pacing may be required in the presence of sinus node and/or AV disease. Due to the anatomic constraints present, atrial and ventricular leads may have to be implanted surgically via an epicardial approach. Antitachycardia pacing has been combined with medical therapy with some success. Atrial rate-responsive pacing is preferred due to the high incidence of sinus node dysfunction. Rapid pacing prevents bradycardia and atrial extrasystoles and may eliminate initiation of reentrant tachycardias. Radiofrequency ablation of atrial arrhythmias is associated with immediate success rates of 83%, but a fairly high recurrence rate of 20% at short term follow-up. Potential causes of recurrence include persistently abnormal hemodynamics, massive right atrial dilatation with distorted anatomic landmarks, stasis related to low flow resulting in poor catheter tissue contact, and the inability

to create deep lesions in markedly thickened and fibrotic atria. More common ablation sites often include the region of the Fontan anastomosis, the lateral right atrial wall and the inferior right atrium. Refractory atrial arrhythmias are an indication for reoperation. Surgical conversion from an atrio-pulmonary anastomosis to a total cavo-pulmonary anastomosis along with electrophysiologically guided cryoablation has excellent results in preventing recurrent arrhythmias and reducing symptoms. Surgical cryoablation and antitachycardia pacing results in 83% of patients being arrhythmia-free without medications. Cryoablation is targeted at predominantly three locations: the infero-medial right atrium between the inferior vena cava and the coronary sinus, the superior rim of the ASD patch and along the lateral right atrial wall corresponding to the length of the crista terminalis. For patients with atrial flutter, cryoablation is employed as part of the modified right atrial MAZE procedure, along with excision of the right



**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 2** Intracardiac electrograms during radiofrequency ablation in a patient with Ebstein's anomaly and dextrocardia. Due to the complex anatomy of the tricuspid valve annulus, coronary angiography (*left lateral view*) was used to locate the AV ring. The accessory pathway was located in a postero-lateral location of tricuspid ring. Radiofrequency lesions at that site resulted in the loss of pre-excitation (*arrow*).

atrial appendage and placement of an atrial pacemaker. In patients with atrial fibrillation, the MAZE-Cox III procedure combines lesions of the right-sided maze with cryoablation lesions extending from the pulmonary veins toward the posterior mitral or tricuspid valve annulus, and from the isolated pulmonary veins to the edge of the excised left atrial appendage.

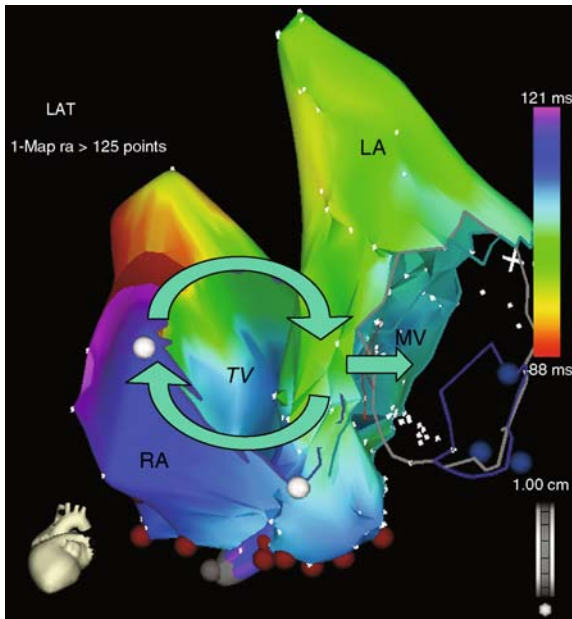
**Tetralogy of Fallot:** RFA has been successfully employed for atrial flutter and VT. A large area of scar seen as low-voltage electrograms, can usually be identified along the free wall of the right atrium, and successful ablation can be accomplished by creating a line of radiofrequency lesions between the lower margin of the scar and the inferior vena cava. Pre-requisites for VT ablation include inducibility on programmed electrical stimulation, hemodynamic stability during the tachycardia to enable adequate mapping, and monomorphic morphology of the VT. VT has been localized to the right ventricular outflow tract and the infundibulotomy scar or the septal surface of the VSD patch repair, with a high immediate success rate and low rate of recurrence. Patients with VT that cannot be ablated are treated with an implantable cardioverter defibrillator (ICD).

Surgical re-operation to correct the hemodynamic substrate has been attempted. A significant reduction in preexisting VT and QRS duration stabilization has been reported following valve replacement for severe pulmonary regurgitation, while concomitant intraoperative electrophysiological-guided cryoablation prevents recurrence of preexisting tachyarrhythmias. For patients requiring re-operation, a modified maze procedure should be considered, if recurrent atrial tachyarrhythmias exist.

In addition to recurrent atrial and ventricular tachyarrhythmias, sinus node dysfunction has been reported in approximately 36% of patients.

**Transposition of the Great Arteries (TGA):** Approximately 20% of adult patients who have had a Mustard repair will require permanent pacing in long-term follow-up for symptomatic sinus node dysfunction, atrio-ventricular block or to facilitate treatment of tachyarrhythmias. Careful evaluation of individual anatomy and exclusion of baffle leaks must be performed prior to determining pacemaker lead placement. The majority of supraventricular arrhythmias (73%) following Mustard repair are due to atrial flutter. Risk factors for development of supraventricular tachycardias include pulmonary hypertension, systemic ventricular dysfunction, and childhood junctional rhythm. Given the high prevalence of arrhythmias in this population, radiofrequency ablation has been employed with a 73–83% success rate, and a 12% rate of recurrence. The common flutter isthmus (tissue between the tricuspid valve and inferior vena cava orifice), the area around the os of the coronary sinus, and the region extending from the tricuspid annulus are critical components of the reentry circuit [5]. Intra-atrial reentry may involve either atrium and may require a retrograde aortic approach to facilitate ablation in the pulmonary venous atrium. (Fig. 3). In addition, focal atrial tachycardias have been localized adjacent to baffle suture lines. Typical AVNRT can also occur although infrequently. The incidence of supraventricular tachycardia is also significantly less with a rate of 5% in patients who have undergone an arterial switch operation compared to 48% in patients who have had a Mustard operation. The arterial switch operation is likely to be





**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 3** Electro-anatomical mapping of an atrial flutter 20 years after a Mustard operation in a patient with d-transposition. Arrows indicate the activation sequence. The flutter circuit (clock-wise) is due to reentry around the tricuspid valve annulus (anterior and systemic AV ring). Activation in the left atrium (venous atrium) follows right atrial activation. A retrograde approach was used to perform catheter ablation (red dots) with restoration of sinus rhythm. LA left atrium (venous); RA right atrium (systemic).

associated with a lower incidence of long-term atrial arrhythmias because there are no atrial scars.

Identification of patients at highest risk, the correction of hemodynamic defects and use of implantable cardioverter defibrillators, will avoid sudden cardiac death. Use of implantable defibrillators in adults with corrected congenital heart disease is safe and effective in reducing mortality from malignant ventricular arrhythmias.

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## Arrhythmias in Acute Myocardial Infarction

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## Definition and Characteristics

Arrhythmias in acute myocardial infarctions (MI) can be classified as supraventricular or ventricular (below the atrioventricular node), early MI (0–48 h post-MI) or late (over 48 h post-MI). Supraventricular arrhythmias include sinus bradycardia (SB, rate < 60 b/m) sinus tachycardia (ST, rate >100 b/m), paroxysmal supraventricular tachycardia (PSVT, conduction of supraventricular impulses arising from pacemakers other than the SA node with a rate of >100 b/m), atrial flutter and fibrillation (AFL, AFB), and junctional dysrhythmias which include AV junctional rhythm at a rate of 35–60 b/m or non-paroxysmal junctional tachycardia (NPJT) with a rate of 70–130 b/m. Myocardial infarction (MI) is classified as ST elevation MI (STEMI) or non-ST elevation MI (NSTEMI). Ventricular arrhythmias include ventricular premature beats (VPB), accelerated idioventricular rhythm (AIVR, a monomorphic consecutive wide QRS rhythm with a rate between 50 and 100 b/m), ventricular tachycardia (VT, three or more consecutive wide QRS complex beats with a rate greater than 100 b/m, and is considered sustained if it lasts more than 30 s, VT is considered monomorphic if it has a single consistent QRS morphology), and ventricular fibrillation (VF, irregular QRS undulations of varying width, contour and amplitude). Primary VF occurs < 48 h of MI, and is generally not associated with recurrent ischemia or heart failure, hence likely a primary event. Non-primary



or secondary VF is associated with hypotension, respiratory or cardiac failure and is agonal and resuscitation usually fails. VF is the most frequent mechanism of sudden cardiac death. Without treatment, asystole occurs invariably. VT is often associated with palpitations, worsening ischaemic symptoms and hemodynamic collapse. VT may degenerate into VF. The increase in ventricular rate that is associated with ST, PSVT, AFL and AFB may also aggravate ischemia and heart failure.

### Prevalence

VPB (10–93%), AIVR (0–50%), ST (30–40%), SB (15–25%), PSVT (0–10%), AFL (0–5%), AFB (10–15%) VT (STEMI: 3.5%, NSTEMI: 0.8%), sustained VT (STEMI: 2–5% during 0–48 h); non-sustained VT (1–7%), polymorphic VT (0.3%). VF (STEMI: 4.1%, NSTEMI: 1%; 3.1% between 0 and 4 hrs post MI with 11% recurrence, 0.6% between 4 and 48 h with 15% recurrence). Primary VF (2.1%; with 60% episodes between 0 and 4 h and 80% episodes between 0 and 12 h), non-primary VF (3.6%). In the pre-thrombolytic era: VPB (10–93%), VT (3–39%), VF (4–20%).

### Molecular and Systemic Pathophysiology

The mechanisms of early and late post-MI ventricular arrhythmias differ. In the early stage, VPB and VF result from transient arrhythmogenic phenomena in ischemic and infarcting tissue such as abnormal automaticity induced by left ventricular wall stress or increased catecholamine release, triggered activity, and reentrant circuits created by heterogeneous conduction and repolarization. While such early ventricular dysrhythmias are associated with a higher in-hospital mortality, the long-term out-of-hospital mortality is not increased [1]. On the other hand, late VT which reflects myocardial scar and permanent arrhythmic substrate is capable of developing reentrant circuits. Late VT occurs more commonly in large transmural MI with left ventricular dysfunction, and is associated with both an increased hospital and long-term mortality [2]. Sustained monomorphic VT could be a marker of permanent arrhythmic substrate even early after an MI [3], as it may reflect a permanent substrate from a prior silent MI. Polymorphic VT is usually due to abnormal automaticity or trigger activity associated with ischemia or reperfusion. There are no clinical features (including VPB) that would predict VF. Factors that increase the risk of VF includes large STEMI, hypotension, hypokalemia, male gender and smoking history. Ventricular arrhythmias, e.g., AIVR, occurring within a period of minutes after reperfusion can be related to reperfusion injury caused by the influx of calcium, oxygen and oxygen free radicals that can further damage the reperfused ischemic myocytes. Occlusion and reperfusion of

coronary vessels supplying the infero-posterior myocardium, trigger the Bezold-Jarish reflex which causes vagotonia and results in hypotension, bradyarrhythmias, and heart blocks. On the other hand, activation of the sympathetic nervous system, and SA or AV nodal ischemia may increase the likelihood of supraventricular tachyarrhythmias such as ST, AFL, and AFB.

### Diagnostic Principles

The 12-lead electrocardiogram, continuous telemetry in the CCU and holter monitoring remain the main tools for the diagnosis of post-MI arrhythmias.

### Therapeutic Principles

The acute treatment of post-MI life-threatening ventricular tachyarrhythmias (VF, VT) is immediate electrical defibrillation [4]. Hemodynamically stable patients with VT can be treated with intravenous (IV) amiodarone followed by synchronized electrical cardioversion with brief anesthesia. Intravenous procainamide is an alternative to amiodarone. Patients who develop sustained VF more than 48 hrs after MI may have to receive an intracardiac defibrillator as well as optimal revascularization and medical therapy. It is important to emphasize that the antiarrhythmic treatment is just an adjunct to the treatment of underlying ischemia with medical or invasive therapy. Other reversible causes such as hypokalemia and hypomagnesemia, adrenergic overstimulation and heart failure should be optimally treated (e.g., with electrolyte replacements, beta-blockers). There is no specific treatment needed for VPB other than beta-blockers. The management of peri-infarction supraventricular tachyarrhythmias includes rate control and pharmacological or electrical conversion [5]. For sustained AFL or AFB with hemodynamic compromise, prompt electrocardioversion is indicated. If this fails, the use of intravenous amiodarone or digoxin may be required. For more stable patients rate control with intravenous beta blockers such as metoprolol or intravenous diltiazem may suffice. PSVT may be treated with intravenous adenosine.

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## Arrhythmias, Supraventricular

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### Synonyms

Narrow complex tachycardias

### Definition and Characteristics

Group of cardiac rhythm disturbances, which require atrial, atrioventricular (nodal) tissue and/or the tissue of the adjacent veins for their initiation and maintenance. The term encompasses sinus tachycardia, inappropriate sinus tachycardia, sinus nodal reentrant tachycardia, atrial tachycardia, multifocal atrial tachycardia, ectopic and persistent junctional tachycardia, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia (e.g. Wolff-Parkinson-White syndrome), atrial flutter and atrial fibrillation. These arrhythmias are paroxysmal or persistent and hardly ever life threatening due to hemodynamic impairment or induction of ventricular arrhythmia. If persistent they can cause tachycardia-induced cardiomyopathy. Atrial flutter and atrial fibrillation carry the risk of arterial thromboembolism [1].

### Prevalence

Supraventricular arrhythmias are common. Atrial fibrillation is the most common clinically significant cardiac arrhythmia with a prevalence estimated at 0.4%, increasing with age [1]. The prevalence of paroxysmal supraventricular tachycardia is estimated at 0.225% [2].

### Genes

Most of the supraventricular arrhythmias are sporadic. Exceptions are familial forms of atrial fibrillation and the Wolff-Parkinson-White-Syndrome. In contrast to some ventricular arrhythmias to date there is no clear and consistent picture of a certain type of supraventricular arrhythmia and causative genes and their respective mutations.

### Molecular and Systemic Pathophysiology

The underlying cause of arrhythmias is abnormal impulse formation, abnormal impulse conduction, endless loop formation or a combination of these. There are three major pathophysiologic mechanisms of arrhythmias: increased automaticity, triggered activity and re-entry. Cells with increased automaticity exhibit enhanced phase-4-depolarization with an increased discharge rate compared to pacemaker cells. Abnormal

automaticity can arise from cells with reduced maximum diastolic potentials [3]. If the discharge rate exceeds that of the sinus node, the sinus node will be overdriven and the ectopic focus will be the predominant pacemaker. Triggered activity is associated with repolarization disturbances of the cell. Depolarization is triggered by oscillations in the membrane potential called after depolarizations that may reach the threshold potential leading to a consecutive discharge. Reentry is the conduction of an impulse around an anatomical or a functional area of conduction block. The classification of supraventricular arrhythmias is based on the ECG appearance, the proposed or clarified electrophysiologic mechanism and the involved morphological and functional substrate. Reentry is the most common cause of supraventricular arrhythmias. Supraventricular arrhythmias can affect otherwise healthy patients with no detectable structural abnormality as well as patients with structural heart disease. Extracardiac physiological and pathological factors, e.g. increased sympathetic tone, hyperthyroidism and drugs, can cause, precipitate and/or worsen supraventricular arrhythmias [1,4].

### Diagnostic Principles

Diagnosis is established by 12 lead ECG recording in the majority of the cases [5]. The usual presentation of supraventricular arrhythmia is a narrow-complex tachycardia (QRS-duration less than 120 ms), but in some cases supraventricular arrhythmias may have wide QRS-complexes due to bundle-branch-block or preexcitation, i.e. premature excitation of the ventricles by an accessory muscle bundle connecting the atria and the ventricles. Electrophysiological testing usually allows the exact delineation of the mechanism of the arrhythmia, but is generally performed only if catheter ablation is considered [4].

### Therapeutic Principles

Therapy is guided by the type of arrhythmia, the associated risks, the symptoms, frequency and duration of the arrhythmia. The basic therapeutic principles are rhythm control (restoration and maintenance of sinus rhythm), or rate control (mitigation of symptoms by slowing the heart rate). The therapeutic spectrum encompasses patient information, vagal maneuvers, treatment with adenosine, beta blockers, calcium channel blockers, digoxin, class I and class III antiarrhythmic drugs, catheter ablation of the arrhythmogenic substrate or – in combination with the implantation of a permanent pacemaker – catheter ablation of the atrioventricular node as well as the prevention of thromboembolic complications. The most common treatment strategies are drug treatment and catheter ablation [1,2,4].

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## Arrhythmias, Ventricular

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### Synonyms

Ventricular tachycardia; Ventricular flutter; Ventricular fibrillation

### Definition and Characteristics

Ventricular arrhythmias include both ventricular tachycardia (VT) and ventricular fibrillation (VF).

### Prevalence

Ventricular tachycardia is a frequent complication of myocardial infarction, a leading cause of death in Europe and North America.

### Genes

A wide variety of genetic defects and polymorphisms predispose to the occurrence of ventricular tachycardia and fibrillation including those causing long QT syndrome (see ► [Long QT syndrome](#)).

## Molecular and Systemic Pathophysiology

VT is characterized by very rapid but regular heart beats (~150 bpm). Because of the very rapid heart rate, if persistent over 30 s, hemodynamic collapse of circulation may occur. In contrast, VF has a totally chaotic rhythm, which makes the heart unable to function as a pump, and again hemodynamic collapse of the circulation occurs but more promptly than with VT. Both VT and VF have a very high correlation with coronary heart disease, acute myocardial infarctions, large chronic scars in the heart, and sudden cardiac death. Both can be caused by a dysfunctional state of the fast, voltage-dependent  $\text{Na}^+$  channel, which initiates an action potential and may cause a fatal reentry arrhythmia as it transmits through the nonhomogeneous conduction pathway in the ischemic myocardium [1]. Excessive fluctuations of ionized  $\text{Ca}^{2+}$  in the cytosol of heart cells causing after-potential discharges, which, if of sufficient magnitude, can trigger ectopic  $\text{Na}^+$  currents that also initiate fatal arrhythmias [2].

## Diagnostic Principles

Ventricular tachycardia is diagnosed by ECG.

## Therapeutic Principles

For many years the pharmaceutical industries have been trying to synthesize an effective antiarrhythmic drug. Despite the expenditure of hundreds of millions of dollars they have been unable to produce a drug, which is both effective and safe. The most effective of their drugs to date cause severe adverse reactions with some 30% morbidity. Most antiarrhythmic medications by their very effect on cardiac ion channels may have proarrhythmic effects. By contrast the n-3 ( $\omega$ -3) long chain, polyunsaturated fish oil fatty acids have been a regular part of the human diet for hundreds of thousands of years during which our genes were adapting to our environment, including our diet, that was high in n-3 fish oil fatty acids and low in plant seed n-6 proarrhythmic fatty acids. They are now known to be safe. These n-3 fish oil fatty acids are also potent antiarrhythmic agents as clearly demonstrated now by epidemiologic, observational [3], and clinical trials in humans [4].

Today the most effective prevention recommended by cardiologist is to have an implanted cardioverter-defibrillator (ICD) placed in patients requiring minimal surgery, who are at high risk for fatal VT or VF. An ICD will sense the presence of a ventricular arrhythmia and defibrillate it. However, the ICD is not perfect in successfully defibrillating all potentially fatal arrhythmias, so even with an ICD some patients will die. In a clinical trial [5] all patients enrolled in the study had ICDs and were randomized to either a supplement of fish oil fatty acids or to a placebo olive oil which has no

antiarrhythmic action. After each patient had completed the 12 months in the study, there was still a marked benefit in those receiving the fish oil supplement compared with those receiving the placebo [5]. So we can conclude that the fish oil fatty acids are more effective in preventing fatal ventricular arrhythmias than are ICDs.

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## Arrhythmogenic Cardiomyopathy

### ► Arrhythmogenic Right Ventricular Cardiomyopathy

## Arrhythmogenic Right Ventricular Cardiomyopathy

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## Synonyms

Arrhythmogenic right ventricular dysplasia; ARVD; Right ventricular dysplasia; Arrhythmogenic cardiomyopathy; ARVC

## Definition and Characteristics

Genetically inherited heart muscle disease characterized pathologically by progressive myocyte loss with fibrofatty replacement.

The classic form shows early predilection for the right ventricle and left ventricular involvement with disease progression.

Variants that preferentially affect the left ventricle are increasingly recognized (left-dominant arrhythmogenic cardiomyopathy).

Clinical manifestations include ventricular arrhythmia and sudden cardiac death. Heart failure is less common but well documented [1].

## Prevalence

Most recently estimated at 1 in 1,000 but remains underrecognized.

## Genes

Commonly transmitted as autosomal dominant trait.

Recessive syndromic variants associated with woolly hair and cutaneous disease (e.g., Naxos disease and Carvajal syndrome).

Identification of causative mutations in plakoglobin (Naxos), desmoplakin, plakophilin-2, and desmoglein-2 has defined ARVC as a disease of the desmosome.

Additional putative mutations in transforming growth factor beta3 ( $\text{TGF-}\beta 3$ ), known to stimulate production of extracellular matrix components and modulate stability of intercellular junctions.

ARVD2 has an atypical phenotype and is linked with mutations in the cardiac ryanodine receptor, the major calcium release channel of the sarcoplasmic reticulum in cardiac myocytes, also isolated in familial catecholaminergic polymorphic ventricular tachycardia [2].

## Molecular and Systemic Pathophysiology

Desmosomes are specialized cell adhesion junctions in cardiac and epithelial tissues that link intermediate filaments with the cytoplasmic membranes of adjacent cells, thereby conferring mechanical strength. Cardiac myocytes are constantly exposed to shear stress, and a defect in any component of the desmosome may compromise cell junction stability. Consequent myocyte detachment and death may be accompanied by inflammation; fibrofatty repair follows [2].

Ventricular arrhythmia may arise from one of the following mechanisms: (i) macro-reentrant circuits caused by islands of fibrofatty tissue, (ii) gap junction remodeling secondary to impaired mechanical coupling of cells, and (iii) bouts of myocarditis occurring in conjunction with myocyte loss [2].

**Arrhythmogenic Right Ventricular Cardiomyopathy. Table 1** Task Force Diagnostic Criteria for ARVD/C

	Major	Minor
Family History	Familial disease confirmed at necropsy or surgery.	Family history of premature sudden death (<35 years of age) due to suspected ARVD/C Family history (clinical diagnosis based on present criteria).
ECG depolarisation/conduction abnormalities	Epsilon waves or localized prolongation (>110 ms) of QRS complex in right precordial leads (V1–V3).	Late potentials on signal-averaged ECG.
ECG repolarisation abnormalities		Inverted T waves in right precordial leads (V2 and V3) in people >12 years of age and in absence of right bundle branch block.
Arrhythmias		Sustained or nonsustained LBBB–type ventricular tachycardia documented on ECG or Holter monitoring or during exercise testing. Frequent ventricular extrasystoles (>1000/ 24 hours on Holter monitoring).
Global or regional dysfunction and structural alterations	Severe dilatation and reduction of right ventricular ejection fraction with no or mild left ventricular involvement. Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulgings). Severe segmental dilatation of right ventricle.	Mild global right ventricular dilatation or ejection fraction reduction with normal left ventricle. Mild segmental dilatation of right ventricle. Regional right ventricular hypokinesia.
Tissue characteristics of walls	Fibrofatty replacement of myocardium on endomyocardial biopsy.	
The presence of two major, one major plus two minor, or four minor criteria from different categories is considered diagnostic. After ref 31.		

### Diagnostic Principles

Clinical diagnosis is difficult owing to the nonspecific nature of associated findings and subtle or absent abnormalities in early “concealed” phase.

Task Force diagnostic criteria (Table 1) are highly specific but lack sensitivity for early and familial forms.

Modifications to the original criteria have been proposed to enhance sensitivity in the diagnosis of familial ARVC [1].

### Therapeutic Principles

Implantation of cardioverter defibrillator recommended for patients at high risk of sudden death. Indicators of adverse prognosis include prior cardiac arrest, sustained ventricular tachycardia with hemodynamic compromise, unexplained syncope, and early onset of structurally severe disease [3].

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## Arrhythmogenic Right Ventricular Dysplasia

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### Synonyms

Arrhythmogenic right ventricular cardiomyopathy; ARVC; ARVD



## Definition and Characteristics

Arrhythmogenic right ventricular cardiomyopathy, (ARVC), is a hereditary cardiac condition most commonly transmitted by autosomal dominant inheritance. Less frequently autosomal-recessive variants of ARVC have also been reported in association with skin and hair disorders. The cardiac manifestations are characterised by progressive fibrofatty replacement of the myocardium. Structural abnormalities of the right ventricle predominate and include myocardial wall thinning, aneurisms and cavity dilatation [1]. Recent investigations suggest that the condition may also present with biventricular or isolated left ventricular dilatation [2]. In addition ARVC is a major cause of sudden death during adolescence and early adulthood. Disease expression is heterogeneous even within families and penetrance is incomplete [3]. The condition has been diagnosed at all ages although it very rarely occurs before adolescence.

## Prevalence

The prevalence of ARVC is largely unknown. Diagnosis is often difficult because many affected individuals have no or limited symptoms in addition to subtle clinical disease manifestations. Many cases are first revealed post-mortem.

## Genes

The condition is a genetically heterogeneous. Disease causing mutations have so far been identified in desmoplakin, (DSP), plakophilin, (PKP2), desmoglein, (DSG2), and desmocollin, (DSC2). These proteins are all constituents of the specialized adhesive junctions between cells known as desmosomes (Table 1).

Results of genetic investigations have suggested that mutation analysis of these genes will uncover a disease causing mutation in 40–70% of all ARVC cases. Autosomal-recessive variants of ARVC have also been described in association with skin and hair disorders [4].

Naxos disease, a triad of ARVC, palmoplantar keratoderma, and woolly hair, is caused by homozygous mutations in plakoglobin, (JUP), which is another component of the desmosomal plaque. Recessive mutations in DSP have been identified in an Arab family with ARVC and a pemphigus-like skin disorder and in an Ecuadorian family with a Naxos like cutaneous phenotype and apparent dilated cardiomyopathy, the so-called Carvajal syndrome (Table 1).

## Molecular and Systemic Pathophysiology

The discovery of mutations in DSP, PKP2, DSG2, DCS2, and JUP has led to the hypothesis that ARVC is a disease of the desmosome which consists of 3 major protein families: cadherins (desmocollins and desmogleins), armadillo repeat proteins (plakoglobin and plakophilins) and plakins (desmoplakin, plectin, etc). Desmosomes are protein structures situated in cell membranes that maintain adhesion between neighbouring cells and serve as anchoring sites for the intermediate filaments. They are found in tissues that experience mechanical stress, including epidermis and myocardium. In addition to cell adhesion they are involved in cell communication, tissue morphogenesis and differentiation. Much has been learnt about pathophysiology from studies of genetically modified mice. For instance mice lacking plakophilin are stillborn with profound cardiac abnormalities. They develop abnormal cardiac desmosomes and their desmoplakin dissociates and accumulate in cytoplasmic aggregates. Recent investigations of mice haploinsufficient of desmoplakin who thereby lack about half of the protein compared to wildtype mice develop an age dependent ARVC like phenotype with cardiac enlargement and ventricular arrhythmia [5]. Their myocardium is dominated by fibrosis and fatty tissue. Apparently, shortness of desmoplakin causes nuclear translocation of plakoglobin and upregulation of genes implicated in formation of adipose and connective tissue.

**Arrhythmogenic Right Ventricular Dysplasia. Table 1** Disease genes in ARVC

Autosomal dominant inheritance	Gene symbol	Clinical characteristics
Desmoplakin	<i>DSP</i>	All disease genes associated with primarily ARVC but with highly heterogeneous disease expression including isolated involvement of the left ventricle. No specific genotype-phenotype correlation is apparent
Plakophilin	<i>PKP2</i>	
Desmocollin	<i>DSC1</i>	
Desmoglein	<i>DSG2</i>	
Autosomal recessive inheritance		
Plakoglobin	<i>JUP</i>	Naxos disease: ARVC, woolly hair, palmoplantar keratoderma
Desmoplakin	<i>DSP</i>	Carvajal syndrome: Dilated cardiomyopathy, woolly hair, palmoplantar keratoderma

## Diagnostic Principles

The diagnosis is based on major and minor diagnostic criteria proposed by The International Task Force of the European Society of Cardiology and International Federation of Cardiology that includes morphological changes, histology, electrical abnormalities, rhythm disturbance and family history [1]. Magnetic resonance imaging, (MRI), is a valuable tool in diagnosing right ventricle abnormalities as well as fatty tissue replacement of the myocardium. Recent genotype-phenotype studies have suggested that the disease expression is very heterogeneous and that the phenotype may even overlap with idiopathic dilated cardiomyopathy, (DCM). Furthermore these studies have indicated that current diagnostic task force criteria lack sensitivity for early disease when clinical findings are subtle. This limitation has prompted proposal of modified diagnostic criteria for ARVC and suggest a key role for genetic analysis identifying individuals with early disease since sudden cardiac death is a frequent first manifestation of the condition.

## Therapeutic Principles

The clinical manifestations of the condition are variable including asymptomatic individuals, palpitations, syncope, heart failure and sudden death. Treatment of the condition is available and includes antiarrhythmic medications, implantable cardiac defibrillator, (ICD), heart failure therapy and percutaneous catheter ablation of arrhythmias refractory to drug treatment.

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## Arteriohepatic Dysplasia

► Alagille Syndrome

## Arteriosclerosis

► Atherosclerosis

## Arteriovenous Fistula

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### Synonyms

AV fistula; AVF; AV shunt

### Definition and Characteristics

An arteriovenous (AV) fistula is an abnormal high flow connection between an artery and vein which allows blood to flow directly from an artery into a vein, thus bypassing the capillary bed.

Normally, oxygenated blood flows from arteries into the capillary bed, where oxygen is released into the tissues. Deoxygenated capillary blood then flows into veins and returns to the heart. When there is a direct connection between a high-pressure artery and low-pressure vein, a short circuit is created which bypasses the high resistance capillary bed. This results in a high flow situation and pulsatile blood flow in the veins. This can cause the veins to bulge and enlarge and become varicose. If the AV communication is very large, tissues downstream may receive insufficient blood supply. In some cases, the volume of diverted blood may be so great that heart failure may occur.

AV fistulas may be present at birth (congenital fistula), or develop after birth (acquired fistula). Congenital arteriovenous fistulas are birth defects and are also known as arteriovenous malformations (AVMs). AVMs may occur anywhere in the body, including intracranially. Acquired arteriovenous fistulas may result from a penetrating knife or bullet injury that damages both an

artery and an adjacent vein. Arteriovenous fistulas may also develop as a complication of arterial and venous punctures performed during angiographic catheterization procedures. In patients with kidney failure who require hemodialysis, arteriovenous fistulas and shunts are surgically created in the wrist or arm in order to increase blood flow and pressure in the veins of the forearm. This enlarges the veins and creates a high flow situation in order to allow sufficient blood to flow through the dialysis machine.

### Prevalence

Congenital AVMs are uncommon and occur with equal frequency among males and females. AVMs are present at birth, may regress after birth and may progress during puberty or pregnancy. Surgically created AV fistulas and shunts are very common in kidney failure patients undergoing hemodialysis. Traumatic and angiographic catheter induced fistulas are being increasingly recognized.

### Genes

Experimental studies reveal that high flow arteriovenous fistulas result in up-regulation of candidate genes involved in cellular proliferation and differentiation. In animals with patent AVF 168 genes with significantly increased expression ( $p \leq 0.05$ ) were identified, including APBA1, PRKDC, TAP1, NEK2, GC, TGF $\beta$ 1, GBA, F8, IMPDH2, AFM, NBL1, LECT2, ANGPT1, KHDRBS1, ITGAM, and RAD52.

### Molecular and Systemic Pathophysiology

A direct connection between a high pressure artery and a low pressure vein short circuits the capillary bed and results in a marked increase in blood flow in the afferent artery. This results in high wall shear stress and compensatory enlargement of the afferent artery with ultimate normalization of wall shear stress levels as the artery dilates. This adaptive enlargement is endothelial dependent and is mediated by endothelial nitric oxide (NO) release. In addition there is up-regulation of pro-inflammatory gene expression, endothelial and smooth muscle proliferation and restructuring of the elastin-collagen extracellular matrix. On the venous side, the increase in intraluminal blood pressure and flow velocity induces up-regulation of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, endothelin-1 and transforming growth factor- $\beta$ 1. Intimal and smooth muscle proliferation results in thickening of the wall of the vein and neointimal hyperplasia.

Large, high-flow arteriovenous fistulae can induce increased cardiac output with systemic effects which may lead to cardiac failure. This clinical situation is associated with increased activity of vasoconstrictor neurohormonal systems such as the renin-angiotensin

system, the sympathetic nervous system, the endothelin system and arginine vasopressin. At the same time there is compensatory activation of systemic vasodilating systems such as atrial natriuretic peptide and nitric oxide. In decompensated patients enhanced sodium-retaining systems overwhelm the effects of vasodilating, sodium excretion systems with net reduction in sodium and water excretion and congestive heart failure.

### Diagnostic Principles

Superficial AV fistulas can be identified by the presence of distended and bulging veins, discoloration and swelling and increased warmth in the region of the fistula. High velocity blood flow in an AVF can be heard with a stethoscope as a continuous pulsating flow signal (bruit or machinery murmur). The turbulence of flow in the AVF induces vibrations in the vein which can be palpated as a thrill over the fistula. Increased pressure in veins close to the fistula can result in pulsatility in the veins, swelling of an extremity, venous varicosities and venous insufficiency. Alternatively, decreased pressure in arteries distal to an AVF can result in ulcerations and distal tissue ischemia. Increased cardiac output and stroke volume due to large AV fistulas can lead to tachycardia, left ventricular dilation and heart failure. Compression and temporary occlusion of an AV fistula may lead to reflex slowing of the heart. A number of imaging modalities can identify and localize both superficial and deep arteriovenous fistulas, including Duplex ultrasound, magnetic resonance imaging, CT scanning with contrast and catheter based angiography.

### Therapeutic Principles

Congenital AVMs usually involve smaller arteries and veins and are most often managed conservatively. Small congenital AVMs can be excised or eliminated with laser coagulation therapy, however, they are often more extensive than they appear on the surface. If there are significant clinical symptoms or complications, treatment usually involves endovascular coiling or embolization. Acquired fistulas usually involve a single large connection which can be effectively treated surgically by repairing the defect in the artery and repairing or ligating the associated vein or veins. Traumatic or catheter induced AV fistulas require direct surgical repair. AV fistulas in the brain, eye or other major structures can be especially difficult to treat. Endovascular treatment strategies with angiographic image guidance to embolize, coil, glue and occlude the arterial and venous branches feeding the fistula have been effective. These procedures are performed using catheters and x-ray imaging and do not require open surgery.

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## Arterial Aneurysm

► Aneurysm, Aortic and Arterial

## Arterial Hypertension

► Hypertension, Arterial

## Arteriolar Nephrosclerosis

► Nephrosclerosis, Arteriolar

## Arteriovenous Malformation, Pulmonary

► Pulmonary Arterio-venous Fistula

## Arteritis Temporalis

► Vasculitis, Large Vessel

## Arthritis, Infectious

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### Synonyms

Suppurative, pyogenic, or septic arthritis are applicable terms for bacterial arthritis

### Definition and Characteristics

Infectious arthritis may involve single or multiple joints, and may be caused by an extensive number of microorganisms: bacteria, and less frequently viruses, fungi, mycobacteria, and other microorganisms [1,2]. Bacterial arthritis is the most common and relevant, due to its potential for rapid joint destruction and functional loss. Viral arthritis is usually part of a systemic disease and may involve multiple joints, but is not burdened by a comparatively severe outcome. Infectious arthritis caused by mycobacteria (*Mycobacterium tuberculosis* and multiple atypical mycobacteria), and more infrequently fungi, parasites, and some bacterial organisms (*Borrelia burgdorferi*, *Treponema pallidum*, *Mycoplasma pneumoniae*, and *Nocardia* spp.), usually appears as chronic, slowly progressive monoarticular disease [3]. Moreover, a reactive or sterile arthritis is occasionally linked to systemic or local infections at a remote localization. Infectious disorders involving articular prosthetic devices are usually caused by gram-positive cocci, and may lead to the frequent need to prosthetic surgical curettage and substitution.

### Prevalence

The reported incidence of native joint bacterial arthritis is 2–10 cases per 100,000 subjects per year, in the general population. It is slowly increasing, due to the increasing number of at-risk patients and invasive and surgical procedures. Estimates of incidence in patients suffering from rheumatoid arthritis may reach 28–38 cases per 100,000 patients per year [1,2]. The crude

mortality of bacterial-septic arthritis in adults ranges from 10 to 30%, but remnants of infectious may be responsible for some sequelae in up to 50% of affected patients.

### Molecular and Systemic Pathophysiology

Infectious arthritis is usually acquired by an occult or a clinically apparent bacteremia. The well-vascularized synovial membrane lacks a limiting basement membrane, and it is therefore highly susceptible to bacterial deposition. The rich synovial supply and the presence of membrane receptors for bacterial structures and products may allow negligible traumatic events to cause septic arthritis. In infants in their first 2 years of life, there is a communication between the arterial supply of the metaphysis and the epiphysis by trans-epiphyseal vessels, so that there is no anatomic barrier to extension of infection from the metaphysis to the epiphysis, and this localization may represent the origin of secondary involvement of the adjacent joint [1,2]. In both children and adults, the articular capillaries lack a basement membrane, and microorganisms in the bloodstream may gain access to the articular space by passing through the capillary walls. When reaching the joint space, all microorganisms encounter an environment rich in nutrients. The subsequent bacterial replication elicits a brisk host inflammatory response involving a rapid polymorphonuclear involvement, the release of lytic enzymes, and the subsequent increase in synovial fluid protein concentration associated with a concomitant decrease of pH and glucose concentration. As a whole, the inflammatory process leads to synovial thinning, leukocyte infiltration, cytokine secretion, and local fibrin deposition. Without rapid therapeutic intervention, irreversible changes may be induced in joint anatomy and function, leading to severe remnants. Besides, the most frequent bacteremic invasion, direct inoculation of microorganisms or contiguous spread from adjacent tissues (i.e. skin-soft tissues or bone), is also possible [1–3].

The clinical manifestation, severity, treatment, and outcome of infectious arthritis directly depend on the identity and virulence of the infectious causative microorganisms, source of joint infection, and eventually, underlying host factors (including immune defense, comorbidity, trauma, and altered joint architecture) [3]. From over 2,300 cases of bacterial septic arthritis [4], the major isolates were *Staphylococcus aureus* (46% of cases) and streptococci as a whole (22%, with *Streptococcus pyogenes* and *Streptococcus pneumoniae* 7%), whereas gram-negative organisms are less frequent (21% as a whole, with *Haemophilus influenzae* and *Escherichia coli* as the leading organisms) [4]. The pathogenesis of gonococcal arthritis (although representing no more than 3% of cases) involve several

microbial virulence factors, mostly cell-surface proteins (especially protein A1), while complement deficiencies (especially C5 and C8), and circulating immunocomplexes may enhance dissemination of gonococci toward joint invasion.

The association of infection with early arthritis and the possible role of such infections with respect to the development of chronic rheumatic complications is also under investigation [1–3]. The role of preceding infection prompting the process of rheumatoid arthritis and other chronic collagen vascular diseases is still an option. In addition, the bacterial *Campylobacter* infection seems to deserve increasing attention and a causative agent of indirect, reactive arthritis. Viral infections (alpha viruses belonging to mosquito-borne viruses and HIV) are frequently associated with arthritis, but the pathogenetic mechanisms are still debated.

### Diagnostic Principles

Prompt recognition and treatment are major determinants in the final outcome of infectious arthritis, and are mandatory in order to prevent potential long-term sequelae. Radiographic and ultrasonographic findings are extremely simple but sensitive imaging techniques. Nevertheless, in selected cases, scintigraphic and computerized tomography scans, as well as resonance magnetic imaging are adequate to detect complication and monitor the follow-up [5]. Due to the extremely variable range of possible organisms and the need of prolonged courses of specific antimicrobials, a definitive ethological diagnosis should be always attempted, possibly with invasive approaches (i.e., arthrocentesis), whenever possible.

The differential diagnosis of infectious arthritis includes several inflammatory joint diseases of noninfectious origin (i.e., gout and pseudogout, and a broad range of collagen vascular disorders).

### Therapeutic Principles

First-line antimicrobial therapy of native joint infection is prompted by synovial fluid gram stain, while definitive treatment should be based on the identification and in vitro antimicrobial susceptibility studies of infected pathogens [1,3]. The penetration of inflamed joints is adequate for a large number of parenteral and oral antimicrobial agents, whereas it is not the same when bone involvement is of concern [1,3]. When gram-positive cocci are isolated, oxacillin-nafcillin or cefazolin are adequate when methicillin resistance is absent, whereas vancomycin is the first-choice agent for resistant gram-positive cocci, and clindamycin or vancomycin should be preferred when patients suffer from allergy to beta-lactam antibiotics. Gram-negative



cocci require a ceftriaxone approach, whereas gram-negative rods are better treated with ceftazime or cefepime or piperacillin-tazobactam or a carbapenem derivative; fluoroquinolones are highly active and have an elevated joint tissue penetration, so that they may represent a first choice when beta-lactam allergy is a problem.

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## Arthro-Ophthalmopathy, Hereditary

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## Synonyms

Wagner-Stickler syndrome; Stickler syndrome

## Definition and Characteristics

Autosomal dominant connective tissue dysplasia with variable expressivity and virtually complete penetrance leading to multiple ocular, cardiac, articular, and bony abnormalities.

## Prevalence

A rare syndrome with a frequency of 0.1–0.3 per million. With increasing recognition of the syndrome, it is now considered the most common autosomal dominant connective tissue disorder.

## Molecular and Systemic Pathophysiology

Recent studies indicate that mutation in the type II procollagen gene COL2A on chromosome 12 along with abnormal amino acid substitution in COL11A2 responsible for coding the alpha chain of type XI

collagen is responsible for the syndrome. Type II collagen is a major contributor to collagen of the vitreous, cartilage and the nucleus pulposus of the intervertebral disc. The ocular abnormalities include myopia (35%) usually occurring before the age of 10 years, retinal detachment (5%) usually occurring by the age of 30 years and in severe cases leading to blindness. Associated abnormalities include maxillary or mandibular hyperplasia cleft palate, and sensory neural deafness. Mitral valve prolapse is reported in 45% of the patients. Osteoarticular abnormalities are common; premature osteoarthritis is found in 16% of patients by the second decade and 50% by the third. Osteoporosis is found by the fourth decade. In the neonatal period, the epiphyses and metaphyses of long bones are enlarged and the joints are hyperextensible. In childhood, there is platyspondyly and anterior wedging of the vertebral bodies. Kyphoscoliosis, coxa and genu valgum, and premature degenerative changes occur. Occasionally, there is an accessory ossification center in the wrist between the capitate and the third metacarpal bones bilaterally. When present, this finding is diagnostic of this syndrome.

## Diagnostic Principles

This disorder should be considered as the diagnosis in cases of unexplained juvenile arthropathy, early degenerative joint disease in a young adult, with severe myopia or retinal detachment. Radiological findings are helpful in distinguishing from other syndromes including spondyloepiphyseal dysplasia, otospondylomegal epiphyseal dysplasia, and Marshall Syndrome. Other conditions including acromegaly, hemochromatosis, alcaptonuria, Wilson disease, and rarely Kashin-Beck syndrome are included in the differential diagnosis; however, none of these syndromes have retinal and maxillofacial abnormalities seen in Stickler's syndrome.

## Therapeutic Principles

Treatment of the ophthalmic manifestations involves surgical repair of the retinal tear, orthopedic management of kyphosis, and total hip arthroplasty for hip dysplasia. Additionally, medical treatment may be required for osteoporosis usually with bisphosphonates and drug treatment of the symptoms of degenerative arthritis.

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## Articular Hypermobility

- Hypermobility Syndrome

## ARVC

- Arrhythmogenic Right Ventricular Cardiomyopathy
- Ventricular Dysplasia

## ARVD

- Arrhythmogenic Right Ventricular Dysplasia

## Asbestosis

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### Definition and Characteristics

Asbestosis is defined as chronic, progressive inflammation and scarring of the lungs caused by exposure to asbestos fibers. It is characterized by diffuse, bilateral interstitial involvement of the lung that often leads to respiratory insufficiency and secondary cardiac complications.

### Prevalence

Asbestosis is most common in men over the age of 40 years who have worked in asbestos-related occupations. Smokers have increased risk of developing the disease. In the United States, more than 10,000 individuals over the age of 15 years died between 1968 and 1992 as a result of asbestosis. It has been estimated that the cumulative number of asbestos-associated deaths in the United States may exceed 200,000 by the year 2030.

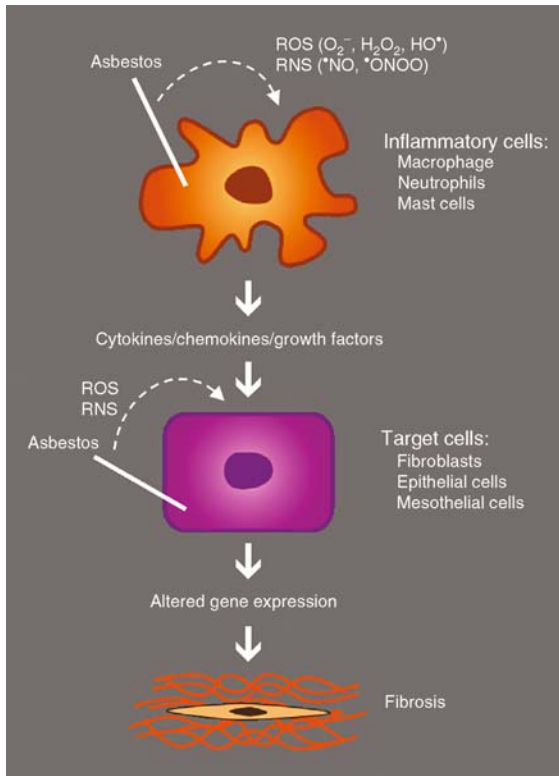
### Genes

No known genetic pattern exists. A deficiency of glutathione-S-transferase is a known risk factor for pulmonary asbestosis.

### Molecular and Systemic Pathophysiology

Asbestosis is caused by inhalation of asbestos, a group of naturally occurring fibrous silicates with crystalline structure, once widely used in the construction, insulation, and manufacturing industries. Asbestos fibers that are long and thin have the greatest fibrogenic potential since they are retained in the lung for extended periods of time. Short fibers are cleared more rapidly and hence are less fibrogenic. The fibers trigger a persistent inflammatory response after being engulfed by alveolar macrophages. The response involves the generation of reactive oxygen and nitrogen species, and the expression of cytokines, growth factors, and chemokines, which together lead to activation of lung fibroblasts and overproduction of extracellular matrix. The precise molecular mechanisms regulating asbestos-induced lung damage are not fully understood; however, it has been found that multiple signaling events are involved in the pathogenesis of this disease. Asbestos exposure induces increased expression of platelet-derived growth factor (PDGF) isoforms, tumor necrosis factor (TNF)- $\alpha$ , transforming growth factor (TGF)- $\beta$ , TGF- $\alpha$ , interleukin (IL)-1, IL-6, IL-8, macrophage inflammatory proteins (MIP), epidermal growth factor (EGF) and insulin-like growth factor (IGF) (Fig. 1). Activation of mitogen activated protein kinase (MAPK) signaling cascades has been implicated in the development of asbestos-associated lung disease through regulation of cell proliferation or apoptosis. In addition, genetic susceptibility may play a role in the development of asbestos-induced disease. In a mouse model of disease, the 129/J strain has been shown to be resistant, whereas the C57BL/6 strain has been shown to be susceptible to asbestos-induced fibrosis. In humans, individuals with a genetic deficiency in glutathione-S-transferase (GST)-mu have a significantly higher risk of non-malignant asbestos-related disease than those who are not deficient.

Symptoms of the disease may first appear years after the initial exposure to asbestos. The early symptoms of asbestosis typically include exertional dyspnea, dry nonproductive cough, and chest pain. Auscultation commonly reveals dry inspiratory crackles (rales). As the disease progresses and lung damage increases, shortness of breath occurs even when the patient is at rest. Recurrent respiratory infections, hemoptysis and clubbing are common occurrences. In advanced asbestosis, the lungs shrink and stiffen, and severe restrictive lung disease occurs. Several serious conditions are associated with asbestosis including



**Asbestosis. Figure 1** The pathogenesis of asbestos-related pulmonary fibrosis.

mesothelioma, bronchogenic carcinoma and congestive heart failure.

### Diagnostic Principles

An evaluation for asbestosis should begin with a detailed medical, occupational and environmental history. Typical findings on chest radiographs and computerized tomography scans, together with a history of asbestos exposure, is the basis for the diagnosis. The gross pathologic picture of asbestosis is that of diffuse interstitial fibrosis, most marked in the lower lung zones. The most severe involvement is generally seen closest to the pleura with relative sparing of the central portions of the lung. Honeycombing is common in advanced cases. The disease is almost always bilateral. Benign asbestos-induced pleural disease may also be present, but it is not synonymous with asbestosis. High-resolution computerized tomography scans will often show parenchymal fibrous bands, thickened intra- and interlobular lines, and curvilinear subpleural lines. The microscopic diagnosis of asbestosis requires two findings: diffuse interstitial fibrosis, which in advanced cases is identical to that seen in usual interstitial pneumonia, and the presence of asbestos (ferruginous) bodies in microscopic sections. Classic pulmonary physiological changes include restrictive

lung disease with reduced lung volumes, impaired gas exchange with hypoxemia and reduced diffusing capacity, and reduced lung compliance.

### Therapeutic Principles

There is currently no effective therapy to reverse the course of asbestosis. Treatment is directed at exposure prevention, amelioration of symptoms, and reduction of risk for related conditions. Coughing can be treated with humidifiers and/or antitussive agents. Regular exercise helps maintain and improve lung capacity. Antibiotics may be prescribed to combat infection. Oxygen should be used to treat hypoxemia. Asbestosis patients should receive vaccines for the influenza and pneumococcus. People with asbestosis who smoke, particularly those who smoke more than one pack of cigarettes per day, are at increased risk for developing bronchogenic carcinoma and should be strongly advised to quit.

### ►Pneumoconiosis

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## Ascites

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### Definition and Characteristics

Ascites is defined as the accumulation of fluid in the peritoneal cavity. A number of primary disorders of the peritoneum and intraabdominal organs may produce ascites. However, liver cirrhosis is the most common cause of ascites in Europe and North America [1].

## Prevalence

Approximately 50% of patients with compensated cirrhosis (without complications) develop ascites after a mean follow-up of 10 years. Moreover, almost 50% of patients with ascites die within 2 years, leading to inclusion of ascites as one of the indications for evaluation for liver transplantation.

## Molecular and Systemic Pathophysiology

Several theories have been postulated to explain ascites formation in cirrhosis. The accumulation of fluid within the abdominal cavity secondary to portal hypertension and hypoalbuminemia was believed to lead to a reduction of the intravascular volume, which in turn would stimulate renal sodium and water retention. This is known as the classic underfilling theory. The most important argument against this theory was the demonstration that plasma volume is increased in cirrhotic patients with ascites. In view of these findings, an alternative theory of renal dysfunction and ascites formation in cirrhosis was proposed. This theory, the overflow theory, suggested that advanced cirrhosis triggers a sodium-retaining signal in the renal tubules. The renal retention of sodium and water would result in expansion of plasma volume and adaptive circulatory changes to accommodate the excess of intravascular volume. The presence of portal hypertension and circulating hypervolemia would lead to ascites formation. This theory did not satisfy many investigators because it did not offer a clear explanation of the main clinical features of cirrhotic patients with ascites. Finally, in 1988 a new theory to explain the pathogenesis of ascites formation and renal dysfunction in cirrhosis was proposed [2]. The peripheral arterial vasodilation theory is probably the best explanation as to why the hemodynamic changes that occur in cirrhosis are directly related to the major clinical consequences, which include the development of ascites and renal failure. According to this theory, portal hypertension is the initial event, with resultant splanchnic arteriolar vasodilation that induces a decreased arterial blood volume. This effective hypovolemia increases the activity of vasoconstrictor systems leading to water and sodium retention. In the early stages of cirrhosis, the arterial circulation is maintained by transient periods of sodium and water retention. In advanced cirrhosis, the arterial vasodilation increases and effective arterial blood volume decreases. In this setting, the activity of vasoconstrictor systems further increases leading to intense sodium and water retention, which results ascites formation.

## Diagnostic Principles

The diagnosis of ascites is simple when a large amount of fluid is accumulated in the peritoneal cavity. On

physical examination the abdomen is distended, the flanks bulge, and a fluid wave may be demonstrable. The diagnosis is more difficult when ascitic volume fluid is small. In this case, ultrasonography is very useful. It can detect as little as 100 ml of abdominal fluid and may also provide information on the etiology of ascites. The diagnosis is confirmed by fluid aspiration by paracentesis. The procedure should be performed by inserting a needle into the left lower abdominal quadrant under strict sterile conditions.

The biochemical and cytological analysis of ascitic fluid provides important information for the differential diagnosis. Traditionally, ascites in cirrhotic patients was considered to have the characteristics of a transudate, with a total protein concentration of less than 2.5 g/dl and with relatively few cells. However, in up to 30% of these patients, total protein concentration is greater than 3 g/dl. It is useful to subtract the ascites fluid albumin concentration from the serum albumin, a serum-ascites albumin gradient of more than 1.1 g/l predicts portal hypertension with great accuracy. The ascitic fluid in cirrhosis usually has fewer than 300–500 white blood cells/mm<sup>3</sup>. Nevertheless 10–15% may have more than 500 cells/mm<sup>3</sup>. Most of these cells (>70%) are mononuclear leukocytes. If the ascitic fluid contains more than 250 neutrophils/mm<sup>3</sup> the diagnosis of spontaneous bacterial peritonitis (SBP) is made, and antibiotic treatment should be initiated.

## Therapeutic Principles

The aim of medical treatment of ascites in patients with cirrhosis is to mobilize the intraabdominal fluid by inducing a negative sodium balance. Treatment strategy is shown in Table 1. In ~10–20% of cirrhotic patients with ascites, this goal can be obtained simply by means of reducing dietary sodium intake and treatment with diuretics such as spironolactone, and loop diuretics. Patients who do not respond or who develop diuretic-induced complications should be considered to have refractory ascites and should be treated with other therapeutics maneuvers.

Therapeutic paracentesis is currently considered in many centers as the treatment of choice for cirrhotic patients with large ascites. An intravenous infusion of albumin (8 g/l of ascitic fluid removed) should always be given after paracentesis to prevent so-called post-paracentesis circulatory dysfunction (PICD).

Transjugular intrahepatic portosystemic shunt (TIPS) is a non-surgical method of portal decompression. Data on the impact of this treatment as compared to paracentesis and albumin on patient survival are, however, conflicting, due to increased incidence of hepatic encephalopathy.

Peritoneovenous shunt is more effective than therapeutic paracentesis in the control of refractory ascites.

**Ascites. Table 1** Treatment of ascites

Uncomplicated ascites
<i>Grade 1 ascites</i> is ascites only detectable by ultrasound examination. It does not require specific treatment.
<i>Grade 2 ascites</i> is ascites that causes abdominal distension and moderate discomfort and is easily detectable by physical examination. It should be treated with sodium restriction and diuretics.
<i>Grade 3 ascites</i> is large ascites. The treatment of choice is large volume therapeutic paracentesis plus intravenous albumin followed by sodium restriction and diuretics.
Refractory ascites
<i>Diuretic-resistant ascites</i> : Ascites that cannot be mobilized or the recurrence of which after large-volume paracentesis cannot be prevented because lack of response to low sodium diet and intensive diuretic treatment (e.g. 400 mg of spironolactone plus up to 160 mg of furosemide)
<i>Diuretic-intractable ascites</i> : Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to the development of diuretic-induced complications. The first line treatment of refractory ascites is repeated total paracentesis plus intravenous albumin. In patients who require frequent paracentesis or in those in whom paracentesis is not effective because of the existence of peritoneal adhesions the use of TIPS should be considered. Patients with refractory ascites should be evaluated for liver transplantation

However, it has many complications and currently, its use is not recommended.

Liver transplantation is a frequent intervention for patients with advanced cirrhosis.

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## ASD

- ▶ Atrial Septal Defect
- ▶ Autism Spectrum Disorders
- ▶ Intra-cardiac Shunts
- ▶ Lutembacher's Syndrome

## Aseptic Necrosis

- ▶ Avascular Bone Necrosis

## ASH

- ▶ Steatohepatitis, Alcoholic

## Ascorbic Acid Deficiency

- ▶ Vitamin C Deficiency

## Aspartoacylase Defect

- ▶ Canavan Disease



## Aspergillosis

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### Definition and Characteristics

Aspergillosis, caused by members of the genus *Aspergillus*, is a spectrum of diseases, ranging from allergic responses to *Aspergillus* molecules/antigens without fungal growth (asthma, hypersensitivity pneumonitis) to colonization with or without allergic responses (allergic bronchopulmonary aspergillosis, aspergilloma, saprophytic growth on devitalized tissue), or to invasion and destruction of lung parenchyma (invasive aspergillosis, chronic necrotizing pulmonary aspergillosis) [1]. The forms and severity of the disease depend on the immunologic state of the patient and sites to be affected. Although almost all sites of humans, such as the skin, peritoneum, kidneys, bones, eyes, and gastrointestinal tract can be affected by *Aspergillus* spp., the respiratory tract is the most commonly affected. Three forms of aspergillosis are most important: (i) allergic bronchopulmonary aspergillosis (ABPA) is a severe allergic pulmonary complication caused by *Aspergillus* spp. in patients with atopic asthma or/and cystic fibrosis. *Aspergillus fumigatus* is usually the causative organism and *Aspergillus niger* is occasionally implicated, (ii) aspergilloma (fungus ball) is overgrowth of *Aspergillus* spp. in preexisting cavity lesions produced by previous lung diseases, such as tuberculosis and sarcoidosis, and (iii) invasive aspergillosis is a serious *Aspergillus* infection that usually occurs in severely immunodeficient patients.

### Prevalence

The exact prevalence of aspergillosis is not clearly known and is different in various study cohorts of patients. The prevalence of ABPA ranges from 2 to 25% in patients with cystic fibrosis and from 1 to 8% in patients with asthma. Aspergilloma occurs in 10–15% of patients with cavitating lung diseases. The incidence of invasive aspergillosis ranges from 7.3 to 10.5% in patients undergoing bone marrow transplantation and from 10 to 25% in patients with leukemia [2,3].

### Molecular and Systemic Pathophysiology

*Aspergillus fumigatus* is one of the most ubiquitous of the airborne saprophytic fungi. The conidia of *Aspergillus* species are usually inhaled to the lungs through

the respiratory tract. Normally, the inhaled conidia are efficiently eliminated in the immunocompetent hosts by innate immune mechanisms. However, in some individuals with high-risk genetic types for ABPA, such as HLA-DR2+ and HLA-DR5+, the inhaled conidia may incite ABPA [4]. Recent studies suggest that genetic factors may play a key role in ABPA. These ABPA patients usually have gene polymorphisms of IL-4Ra and promoter region of the IL-10 gene. It is hypothesized that in these hosts predisposing for suffering from ABPA, the inhaled conidia germinate in the airways and release antigenic molecules, resulting in increased synthesis of IgE by B cells and the attraction of eosinophils into the airway tissue. Additionally, the expression of cytokines, such as IL-10 and IL-4, attracts Th2 lymphocytes into airways. All these factors incite clinical pictures of ABPA: increased mucus secretion into the airway, episodic eosinophilic-rich pulmonary infiltrations, and remodeling of the airway [3].

In patients with preexisting pulmonary cavities produced by tuberculosis and sarcoidosis, *Aspergillus* species may colonize in the cavities and overgrow to form fungal ball (aspergilloma). Aspergilloma are usually confined to a limited area. Slight or mass bleeding usually develops due to disruption of blood vessels in the wall of the cavity or in the bronchial artery supply.

In severely immunosuppressed patients, such as hematopoietic stem cell transplants or solid organ transplant recipients receiving neutropenia inducing chemotherapy, *Aspergillus* species may cause fatal invasive infections of central nervous system, heart, liver, kidney, and especially lung. Production of invasive aspergillosis depends on the defense of hosts and the virulence of *Aspergillus* spp. The virulence of *Aspergillus* spp. is multifactorial, including adhesions, pigments, toxic molecules, and enzymes [2]. To invade the hosts, conidia bind to various epithelial cells through nonspecific physicochemical interactions and/or specific receptor-mediated recognition. Then, *Aspergillus fumigatus* produces toxic molecules (i.e., gliotoxin) to inhibit macrophage phagocytosis and induce apoptosis in macrophages, and proteases (i.e., oxidative enzymes) to counteract the killing effect of reactive oxygen species. In comparison to the role of virulence of the organism, defense factors of hosts undoubtedly play a key role in the invasive *Aspergillus* infection. Animal experimental studies show that, although high doses of conidia are challenged, the majority of inoculums can be eliminated in immunocompetent hosts within hours. In contrast, fatal invasive infection usually occurs in severely immunosuppressed subjects. The host defense against *Aspergillus* may include the following: anatomical barriers, humoral factors (i.e., complement), and phagocytic cells (i.e., macrophages, neutrophils) and their related antimicrobials [2].

The role of acquired immunity in protection against *Aspergillus* and the mechanism of immunosuppressive agents in the development of invasive aspergillosis are less clearly known.

### Diagnostic Principles

Clinical findings, patient history, physical examination, radiographic features, and laboratory tests are important in the diagnosis of ABPA. Transient or permanent pulmonary infiltrates and central bronchostasis are usually seen by chest radiographs and computed tomography scan in ABPA. Laboratory tests show that ABPA is usually associated with an increased serum IgE level, peripheral blood eosinophilia, as well as positive reaction of antibody against *Aspergillus* antigen [3].

Aspergilloma (fungus ball) in the lungs may cause no symptoms or hemoptysis and may be merely discovered with a chest X-ray. Although the radiographic feature (spherical masses surrounded by a radiolucent crescent) is usually characteristic for diagnosis of aspergilloma, occasionally, other fungi may produce similar lesions.

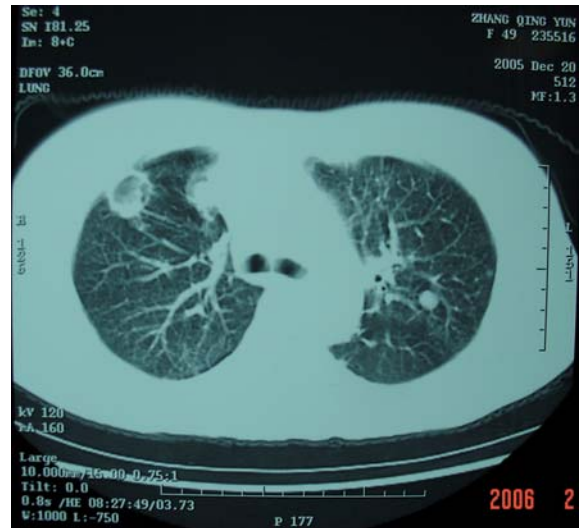
For diagnosis of invasive aspergillosis, nonspecific *Aspergillus*-positive culture from the upper/lower respiratory tract specimens bears limited significance. Galactomannan enzyme immunoassay (GM EIA) has an acceptable sensitivity and a high specificity. The radiographic features (Figs. 1 and 2) revealed by computed tomography (CT), especially high-resolution CT, have significant suggestive role in diagnosis of invasive pulmonary aspergillosis.

Invasive examination, such as fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL),

transbronchial biopsies (TBB), CT-guided percutaneous transthoracic lung biopsies, and surgical lung biopsy for histopathological examination and culture are undoubtedly the most reliable methods (Fig. 3) [5].

### Therapeutic Principles

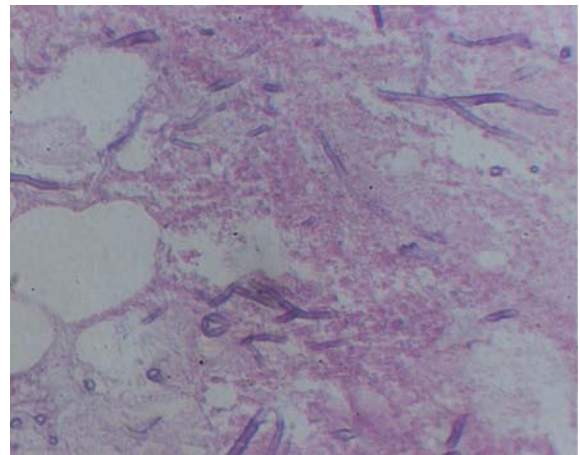
Corticosteroids are the primary treatment of ABPA. Antifungal therapy using itraconazole or other agents is adjunct [3]. More recently, recombinant anti-IgE antibody has been used to successfully treat ABPA.



**Aspergillosis. Figure 2** Computed tomography scan of histopathologically proven invasive pulmonary aspergillosis due to *A. fumigatus* in a patient with acute lymphoblastic leukemia.



**Aspergillosis. Figure 1** Chest radiographs of histopathologically proven invasive pulmonary aspergillosis due to *A. fumigatus* in a patient with acute lymphoblastic leukemia.



**Aspergillosis. Figure 3** Septal hypha with 45° branch in affected tissue.

Aspergilloma does not require treatment unless repeat bleeding or mass bleeding is associated with the disease; then, surgery is required. Surgical treatment for both simple and complex aspergilloma can achieve satisfactory long-term outcomes [5].

Intravenous voriconazole or/and amphotericin B (deoxycholate and lipid preparations) is the primary choice for treating invasive aspergillosis. Itraconazole, posaconazole, and caspofungin are also active against *Aspergillus* spp. However, they are usually used as alternative treatment of voriconazole and amphotericin B. Considering the high mortality associated with invasive aspergillosis despite introduction of new antifungal agents, lung resection may be a choice for invasive pulmonary aspergillosis [5].

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## Asphyxiating Thoracic Dystrophy

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## Synonyms

Jeune syndrome; Thoracic-pelvic-phalangeal dystrophy

## Definition and Characteristics

A rare autosomal recessive chondrodysplasia, with variable renal, hepatic, pancreatic and retinal abnormalities. ATD is characterised by abnormal skeletal development, with typical radiographical findings.

## Prevalence

Estimated at 1 per 100,000 live births.

## Genes

A genetic locus, ATD1, has been mapped to chromosome 15q13 [1], and there is a report of a single affected

case with a de novo deletion of chromosome 12p11–p12 [2]. Mutations in the IFT80 gene, encoding the human intraflagellar transport 80 protein, are causative in a subset of ATD patients with a milder form of the condition that lack extraskelatal features [3]. Further genetic heterogeneity in ATD may be caused by mutations in other IFT-associated genes. A similar phenotype occurs in Ellis-van Creveld syndrome (EVC).

## Molecular and Systemic Pathophysiology

The intraflagellar transport 80 (IFT80) protein is a component of primary cilia, a ubiquitous organelle of many cell types, including epithelial cells. Almost all epithelial cells are ciliated, and they commonly exist as a sheet of polarised cells forming a tube or tubule with the primary cilia projecting into the lumen. The cilia are then exposed to the extracellular environment of the lumen where it can provide a mechano- or chemosensory role that can mediate specific signalling cues. For example, a failure of mechanosensation in the primary cilia of renal tubular cells is a cause of polycystic kidney disease (PKD). A class of human disorders that arise from defects in the structure or function of primary cilia are now known as “ciliopathies” [4]. These comprise a broad range of phenotypes encompassing a number of different autosomal recessive and dominant syndromes of previously unknown aetiology, with cystic dysplasia of the kidneys as a common feature for most conditions. ATD is the only known human ciliopathy that is associated with mutations in an intraflagellar transport (IFT) protein. IFT is the process by which protein complexes, called IFT particles that contain cargo proteins, are transported bi-directionally along the axoneme of cilia and flagella by the coordinated action of IFT motors. The axoneme is essentially the cilia “backbone” which consists of a polarized array of microtubules which guide the movement of large vesicular complexes or IFT particles. IFT may also have an important role in vertebrate Sonic Hedgehog (Shh) signalling. During zebrafish embryonic development, the orthologue *ift80* may act downstream of *ptc 1* (the zebrafish Hedgehog receptor, Patched 1) in the Shh pathway [3]. Most cases die in infancy because of a severely constricted thoracic cage and respiratory insufficiency. For those patients who survive infancy, the thorax tends to revert to normal with improving respiratory function. The main visceral abnormality is renal in this condition, and approximately one-fifth of children with ATD survive beyond the neonatal period, only to develop significant renal impairment, with cystic changes and peri-glomerular fibrosis leading to chronic renal failure. Polydactyly is an inconstant feature of ATD and, when present, usually also affects the feet. Nail dysplasia is absent in this condition. Liver

involvement may be severe and biliary cirrhosis can cause early morbidity. Ophthalmological involvement is not a presenting symptom, but retinal dystrophy is an occasional feature.

### Diagnostic Principles

Characteristic findings of prenatal ultrasonography at the second- and third-trimester include a narrow thorax, short hypoplastic ribs, and short tubular bones. Newborn and infant radiography reveals typical findings that include a long, narrow “bell shaped” thorax with short, abnormal ribs, metaphyseal irregularities and short long bones (involving predominately ulnae, radii, fibulae and tibiae) [4,5]. Clavicles can be abnormal (“bicycle handlebar-shaped”) and cone-shaped epiphyses of the hands and abnormalities of the pelvis are considered to be diagnostic [4]. Features of the latter, in the neonatal period, comprise small ilia and irregularity of the acetabulum (“trident shaped”), from which a medial and lateral bony projection is visible. Severe restrictive lung disease is supported by pulmonary function testing and arterial blood gas analysis, which reveals hypoxia and hypercarbia in room air. Urinalysis may reveal haematuria and proteinuria. Renal biopsy may reveal cystic tubular dysplasia.

### Therapeutic Principles

Mechanical ventilation is indicated for severe cases when respiratory distress develops in neonates. Multiple recurrent pulmonary infections should be treated with antibiotics, endotracheal suctioning, and postural drainage. Surgical procedures, to enlarge the thoracic cage and reconstruct the chest by sternotomy or lateral thoracic expansion, may be considered for severe cases. Dialysis and renal transplantation are indicated for renal failure.

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## Asplenia

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### Synonyms

Absence of the spleen; Splenic agenesis; Ivemark syndrome; Right atrial isomerism; Asplenia syndrome; Congenital asplenia

### Definition and Characteristics

Asplenia refers to the absence of the spleen, while functional asplenia (or hyposplenia) refers to the absence (or impairment) of the normal splenic function. Both conditions are associated with a significantly increased risk of overwhelming infection (postsplenectomy sepsis), particularly involving the encapsulated bacteria *Streptococcus pneumoniae* and *Haemophilus influenzae*. In 1919, Morris and Bullock recognized the importance of the spleen in resistance to infection in studying splenectomized rats. The first reported case of postsplenectomy infection was by O'Donnel in 1929. It was not until 1952 that attention focused on the subject, when King and Shumacker reported five cases of severe infection in infants who had undergone splenectomy for spherocytosis.

Asplenia may be congenital, or acquired through surgery (splenectomy). In infants, asplenia usually is linked to serious organ malformations (Ivemark syndrome), but isolated congenital asplenia diagnosed in adults can occur. Surgical removal of the spleen is performed for several reasons, including trauma, immunologic diseases, hypersplenism and malignancy. Functional hypo- or asplenia is associated with a wide variety of diseases, including several immunologic and hematologic diseases. Among the mechanisms responsible for splenic dysfunction are repeated infarction, infiltration, intrasplenic blood flow redistribution, and antigen-antibody complex blockade.

### Prevalence

The true prevalence of functional hypo- or asplenia is unknown. However, the frequency of splenectomies has decreased during the last decades. Growing awareness of possible long-term complications has led to greater efforts to preserve splenic tissue.



In Hodgkin's disease splenectomy is no longer a routine procedure. However, it remains important in the management of hereditary hemolytic anemias, spherocytosis in particular.

### Molecular and Systemic Pathophysiology

The spleen is the largest lymphoid organ and has several immunologic functions (next to removal of old and damaged red blood cells from the circulation). These include the production of opsonizing antibodies and the efficient clearance of encapsulated bacteria. In asplenic patients the immunologic defects include decreased production of serum type-specific IgM and decreased levels of tuftsin (phagocytosis-stimulating tetrapeptide) and properdin, which both promote phagocytosis and initiate the alternate pathway of complement activation. Importantly, well-opsonized bacteria are largely cleared by the Kupffer cells of the liver, while encapsulated bacteria such as *Streptococcus pneumoniae* resists antibody binding, presenting a unique challenge to the immune system and are primarily removed by the spleen. Exposure of the asplenic patient to such encapsulated organisms as *S. pneumoniae* and *Hemophilus influenzae*, could lead to uninhibited bacterial overgrowth and subsequent invasive disease.

### Diagnostic Principles

The presence of Howell-Jolly bodies in the erythrocytes on a peripheral blood film is an important clue to the diagnosis of asplenia, representing a risk for postsplenectomy sepsis. Howell-Jolly bodies are nuclear remnants normally removed by the spleen and may not occur with mild hyposplenism. The "pocked erythrocyte count" (or "pit count") is a more sensitive indicator of splenic clearance and can be visualized by interference phase microscopy. Pocks (or pits) are membrane vesicles removed only by the spleen. Counts seen in normal persons, persons with functional hyposplenism and with asplenia, are less than 2%, more than 3.5%, and more than 12%, respectively. The absence of the spleen is best confirmed with a technetium-99m radionuclide scan.

### Therapeutic Principles

The risk of overwhelming infection is highest in infants and young children, but adults are also at risk. Preventive strategies are very important and fall into three major categories: (i) immunoprophylaxis (most important the pneumococcal polysaccharide vaccine (PPV23)); pneumococcal conjugate vaccine (PCV7) in children under 5 years of age); (ii) antibiotic prophylaxis (including daily antibiotic prophylaxis for the first 2 years after splenectomy in children and "stand-by" antibiotics for all individuals at risk); and (iii) patient

education (patients should be aware of their increased risk for serious infection and the appropriate health precautions that should be undertaken).

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## Asplenia and Polysplenia Syndrome

### ► Viscero Atrial Situs Abnormalities

## Asplenia Syndrome

### ► Asplenia

## ASS

### ► Hyperammonemia



## Asthma

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### Synonyms

Bronchial asthma

### Definition and Characteristics

A chronic inflammatory disease of the bronchi, manifested as episodic airway narrowing – reversible spontaneously or with medication – accompanied by chest tightness and wheezing. Non-specific hyperresponsiveness to bronchoconstrictor stimuli is a cardinal feature. The disease may progress to a stage where a component of airflow obstruction becomes irreversible.

### Prevalence

Asthma was reported in 1997 to affect 14–15 million people in the USA (~6.4%), including an estimated 4.8 million children. More than 5,000 people die annually in the USA from asthma [1].

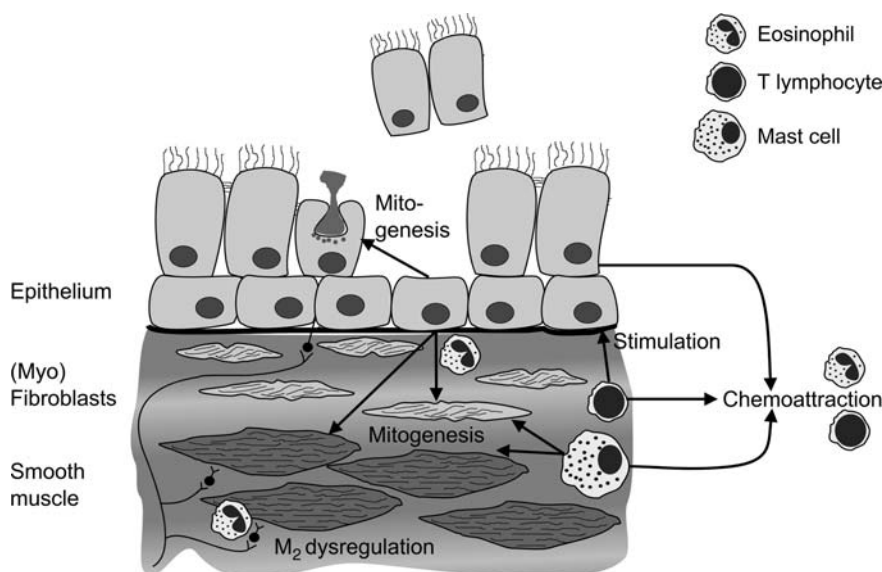
### Genes

The clustering of asthma in families indicates that heritable factors are involved in this disease. However, the rapid increase in the incidence of asthma over recent decades cannot be explained by genetic changes alone, but rather point to an important role for environmental factors. Therefore, it is likely that the development of asthma requires the involvement of environmental stimuli acting on genetically susceptible individuals. In the search for markers of genetic susceptibility to asthma, the ADAM-33 (a disintegrin and a metalloproteinase-33) gene has been found to be associated with asthma, and in particular, bronchial hyperresponsiveness [2].

### Molecular and Systemic Pathophysiology

Damage to the bronchial epithelium is observed, with focal shedding of columnar cells (Fig. 1).

This epithelial damage leads to the release of mitogenic cytokines that produce tissue remodeling, manifested as sub-epithelial fibrosis, increases in smooth muscle mass and goblet cell hyperplasia. The bronchial smooth muscle becomes populated by increased numbers of chymase-containing mast cells and the lamina reticularis is thickened. This last feature is pathognomonic for asthma and has been observed in children with asthma, suggesting that changes in airway structure occur at an early stage in the disease, perhaps even before the appearance of symptoms [3]. The airways of asthma patients contain an infiltrate of inflammatory leukocytes, particularly eosinophils and Th2 helper T cells, and in severe cases may be plugged by an excess of mucus. The recruitment of eosinophils



**Asthma. Figure 1** Cellular interactions in asthmatic bronchi.

and Th2 cells results from allergen-induced activation of airway-resident T-cells and mast cells, which also stimulate signaling in the epithelium and fibroblasts [2,3]. Activated eosinophils contribute to epithelial damage through the liberation of reactive oxygen species and cytotoxic proteins. An apparent dysfunction of autoinhibitory M<sub>2</sub> muscarinic receptors in parasympathetic nerves, possibly also caused by eosinophil proteins, leads to increased acetylcholine release with consequently increased smooth muscle contraction, augmented by the increase in smooth muscle mass [2,4]. In allergic forms of the disease, elevated serum IgE levels correlate with the degree of bronchial hyperresponsiveness; this appears to reflect both increased IgE-dependent mast-cell activation and as yet uncharacterized effects on smooth muscle contractility [5].

### Diagnostic Principles

Episodes of wheezing, coughing, tightness of the chest or shortness of breath may occur. Bronchial provocation tests will reveal hyperresponsiveness to inhaled direct (histamine, methacholine) or indirect bronchoconstrictors (adenosine monophosphate). Untreated asthma patients are likely to show appreciable diurnal variability in lung function as determined by measurement of the forced expiratory volume in one second (FEV<sub>1</sub>) or peak expiratory flow rate (PEFR). The lung function of patients with asthma should improve following inhalation of bronchodilators or on completion of a short course of corticosteroids.

### Therapeutic Principles

Bronchoconstriction in an asthma attack can be relieved by short-term relaxation of bronchial smooth muscle *via* activation of  $\beta_2$ -adrenoceptors, and can be prevented by long-term activation of  $\beta_2$ -receptors or, to a lesser extent, by antagonism of specific receptors for endogenous bronchoconstrictors (e.g., acetylcholine, cysteinyl leukotrienes). Nocturnal asthma attacks are particularly susceptible to inhibition by long-acting  $\beta_2$ -agonists. Chronic airway inflammation can be suppressed by the use of inhaled – or, during periods of severe disease, oral – corticosteroids, leading to reduced frequency and severity of attacks. Methylxanthines are weak bronchodilators but may provide some benefit given prophylactically. Cromones exert some anti-inflammatory actions that can give effective prophylaxis of mild asthma in children.

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## Ataxia due to Vitamin E Deficiency

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### Synonyms

AVED; Familial isolated deficiency of vitamin E; Tocopherol transfer protein deficiency

### Definition and Characteristics

Familial ataxia due to vitamin E deficiency (AVED), (MIM 277460) is an autosomal recessively inherited disorder characterized by the absence of a plasma protein specific for the transport of alpha-tocopherol (vitamin E). The condition is associated with a progressive neurological disorder (mainly presenting as spinocerebellar ataxia and neuromyopathy, closely resembling ►Friedreich ataxia) which is caused by the degeneration of tissues that are highly dependent on an adequate tocopherol supply.

### Prevalence

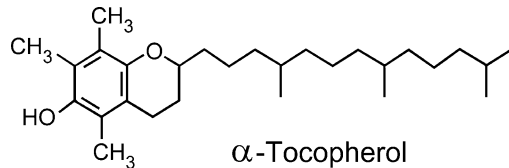
A rare or insufficiently recognized disorder. Most reported cases were from Germany, North Africa, and Italy [1–3].

### Genes

The disease is caused by mutations in the tocopherol transfer protein (TTP) gene on chromosome 8q13.1–q13.3 [2,3]. The exclusion of a TTP gene mutation in one case suggests the existence of a second gene defect causing AVED.

### Molecular and Systemic Pathophysiology

Patients with TTP deficiency do not have intestinal disease and have normal plasma lipoproteins. They



### Ataxia due to Vitamin E Deficiency.

**Figure 1** Chemical structure of vitamin E.

are, however, unable to transport vitamin E, the major lipid-soluble antioxidant *in vivo* (Fig. 1) to their tissues and develop a neurological disease due to the degeneration of membranes within the nervous system that are specifically dependent on vitamin E.

The resulting condition [4] is similar to that seen in cases of abetalipoproteinemia and nutritional vitamin E deficiency and is caused by a “dying-back” axonal neuropathy, which predominantly involves the centrally directed fibers of sensory neurons, with the large-caliber myelinated fibers being particularly affected. It is assumed that the primary abnormality is a degeneration of the axons, which then results in a secondary demyelination and that lipid peroxidation of neuronal membranes, as a consequence of a deficient anti-oxidant protection, is part of the mechanisms involved. The primary clinical manifestations include spinocerebellar ataxia, skeletal myopathy, and retinopathy. Other common symptoms are diminished proprioception, loss of vibratory sensation, and ophthalmoplegia.

### Diagnostic Principles

The diagnosis is based on a neurological picture suggestive of Friedreich ataxia and the demonstration of very low plasma levels of vitamin E in the absence of a significant nutritional disorder and the presence of normal plasma lipoproteins.

### Therapeutic Principles

Although the patients lack the specific transport protein for vitamin E in their blood, neurological progression can be halted by large amounts of vitamin E supplements. Under these conditions vitamin E is transported non-specifically within plasma lipoproteins. Plasma vitamin E levels should be brought into the normal range and monitored, as the right dosage has to be titrated and even a short discontinuation of supplements leads to rapid loss of vitamin E from the circulation. The first AVED patient discovered [1] and treated by the author for over 20 years has not shown any further neurological progression while under massive vitamin E supplements. Several studies have documented the efficacy of such supplements to prevent disease progression [5].

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## Ataxia, Episodic

### ► Episodic Ataxia Type 1 and Type 2

## Ataxia Friedreich

### ► Friedreich's Ataxia

## Ataxia Telangiectasia

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### Synonyms

Louis-Bar syndrome

### Definition and Characteristics

Ataxia telangiectasia (AT) usually begins in early childhood. It is clinically characterized by a combination of neurological and non-neurological symptoms. Cerebellar ataxia is the clinical hallmark of AT. In addition, many patients have choreoathetosis and

dystonia. Muscle reflexes are usually weak or absent. AT patients have a peculiar difficulty in initiating saccades (oculomotor apraxia). Telangiectasias are the second hallmark of AT. They develop after the onset of ataxia and are most frequently found in the lateral angles of the conjunctivae and the external earlobes. Approximately 60% of AT patients have immunodeficiency. The most frequent clinical manifestations are recurrent sinopulmonary infections. AT patients have a considerably increased risk of malignancies. Overall, one third of AT patients develop a malignant disease during their lives. Before the age of 20 years, malignancies are mainly lymphoid. In older patients, solid tumors are more frequent. Increased radiosensitivity is a typical feature of AT.

### Prevalence

According to an Italian epidemiological study the prevalence is 1.2:100,000.

### Genes

AT is an autosomal recessively inherited disorder caused by mutations in the ATM gene. More than 200 distinct mutations distributed over the entire gene have been reported.

### Molecular and Systemic Pathophysiology

ATM acts specifically in the cellular response to ionizing radiation and DNA damage. The ATM protein is a kinase phosphorylating more than eight different substrates and thereby setting in motion several different signal transduction pathways that result in at least three distinct cell cycle checkpoints. As a consequence of reduced ATM activity, DNA repair is severely impaired. While these abnormalities provide clues for the understanding of the abnormal radiosensitivity and malignancies, the cellular mechanisms underlying neurodegeneration are not well understood.

### Diagnostic Principles

A diagnosis of AT is probable in patients with a typical clinical phenotype and elevated serum levels of  $\alpha$ -fetoprotein. In vitro demonstration of radiosensitivity of lymphocytes is used as a laboratory test to confirm the diagnosis. Genetic testing is not routinely offered due to the diversity of mutations causing AT.

### Therapeutic Principles

There is no effective treatment for the neurological disturbances of AT. Treatment of infections should be initiated early and maintained over prolonged time. Administration of immunoglobulins can be considered in

patients with repeated infections. Treatment of malignant neoplasias is a particular problem because AT patients have increased sensitivity to radiation and chemotherapy. Therefore, conventional radiotherapy should be avoided and chemotherapy should be administered only on an individual basis.

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## Ataxias, Spinocerebellar

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### Synonyms

Autosomal dominant cerebellar ataxia; ADCA; Dominant ataxia; Dominant olivo-ponto-cerebellar atrophy; dOPCA; Menzel's ataxia; Marie's ataxia; SCA

### Definition and Characteristics

The spinocerebellar ataxias (SCA) comprise a group of dominantly inherited progressive ataxia disorders. Up to now, more than 25 different gene loci (SCA1-28) have been found in association with SCA. Neurodegeneration is mainly found in the cerebellum, brainstem and spinal cord, but other parts of the central and peripheral nervous system may be involved. The most common SCA disorders, SCA1-3, usually present with progressive ataxia accompanied by a variety of additional neurological symptoms with an onset of ataxia between 30 and 40 years. This group of disorders was previously named autosomal dominant cerebellar ataxia type I (ADCA-I). Only a few disorders, formerly named ADCA-III, are characterized by an almost purely cerebellar syndrome and isolated degeneration of the cerebellar cortex. The most frequent disorder of this group is SCA6. Age of onset in SCA6 is later than in SCA1-3 and varies between 30 and 75 years. SCA7 (or ADCA-II) has the unique feature of cerebellar ataxia combined with retinal degeneration [1].

## Prevalence

In a recent epidemiological study, the prevalence of SCA in the Dutch population was estimated to be 3.0:100,000. The prevalence may vary considerably from region to region due to founder effects.

## Molecular and Systemic Pathophysiology

In 13 SCA disorders (SCA1-3,5-8,10,12-14,17,27), the causative mutations have been identified. In six of them (SCA1-3, 6,7,17), the mutation is a translated CAG repeat expansion coding for an elongated polyglutamine tract within the respective proteins. These disorders belong to a larger group of polyglutamine disorders that also includes Huntington's disease and spinobulbar muscular atrophy. It is assumed that the polyglutamine disorders share important pathogenetic features including intracellular aggregation of polyglutamine-containing proteins resulting in dysregulation of essential cellular functions such as transcription [2,3].

In other SCA disorders, repeat expansions are found in the 5' untranslated region (SCA12), in an intron (SCA10) and in the 3' untranslated region (SCA8). SCA5 is due to mutations of the gene encoding beta-III spectrin [4], SCA14 is due to a missense mutation in the gene coding for protein kinase C  $\gamma$  and SCA27 is caused by a point mutation in the FGF14 gene encoding a fibroblast growth factor.

## Diagnostic Principles

A diagnosis of SCA is suspected in patients with otherwise unexplained progressive ataxia and a family history compatible with autosomal dominant inheritance. A definite diagnosis can be made by genetic tests in those disorders, in which the causative mutation is known. Genetic tests for the most common SCA disorders, SCA1-3,6 are widely available.

## Therapeutic Principles

To date, there are no rational treatment approaches for SCA. Patients should receive physiotherapy and speech therapy.

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## Ataxias, Sporadic

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## Synonyms

Idiopathic cerebellar ataxia; IDCA

## Definition and Characteristics

The sporadic ataxias are a heterogeneous group of adult-onset ataxia disorders that have a defined acquired cause (acquired or symptomatic sporadic ataxias) or occur without a discernible cause (sporadic ataxia of unknown etiology, SAOA) [1]. The latter category has been recently defined and distinguished from multiple system atrophy (MSA). The major categories of acquired ataxias are alcoholic cerebellar degeneration (ACD) [2] and paraneoplastic cerebellar degeneration (PCD) [3]. Sporadic ataxias are characterized by progressive cerebellar ataxia without major accompanying symptoms. Disease severity and progression rate are variable and partly depend on the underlying cause. In contrast to SAOA, which usually starts insidiously, ACD and PCD may have a subacute onset.

## Prevalence

A recent population-based study of SAOA found a prevalence rate of 9.4:100,000. Prevalence rates of ACD and PCD are unknown.

## Molecular and Systemic Pathophysiology

The etiology and pathogenesis of SAOA are unknown.

ADC is due to the toxic action of alcohol and its degradation product acetaldehyde on cerebellar Purkinje neurons. In addition, a nutritional deficiency in vitamin B1 (thiamine) strongly contributes to the development of this disorder.

PCD degeneration is an immune-mediated disorder occurring in patients with malignant tumors, mainly small cell lung and breast cancer as well as malignant lymphomas. Many PCD patients have circulating anti-neuronal antibodies. However, these antibodies do not cause PCD. Instead, PCD is caused by a T-cell-mediated immune attack directed against cerebellar Purkinje neurons.

## Diagnostic Principles

SAOA is diagnosed by exclusion of MSA and acquired as well as genetic causes of ataxia.



ACD is diagnosed by history and the typical clinical presentation of alcoholic patients.

A definite diagnosis of PCD can only be made by demonstration of an underlying malignant tumor. Screening for antineuronal antibodies alone is not sufficient, since PCD may occur in the absence of antineuronal antibodies.

### Therapeutic Principles

SAOA is an untreatable condition. As in other ataxias, physiotherapy and speech therapy may be helpful.

A diagnosis of ACD should prompt immediate administration of vitamin B1 (thiamine). Alcohol intake should be completely and lastingly stopped.

In PCD, the underlying tumor should be treated. In most cases, this does not improve ataxia.

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## Atelectasis

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### Synonyms

Collapsed lung

### Definition and Characteristics

Atelectasis is a condition in which the volume of the lung is diminished. Causes of atelectasis can be categorized as either obstructive or non-obstructive. Obstructive atelectasis results from airway occlusion of either large or small airways. Over time, gas distal to the obstruction is resorbed, causing alveolar collapse. Obstruction may be due to tumor, foreign body aspiration, inflammatory processes, or mucous impaction.

By contrast, non-obstructive atelectasis refers to a loss of lung volume caused by (i) external compression of the lung by space-occupying lesions, (ii) infiltrative lung disease, or (iii) surfactant dysfunction. Adhesive atelectasis is caused by loss or dysfunction of surfactant [1]. The disease results primarily from surfactant deficiencies in respiratory distress syndrome of the preterm infant (RDS) and from acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in the adult.

### Prevalence

There are ~150,000 cases of (ARDS) per year in the United States according to the NHLBI ARDS Act study. RDS affected ~24,000 infants in the United States in 2003 according to the National Vital Statistics Reports. Atelectasis is a characteristic feature of both of these disorders.

### Genes

There are currently three recognized genetic forms of surfactant deficiency, caused by mutations in the SP-B, SP-C, and ABCA3 genes. SP-B deficiency, with an autosomal recessive inheritance pattern, is most commonly caused by a frameshift mutation in codon 121 of SP-B gene (SFTPB), located on chromosome 2. SP-B deficiency results in rapidly progressive respiratory failure that is ultimately fatal. Exogenous surfactant does not alter the course of disease, with lung transplantation being the only effective treatment option. The clinical severity of SP-C deficiency is more variable. SP-C deficiency is caused by mutations in the SP-C gene (SFTPC) on chromosome 8 which result in a misfolded protein. The inheritance pattern is autosomal dominant, with incomplete penetrance. SP-C deficiency has been associated with familial forms of ILD, with age of onset in the neonatal period to the sixth decade of life. ABCA3 is a transmembrane protein located on lamellar bodies within the type II cell. The ABCA3 gene is located on chromosome 16. Infants with ABCA3 deficiency are severely surfactant deficient, with a clinical course similar to SP-B deficiency. It is thought that ABCA3 is most likely involved in the transport of surfactant lipids into the lamellar bodies [2].

### Molecular and Systemic Pathophysiology

Elasticity is a property of the lung that causes it to return to its resting shape after deformation by an external force during inspiration. Elastic tensions in the lung are borne mainly by two components, (i) the fibrous network of collagen and elastin that supports the alveolar septa, airways, and pleura, and (ii) the

air-liquid interface within the alveolus. The normal alveolus is lined with a thin layer of liquid. Surface tension is created by the interaction of molecules at the interface between this thin layer of liquid and alveolar air. The two forces are additive.

Due to the presence of surface active agents, or surfactants, the surface tension of the alveolar fluid is less than that of water alone. By lowering surface tension in the alveoli, lung elastance is decreased and the work of breathing reduced. Surfactant is especially important at low lung volumes where the decrease in surface tension prevents alveolar collapse thereby maintaining alveolar and small airway stability. It also prevents fluid from being drawn into the airspaces from the interstitium [3]. The absence of surfactant contributes to alveolar instability and subsequent atelectasis.

Pulmonary surfactant consists of ~90% phospholipids and 10% surfactant-associated proteins. Phosphatidylcholine (PC), is the predominant phospholipid, of which dipalmitoylphosphatidylcholine (DPPC) forms the largest component. This molecule has been shown to be primarily responsible for the surface tension lowering properties of surfactant. The hydrophobic components of the phospholipid adhere to the alveolar wall and the hydrophilic components disrupt water molecules in the lining fluid; thereby reducing the interactions among water molecules and decreasing surface tension. The other lipids in surfactant include unsaturated phospholipids and cholesterol. These facilitate spreading of the surface film as the lung expands during inspiration. There are four surfactant-associated proteins, SP-A, SP-B, SP-C and SP-D. Two hydrophobic proteins, SP-B and SP-C, work in concert with phospholipids to modify surface tension. Hydrophilic SP-A and SP-D play an important role in the host defense and immune functions of the lung.

Surfactant is synthesized by type II alveolar cells, stored intracellularly within lamellar bodies, and excreted via exocytosis. The hydrophobic SP-B and SP-C are assembled and secreted along with the phospholipid components of surfactant. Synthesis of the hydrophilic proteins occurs via separate pathways. Tubular myelin is a cross-hatched complex of lipid and protein formed following exocytosis of the lamellar bodies into the alveolar lining fluid. Individual lipids then separate from the tubular myelin to form the functional surfactant film [3]. The regulation of surfactant synthesis in the developing lung is complex and is affected by a number of hormones, growth factors, and cytokines [4]. The study of a number of these substances, including glucocorticoids, retinoic acid, keratinocyte growth factor, Vitamin D ( $1\alpha$ , 25-dihydroxyvitamin  $D_3$ ), triiodothyronine, thyrotropin releasing hormone, prolactin, catecholamine agonists, ATP, and prostaglandins, has produced some insight

into the regulation of surfactant associated protein gene expression.

### Diagnostic Principles

The incidence of RDS is inversely proportional to gestational age. Over 75% of infants born at less than 30 weeks gestation will develop RDS [4]. RDS is diagnosed in the appropriate setting based upon oxygen requirement, physical examination, and chest radiograph. An inheritable form of surfactant deficiency should be suspected when a full-term infant presents with the clinical and radiologic findings of RDS. A positive family history is helpful as well. The diagnosis of ALI/ARDS is made based upon physical examination, chest radiograph showing bilateral airspace filling disease, and the presence of severe hypoxemia, with  $PaO_2/FiO_2$  ratios of  $\leq 300$  for ALI and  $\leq$  for ARDS.

### Therapeutic Principles

Glucocorticoid therapy given prior to birth may enhance surfactant activity and be helpful in preventing RDS when premature delivery is known to be imminent. Prophylactic surfactant treatment is also given to the high-risk premature neonate. Treatment of RDS consists of the instillation of surfactant preparations containing both phospholipids and surfactant proteins SP-B and SP-C into the trachea of premature infants. Treatment has been shown to significantly reduce the rate of mortality and severity of respiratory complications [3,4]. Inherited SP-B deficiency is rapidly fatal, and mortality is not improved by exogenous surfactant therapy. The only known effective treatment is lung transplantation. ABCA3 deficiency appears to be largely fatal as well [2]. Exogenous surfactant therapy in ALI/ARDS has thus far met with disappointing results in clinical trials [3]. The mainstay of care remains supportive with low tidal volume ventilation. The use of positive end-expiratory pressure (PEEP) may be useful in alveolar recruitment and prevention of atelectasis in the setting of both RDS and ARDS.

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## Atheroembolism

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### Synonyms

Cholesterol crystal embolism; Shaggy aorta syndrome;  
Cholesterol embolism

### Definition and Characteristics

Atheroembolism is a complication of systemic atherosclerosis with renal impairment, skin manifestations, and diffuse microinfarctions in the head and abdomen. Recurrent salvos of cholesterol crystal microemboli originate from ulcerated atheromatous plaque, usually in the aorta. Bombardment of small arterioles with crystal emboli causes characteristic lesions, which may manifest as catastrophic events, slow deterioration, or chronic asymptomatic impairment. Embolic events often occur after plaques are destabilized by mechanical means, such as surgery and catheter-based endovascular treatments, or medical therapies such as anticoagulation or thrombolysis [1–3].

### Prevalence

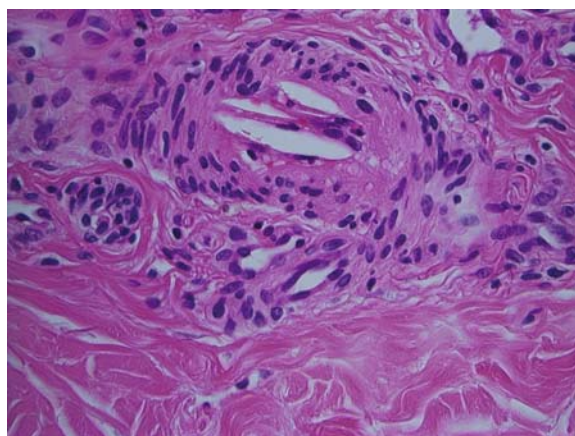
The true prevalence of atheroembolism is difficult to assess, as embolization may be asymptomatic and undetected despite substantial renal impairment. Patients with clinical symptoms represent only a small subset of patients with the most catastrophic forms of the disease. The variable time course of atheroembolization also complicates diagnosis. Patients may present with acute embolic crises, sub-acute deterioration, or asymptomatic chronic kidney disease.

Atheroemboli are found in <3% of unselected autopsies, but more frequently in autopsies of patients with severe aortic atherosclerosis. Renal atheroemboli have been found in ~5% of biopsies in elderly patients.

Risk factors for atheroembolic events mirror those of complex aortic atheromata, including age, male sex, tobacco, hyperlipidemia, and pre-existing atherosclerosis. The ‘typical’ patient is an elderly white hypertensive male smoker, who has vascular disease.

### Molecular and Systemic Pathophysiology

The *sine qua non* of atheroembolism is the exposure of friable material from an eroded atherosclerotic plaque. Resultant microemboli are distributed in proportion to blood flow, and lodge in small (150–200 µm) arterioles. The kidney, which receives 20–25% of aortic output, is targeted frequently and severely. Arterioles in the retinas, the central nervous system,



**Atheroembolism. Figure 1** Skin biopsy showing cholesterol clefts surrounded by a giant cell reaction (Hematoxylin-eosin stain).

and the gastrointestinal tract are also commonly affected, resulting in Hollenhorst plaques, cerebrovascular symptoms, and bowel ischemia.

Impaction of cholesterol crystals is irreversible, as the body has no mechanism for phagocytizing or dissolving them. These intractable foreign bodies provoke secondary inflammation, attracting mononuclear infiltrates which transform into giant cell reactions and granulomata (Fig. 1). Local inflammatory processes lead to intimal proliferation and fibrosis which causes stenosis or occlusion of the arteriole. The symptoms of atheroembolic disease are due to ischemia in the territories served by the affected vessels.

Given this mechanism, inciting factors for atheroembolic events can be readily predicted. Mechanical manipulation of the aorta during surgical or catheter-based interventions exposes freshly traumatized atheroma to the circulation. The potential for anticoagulation or thrombolysis to disrupt a stabilizing thrombus atop an ulcerated plaque is also intuitively evident.

### Diagnostic Principles

This diagnosis is made primarily on clinical grounds, as there are no pathognomonic laboratory findings. Atheroembolism should be suspected in patients at risk for advanced atherosclerosis, who have the triad of: inciting event (anticoagulation, or manipulation of the aorta by scalpel or catheter), renal failure, and stigmata of peripheral embolization. Retinal emboli can be seen on ophthalmoscopic examination. Typical skin manifestations include toe lesions and livedo reticularis.

Hyperlipidemia suggests the risk of atheroembolism. Common findings include increased urea nitrogen, creatinine, LDH, ESR and CRP, none of which are specific for this condition. Mild transient hypocomplementemia often occurs. Eosinophilia and eosinophiluria have been reported, with variable frequencies. The urinary

sediment can be bland or non-diagnostic, though non-nephrotic proteinuria and microhematuria are common.

Histological evaluation of affected tissues may confirm the diagnosis. Biopsy of typical ischemic or purpuric skin lesions is simple, non-invasive, and diagnostic in > 90% of cases. Renal tissue is more difficult to obtain, and patchy involvement of small arterioles can lead to areas of misleadingly normal renal parenchyma. Atheroemboli have also been documented in biopsies of gastrointestinal tissue and lung. Affected arterioles have characteristic empty 'clefts' where the needle-shaped cholesterol crystals have been removed by tissue processing (Fig. 1). The birefringent crystals can be seen on frozen sections. Crystals are surrounded by occlusive inflammatory endothelial reactions, which can be distinguished from small-vessel vasculitis by negative testing for ANCA.

### Therapeutic Principles

No treatment modifies outcome after crystals have embolized, so therapy is directed at reducing the risk of further embolic showers. Procedural disruption of aortic plaque must be avoided, as well as anticoagulation and thrombolysis. These provocations may be difficult to avoid, if the initial atheroembolic insult requires dialysis support. Surgical approach of the aorta has potential for either prevention or provocation of recurrent embolization. Preliminary evidence suggests a protective effect of therapy with HMG-CoA-reductase inhibitors (statins), which may stabilize plaques by reduction of lipid levels or via the immunomodulatory properties of these drugs.

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## Atherosclerosis

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### Synonyms

Arteriosclerosis

### Definition and Characteristics

In most parts of the world, many people develop some degree of atherosclerosis or "hardening of the arteries" as they get older. Atherosclerosis is the result of an inflammatory response to oxidized apolipoprotein (Apo) B-containing lipoprotein, especially low-density lipoprotein cholesterol (LDL-C) [1]. However, only some of those affected with atherosclerosis develop the serious and often life-threatening complications of heart attack or stroke. In the arterial tree, these are the main cause of vascular occlusion with manifestations in different areas including coronary, cerebrovascular or peripheral vascular districts. Arterial thrombosis superimposed on atherosclerotic lesions is responsible for most fatal and nonfatal events worldwide.

### Prevalence

The prevalence of atherosclerosis is estimated to be approximately 1 in 58 or 1.7%. These estimates may have limited relevance to the actual prevalence of atherosclerosis in different countries.

### Genes

Atherosclerosis is a multifactorial disease involving circulating blood cells and the vessel wall. This makes it difficult to identify a single gene underlying the disease. A number of gene mutations and polymorphisms, however, are known to affect the risk for atherosclerotic cardiovascular disease. For instance, mutations in the LDL receptor (LDL-R) gene underlie a disease called familial hypercholesterolemia, whose prevalence in the heterozygous form is roughly one in 500 individuals. These patients have one-half the number of normal LDL-R and develop elevated plasma LDL-C levels because the liver removes cholesterol from the blood as LDL via LDL-R.

### Molecular and Systemic Pathophysiology

Atherosclerosis mainly affects large and medium-sized arteries, including the aorta, the carotid arteries, the coronary arteries and the arteries of the lower extremities. Atherosclerotic lesions or plaques develop within, rather than on, the arterial wall. The earliest lesion of atherosclerosis is called the fatty streak, which is common even in infants and young children. The fatty streak is a pure inflammatory lesion, consisting only of monocyte-derived macrophages and T lymphocytes [2]. In patients with hypercholesterolemia, this influx of cells is preceded by lipid deposition. Up to a few years ago, it was thought that the more severe the extent of vascular stenosis, the more was heart attack and stroke likely to occur. However, more recent research indicates that this is not always the case. Rather, heart attack and stroke are likely to happen to people who have patches of atherosclerosis of only



moderate extent. These unstable lesions are rich in cells, indicating a high level of metabolic activity, and contain a cholesterol-rich core that is separated from the blood stream only by a thin fibrous cap. Recent research indicates that minor injuries and tears in the lining of the arteries occur all the time but most of them do not cause serious problems. If a complete tear of the thin fibrous cap occurs, however, the contents of the culprit lesion are spilled into the bloodstream and the underlying tissue is exposed to the circulating blood. Like any wound, this exposure of tissue activates the clotting system so that a clot or thrombus forms at the site of the lesion. This clot blocks off the affected blood vessel, most commonly an artery in the heart or the brain, so that the tissue supplied by that blood vessel is deprived of oxygen and dies. This death of tissue is what we call heart attack or stroke.

### Diagnostic Principles

In people who do not have any symptoms and have not been diagnosed with cardiovascular disease, it is not easy to foresee if arteries are developing atherosclerotic lesions or plaques. However, in those people who have high blood cholesterol, are overweight and get little exercise, smoke, or have other risk factors, the odds increase of having atherosclerosis.

There are a number of tests used in diagnosing cardiovascular diseases, including blood tests, electrocardiograms, stress testing, coronary angiography, ultrasound, and computer tomography. These tests are advisable in people at high risk for cardiovascular disease.

### Therapeutic Principles

Global risk assessment is essential to identify the patients who will most benefit from risk-factor modification. The primary target of therapy is control of plasma LDL-C levels via lifestyle changes and drug treatment. Therapeutic lifestyle changes include a multifaceted nonpharmacologic approach to reduce the risk for atherosclerotic cardiovascular disease essentially comprising reduced dietary intake of saturated fat and cholesterol, weight reduction and increased physical activity. The primary drugs for the treatment of dyslipidemia are statins, which have been shown to reduce atherosclerotic cardiovascular events in patients at moderate to high risk [3]. Statins may be of particular benefit because they have anti-inflammatory properties in addition to their cholesterol-lowering action. Other drugs include fibrates, niacin, bile acid sequestrants and ezetimibe. These drugs work with different mechanisms of action but ultimately all of them reduce plasma lipid levels. Combination therapy with low doses of individual agents has the potential to reduce adverse effects and may be of use in selected

groups of patients. Emerging protein biopharmaceuticals provide vascular benefits beyond those of hypolipidemic drugs [4].

### ►Peripheral Artery Disease

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## ATLL

### ►T-Cell Leukemia/Lymphoma, Adult

## Atopic Dermatitis

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### Synonyms

Atopic eczema; Endogenous eczema

### Definition and Characteristics

Chronic, highly pruritic, recurring inflammatory skin disease with various stages and different types of skin lesions. Acute AD is characterized by intensely pruritic, erythematous papules over erythematous skin with extensive excoriations, erosions, and serous exudates. Subacute dermatitis is associated with erythematous, excoriated, scaling papules and chronic dermatitis with thickened skin, lichenification, and fibrotic papules. Lesions predominantly occur in the flexural folds of the extremities.

At least two types of AD have been postulated: an extrinsic type that is associated with elevated serum IgE



levels, IgE-mediated sensitization to aeroallergens, and a history of atopic diseases accounting for ~70% of the patients, and an intrinsic type without these characteristics accounting for ~30% of patients.

### Prevalence

The prevalence of AD varies for different countries and was raised during the last decades. The live time incidence in children is estimated to be 10–20%; the prevalence in adults is in the range between 1 and 3%.

### Genes

AD is a genetically complex, familially transmitted disease. Several genes responsible for skin barrier function and the expression of various cytokines, chemokines and their receptors are discussed to be involved in the development of atopic dermatitis. Of special interest is chromosome 5q31–33 since it contains a clustered family of Th2 cytokine genes.

### Molecular and Systemic Pathophysiology

A lipid deficiency with a decreased ceramide production and a disruption of the skin barrier function, increasing the permeability to environmental irritants and allergens and increasing the transepidermal water loss are important factors in the pathogenesis of AD.

The pattern of immune effector cells and the cytokine expression is biphasic in AD. In the acute phase of AD, significantly more inflammatory cells express mRNA of the interleukins 4, 5, and 13; however, acute AD does not contain significant numbers of expressing mRNA of IFN- $\gamma$  or interleukin 12. In chronic skin lesions, significantly fewer cells express mRNA of IL-4 and IL-13, but increased numbers of cells express mRNA of IL-5, GM-CSF, IL-12, and IFN- $\gamma$  than do those of acute atopic dermatitis.

In this concept of extrinsic AD, the initiation of the skin inflammation is driven by allergen-induced activation of TH2 cells and switches in the chronic phase to a TH1-type response driven by the infiltration with IL-12 expressing eosinophils and macrophages, which accompanies the initial TH2 response. The cause initiating the skin inflammation of intrinsic AD is still under investigation, here autoimmune phenomena are discussed.

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## Atopic Eczema

► Atopic Dermatitis

## Atretic Aortic Arch

► Interrupted Aortic Arch

## Atrial Fibrillation

► Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Atrial Flutter

► Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Atrial Septal Defect

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### Synonyms

ASD

## Definition and Characteristics

Atrial septal defect (ASD) is a congenital heart defect (CHD) characterized by left-to-right shunting through the atrial septum and increased right ventricular overload.

Defects of the atrial septum include various anatomic types and different embryological origin:

1. “Ostium secundum type” is the most common defect (80%). It is localized at the central part of atrial septum and involves the foramen ovalis. It may be singular or can consist of multiple fenestrations. In agreement with the pathogenetic classification by Clark, this type of ASD is listed among the abnormal intracardiac blood flow defects. In 10% of the cases ASD is associated with other CHDs.
2. “Patent foramen ovale” is the result of a failure of fusion between atrial septum primum and septum secundum. This is not a true defect, since the higher pressure inside the left atrium closing the valve of the foramen ovale avoids the left-to-right shunt.
3. The “sinus venosus type” ASD can occur either high up in the atrial septum (superior sinus venosus defects), or, less commonly, low down in the atrial septum astride the entry of the inferior caval vein into the right atrium. Superior sinus venosus defect is frequently associated with anomalous drainage of the right superior pulmonary vein into the right atrium. It is pathogenetically included in the group of abnormal targeted growth defects.
4. “Ostium primum” ASD consists in a communication in the lower part of the septum often involving mitral valve anomalies (cleft). This anatomic variant is characteristic of the partial form of atrioventricular canal defect (or atrioventricular septal defect), and can be considered in the pathogenetic group of the extracellular matrix abnormalities.
5. The absence of the entire atrial septum is known as “common atrium,” and can be associated with cardiac abnormalities of the situs and looping.

## Prevalence

The prevalence of ASD is about 1 in 1,000 livebirths and 8% of all CHDs. Females are more frequently affected than males (M:F 1: 2). ASD is associated with extracardiac malformations in 25% of the cases.

## Genes

Genes implicated in ASD include

*NKX2.5*: Heterozygous mutations in *NKX2.5* (5q34) encoding a homeobox transcription factor [1].

*GATA4*: Heterozygous mutations in *GATA4* (8p23.1) encoding a zinc finger transcription factor [1,2].

*MYH6*: Heterozygous mutations in *MYH6* (14q12) encoding a structural protein [3].

*TBX5*: Heterozygous mutations in *TBX5* (12q24.1) encoding a T-box transcription factor [4].

*PTPN11*: Heterozygous mutations in *PTPN11* (12q22) encoding the protein tyrosine phosphatase SHP-2 [5].

*SOS1*: Heterozygous mutations in *SOS1* (2p21) encoding a RAS-specific guanine nucleotide exchange factor.

## Molecular and Systemic Pathophysiology

Familial nonsyndromic ASD: Genetic factors play a role in causing nonsyndromic ASD, particularly in families segregating concordant CHD with autosomal dominant inheritance. Heterozygous mutations in three genes, *NKX2.5* [1], *GATA4* [1,2], and *MYH6* [3] have been identified in a subset of familial ostium secundum ASD. *NKX2.5* is known to cause ASD with atrioventricular conduction abnormalities, while *GATA4* mutations are associated with ASD and pulmonary stenosis (Table 1). *MYH6* mutation has been detected in a large family segregating autosomal dominant ASD ostium secundum type.

The *NKX2.5* gene is important for regulation of septation during cardiac morphogenesis and plays a central role in the determination of myocardial cell fate. Additionally, it is involved in the maturation and maintenance of atrioventricular node function throughout life.

The *GATA4* gene is expressed during cardiogenesis in the atrial and ventricular myocardia, endocardium, endocardial cushions, and outflow tract.

The *MYH6* gene is highly expressed in the developing atria, and its expression is regulated by *TBX5*, the gene causing Holt–Oram syndrome. *TBX5* mutations not only reduce *MYH6* expression, but also disrupt the interactions with *GATA4* and *NKX2.5*. In addition, *GATA4* mutants causing ASD decrease *MYH6* transactivation. On the whole, it seems that all these genes form a transcriptional complex necessary for atrial septation.

A multifactorial mechanism of inheritance, due to genetic-environmental interaction, could be involved in cases without identifiable mutations in known genes.

Syndromic ASD: Genetic syndromes associated with ASD include Holt–Oram syndrome due to *TBX5* mutations [4], Noonan syndrome due to *PTPN11* and *SOS1* mutations [5], and Down syndrome (Table 1).

*TBX5* is a member of the large T-box transcription factor family, and may contribute to cardiogenesis by regulating cell proliferation in specific cardiac domains. It interacts with *NKX2.5*, *GATA4*, and *MYH6* genes.

*PTPN11* and *SOS1* genes cause Noonan syndrome, dysregulating the RAS-MAPK pathway.

## Diagnostic Principles

Patients with nonsyndromic ostium secundum ASD with conduction defects may be screened for mutations in the *NKX2.5* gene, while the *GATA4* gene is a candidate in patients with nonsyndromic ostium secundum ASD with pulmonary stenosis.

**Atrial Septal Defect. Table 1** Genetic conditions associated with atrial septal defect (ASD) ostium secundum type

Condition	Cardiac characteristics	Genetic defect	Chromosome location	References
Isolated/Familial				
Familial ASD	ASD ostium secundum ± atrioventricular conduction abnormalities	NKX2.5 gene mutations	5q34	[1]
	ASD ostium secundum ± pulmonary stenosis	GATA4 gene mutations	8p23.1	[1,2]
	ASD ostium secundum	MYH6 gene mutations	14q12	[3]
Syndromic ASD				
Holt-Oram syndrome	ASD ostium secundum	TBX5 gene mutations	12q24.1	[4]
Noonan syndrome	ASD ostium secundum ± pulmonary stenosis	PTPN11 gene mutations	12q22	[5]
		SOS1 gene mutations	2p21	
Down syndrome	ASD ostium secundum	Trisomy 21	chromosome 21	

Mutations in the TBX5 gene may be searched in patients with ostium secundum ASD and skeletal anomalies in Holt-Oram syndrome.

Ostium secundum ASD associated with phenotypical features of Noonan syndrome can be screened for PTPN11 and SOS1 gene mutations.

### Therapeutic Principles

Management of ASD include surgery by primary or patch closure or, when the anatomy is permissive, percutaneous device closure.

### ► Intra-cardiac Shunts

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## Atrial Tachycardia

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### Synonyms

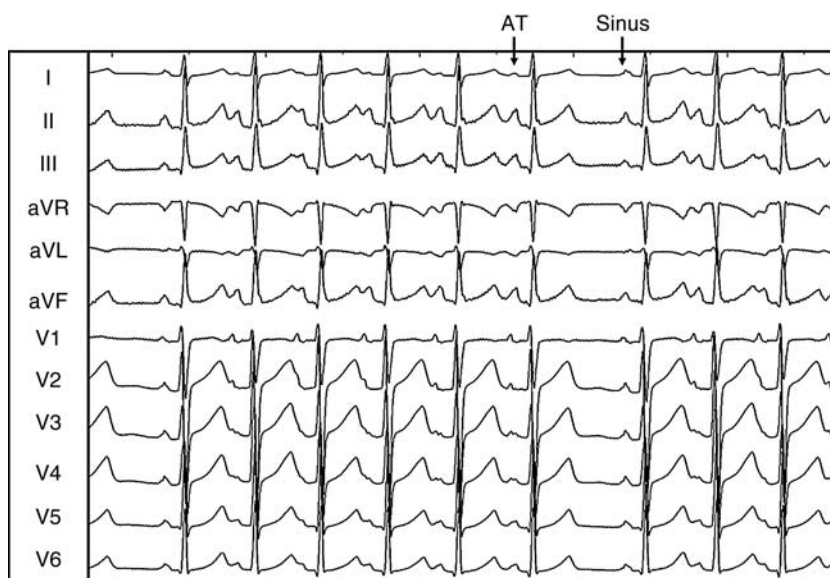
Focal atrial tachycardia

### Definition and Characteristics

Focal atrial tachycardia is an abnormal heart rhythm arising from a point source (focus) in the atria. It is usually manifest by atrial rates between 130 and 250 beats per minute. The P wave morphology is generally different to sinus rhythm but foci arising from the posterior right atrium, near the sinus node, may have morphology similar consistent with a sinus origin. The most common sites of origin include the crista terminalis, tricuspid annulus, coronary sinus ostium, and septum in the right atrium and the pulmonary veins and mitral annulus in the left atrium. Patients experience a variety of symptoms including palpitations, dizziness, chest pain, dyspnea, fatigue and syncope. Occasionally rapid atrial rates may cause a deterioration in left ventricular function.

### Prevalence

In asymptomatic young individuals the prevalence is 0.34%. In symptomatic individuals the prevalence is



**Atrial Tachycardia. Figure 1** Burst of atrial tachycardia arising from the crista terminalis in the posterior right atrium. Note the similarity to the sinus P wave and the variability in the QRS to P interval which is diagnostic of atrial tachycardia.

0.46% [1]. Atrial tachycardia accounts for 5–15% of adults undergoing electrophysiological studies for supraventricular tachycardia.

### Molecular and Systemic Pathophysiology

The three putative mechanisms of atrial tachycardia are abnormal automaticity, triggered activity, and micro-reentry. Abnormal automaticity occurs when myocardial fibers are depolarized to low membrane potentials. Triggered activity is due to early (EADs) or delayed (DADs) after depolarizations. DADs occur at high intracellular calcium levels and are due to spontaneous release of calcium from the sarcoplasmic reticulum. EADs usually occur in the setting of prolonged depolarization due to alterations in potassium or sodium currents. The mechanism of micro-reentry has not been fully elucidated however appears to be related to slow conduction around a small central obstacle [2]. Generally, atrial tachycardia arises from normal atrial myocardium but may also originate from regions of fibrosis, fatty infiltration and myopathic areas (Fig. 1).

### Diagnostic Principles

In the majority of cases, atrial tachycardia can be diagnosed from the electrocardiogram. A discrete P wave with an intervening isoelectric interval and a variable interval from R wave to P wave suggests atrial tachycardia. Automatic atrial tachycardias may manifest with recurrent self-limiting bursts of tachycardia.

However, in some cases differentiation from other forms of supraventricular tachycardia may be difficult. The presence of upright P waves in the inferior leads excludes atrioventricular nodal reentrant tachycardia but not atrioventricular reentry tachycardia. Ultimately, an electrophysiological study is required for a definitive diagnosis of focal atrial tachycardia.

### Therapeutic Principles

The efficacy of medical therapy is limited. Calcium channel blockers and beta-blockers are first line due to their low side effect profile. Flecainide, sotalol and amiodarone may be used subsequently. For patients with significant symptoms radiofrequency ablation is the treatment of choice.

### ► Arrhythmia, Cardiac in Adults with Congenital Heart Disease

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## Atrial Ventricular Complexes

### ► Premature Complexes, Atrial and Ventricular

## Atrial/Ventricular Premature Complexes/Contractions/Beats

### ► Premature Complexes, Atrial and Ventricular

## Atrioventricular Block

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### Definition and Characteristics

Atrioventricular (AV) block is a disturbance in conduction of sinus or atrial impulse through the specialized conducting system (AV node and bundle of His); it may be complete or incomplete. Incomplete AV block includes first-degree AV block (FAVB), second-degree AV block Mobitz Type I (MTI), and second-degree AV block Mobitz Type II (MTII). FAVB is characterized by prolongation of PR interval beyond 0.20 s in an adult, and beyond 0.18 s in children. MTI is characterized by progressive lengthening of successive PR interval till one sinus P is blocked, the PR interval immediately postblock returns to baseline interval, and the Wenckebach sequence begins again. As the PR intervals get longer, the RR intervals get shorter. There is a pause including the nonconducted P wave that is less than the sum of any two consecutively conducted beats. Group beating occurs when the RR intervals are irregular due to drop beats causing the QRS complexes to appear in clusters. MTII is characterized by constant PR intervals followed by sudden failure of a P wave to be conducted to the ventricles. The PP intervals remain constant and the pause including the blocked P wave equals two PP

intervals. Third-degree AV block or complete AV block (CAVB) is characterized by complete or permanent obstruction to the conduction between the atria and the ventricles. Usually a faster supraventricular rhythm is completely dissociated from a slower ventricular rhythm, which may be either a slow idionodal, <45 b/m, or idioventricular, <35 b/m, escape rhythm. Individuals with FAVB are usually asymptomatic. Symptoms of dizziness or syncope, Stokes-Adams attack, fatigue, congestive heart failure, dyspnoea on exertion, angina, mental status change, and epilepsy can occur with acquired high grade or CAVB. MTI is generally benign and transient in acute inferior myocardial infarction and healthy athletes. On the other hand, MTII is usually seen with bundle branch block or associated with acute anterior myocardial infarction and carries a high risk of progression to advanced or complete heart block. The prognosis for patients with symptomatic CAVB is poor without pacemaker. Patients with congenital CAVB are generally asymptomatic and have a more favorable prognosis than patients with the acquired form when not associated with underlying heart disease. However, with time it congenital CAVB does carry a significant risk of syncope and sudden death especially when associated with concomitant structural heart disease [1].

### Prevalence

FAVB (pilots 0.52%, adults over 20 years of age 2%, adults > 60 years 5%, athletes 8.7%, adults > 60 years with heart disease 10%), second-degree AV block (SAVB) (young adults 0.003%, athletes 2.4%, patients with heart disease 2.7%), CAVB (congenital 0.007–0.004%, USA 0.02%, international 0.04%) [2].

### Molecular and Systemic Pathophysiology

The blood supply to the AV node is via the AV nodal artery, which is a branch of the right coronary artery in 90% of hearts with the remaining 10% arising from the circumflex artery. The His bundle has a dual blood supply from the branches of the anterior and posterior descending coronary arteries. Approximately 87% of FAVB is caused by delay within the AV node when the QRS complex is narrowed. When FAVB is associated with a bundle branch block, infra-nodal conduction delay is present in 45% of these cases. MTI is almost always within the AV node when a narrow QRS complex is present. When MTI is associated with a bundle branch block, the block is still more likely to be in the AV node, but it can also be localized below the bundle of His when MTI is associated with bundle branch block or bifascicular block; the majority of the site of block is within or below the bundle of His. For FAVB, the level of the block may be at the AV node or the His-Purkinje system. FAVB with narrow conducted beats is



usually caused by block in the AV node. Features pointing toward block in the His-Purkinje system are conducted beats with bundle branch block and no improvement in block with atropine. Congenital CAVB within the AV node is characterized by narrow QRS complexes and with an escape rate between 40 and 60 b/m, which would increase with exercise or atropine. Acquired CAVB is usually associated with a block in the His-Purkinje system resulting in a wide complex with an escape rate between 20 and 40 b/m.

### Diagnostic Principles

ECG is the most important diagnostic tool. Carotid sinus massage increases vagal tone and worsens AV nodal block. Exercise or atropine improves AV nodal conduction because of sympathetic stimulation. In contrast, carotid sinus massage improves infranodal block whereas exercise and atropine worsen infranodal block because of the change in the rate of the impulses being conducted through the AV node. The electrophysiology study allows analysis of the His bundle electrogram and is the best definitive test to locate the site of the AV block.

### Therapeutic Principles

Pacing is the mainstay of treatment for symptomatic heart block [3]. Permanent pacing is usually recommended for asymptomatic patients with documented pause of greater than 3 s or a ventricular escape rhythm of less than 40 b/m [3]. Other situations where asymptomatic individuals are recommended to be paced include infranodal MTII and asymptomatic children with congenital heart block in association with a wide complex escape rhythm, complex congenital heart disease, ventricular dysfunction, or a long QT interval.

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## Atrioventricular Conduction Disturbances

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### Synonyms

Atrioventricular block; Heart block; Mobitz AV block; Wenckebach's AV block; Lev's disease; Lenegre disease; Lenegre-Lev syndrome; Wolff-Parkinson-White (WPW) syndrome; Preexcitation syndrome; Accessory atrioventricular pathways; (note: these synonyms do not necessarily describe the identical condition)

### Definition and Characteristics

Atrioventricular (AV) conduction disturbances result from aberrant propagation of the cardiac conduction impulse through components of the AV junctional tissues and/or abnormal conduction through parts of the AV conduction system (Fig. 1a).

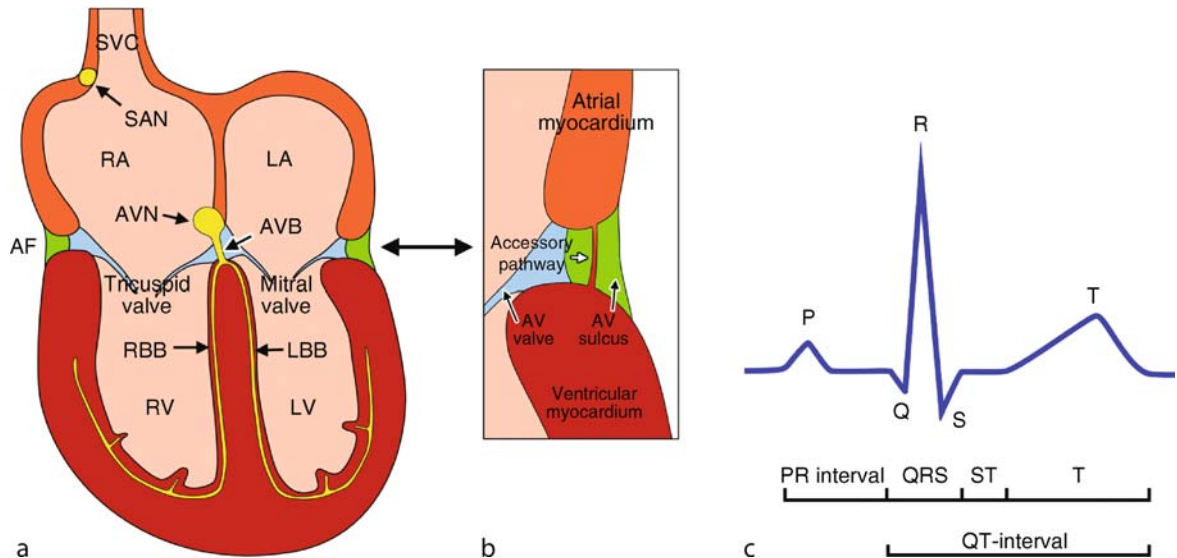
These disturbances lead to perturbation of the normal heart rate (tachycardias and bradycardias) and/or irregular heart beat (cardiac arrhythmias).

### Prevalence

First degree AV block is defined as prolongation of the interval between the onset of the P-wave and the onset of the QRS. It is usually asymptomatic and affects approximately 1% of young adults (>20 years), the prevalence increasing with advancing age. A significantly higher prevalence (~9%) is, however, seen in trained athletes. Second degree AV block is intermittent failure of atrial impulses to reach the ventricle and occurs in two forms, Mobitz Type I (also known as Wenckebach conduction) and Mobitz Type II. Mobitz type II is associated with risk of progression to complete heart block while Mobitz type I is generally benign. Complete heart block is defined as complete failure of atrioventricular conduction and is found in approximately 0.04% of adults [1], and while it can be temporary, it is potentially life-threatening and often requires implantation of a pacemaker.

Abnormal electrical connections may exist between the atria and ventricles and can form the anatomic substrate for arrhythmias. If abnormal ventricular

## Atrioventricular Canal Defect



**Atrioventricular Conduction Disturbances. Figure 1** (a) This panel is a cartoon depicting the respective components of the cardiac conduction system in relation to other structures in the normal heart. Note that the atrial myocardium (orange) is separated from the ventricular myocardium (red) by the annulus fibrosus, formed by the fusion of (epicardial) AV sulcus tissue (green) and valvular tissue (blue). The only myocardial connection between atrial and ventricular myocardium occurs via the proximal component of the AVCS (i.e. the AVN and AVB). (b) This is a simplified representation of an accessory atrioventricular pathway as found in cases with WPW syndrome (note: the actual localization of the pathway may vary). (c) A schematic diagram of a typical electrocardiogram (ECG) as derived from an individual with normal electric heart activity. Abbreviations: AF = annulus fibrosus, AVB = atrioventricular bundle (or His bundle), AVN = atrioventricular node, LA = left atrium, LBB = left bundle branch, LV = left ventricle, RA = right atrium, RBB = right bundle branch, RV = right ventricle, SAN = sinoatrial node; SVC = superior vena cava.

depolarization is created by an aberrant conduction pathway the ECG diagnosis of Wolff-Parkinson-White syndrome (WPW, or ventricular preexcitation syndrome) can be made (Fig. 1b).

WPW is found in 1.5–3.1 per 1,000 persons in western countries. However, this percentage is higher (0.55%) in the group of first-degree relatives of patients with WPW.

## Genes

A number of different genes have been associated with AV conduction disturbances. Mutations in the gene encoding the homeobox transcription factor NKX2.5 were found to be associated with congenital heart malformations including atrial septal defects and AV block [2]. The AV block phenotype observed in patients with NKX2.5 mutations appears to be associated with progressive degeneration of the AVCS. Interestingly a similar phenomenon was also observed in the postnatal hearts of mice that are haploinsufficient for *Nkx2.5*. AV conduction defects are also seen in Holt-Oram Syndrome (HOS), an autosomal dominant heart-hand syndrome caused by mutations in the *TBX5*

gene. Humans with *TBX5* mutations (HOS) are characterized by structural congenital heart malformations, including atrial septal defects, and associated progressive AV and bundle-branch block [3]. Some HOS patients have electrophysiological defects in the absence of structural defects. Studies on mice that are haploinsufficient for the *Tbx5* gene demonstrate that *Tbx5* is required for normal development and patterning of the AV conduction system. Thus, heterozygous *Tbx5* mice showed severe AVCS patterning defects, including absence or severe abnormalities of the RBB [4]. Familial WPW has also been linked to mutations in *PRKAG2*, a gene that encodes for the gamma-2 regulatory subunit of AMP-activated protein kinases [5]. Additionally, some mutations in the *SCN5A* gene result in familial progressive atrioventricular conduction defects; other mutations in *SCN5A* are causative of Long QT syndrome and Brugada syndrome. Other genes that are associated with Long-QT Syndrome, a cardiac arrhythmia characterized by ventricular repolarization, but not necessarily involving AV tissues, include *KVLQT1* (*KCNQ1*), *HERG*, *ANKB*, *MinK* (*KCNE1*), *MirP1*, and *KCNJ2*.

## Molecular and Systemic Pathophysiology

The molecular pathophysiology of AV conduction disturbances is poorly understood; so, too with aberrant conduction pathways. AV block can be either congenital or acquired; acquired causes include fibrosis secondary to ischemia and surgical trauma. In the congenital setting, it is most often seen in pregnancies complicated by lupus erythematosus and caused by transplacental transport of maternal SSA/Ro and SSB/La antibodies. Fibrosis and degeneration of the conductive tissues is a frequent finding.

## Diagnostic Principles

AV conduction disturbances can be diagnosed using electrocardiography. The atrioventricular conduction system (AVCS) includes the sinoatrial node (SAN), the atrioventricular node (AVN), the atrioventricular bundle (AVB), and the left and right bundle branches (LBB and RBB). In first degree AV block, every impulse generated in the SAN reaches the ventricles through the AVN and AVB. However, the length of the PR interval exceeds 0.2 s (upper limit of normal in an adult) indicating decreased conduction through the AV conduction axis. Individuals with first degree block are usually asymptomatic. In second degree AV block not all atrial impulses reach the ventricles. As a result, in the ECG not every P wave is followed by a QRS complex. There are two types of second degree AV blocks. Type I second degree block (or “Wenckebach” block) is characterized by progressive prolongation of the PR interval and a resulting shortening of the R-R interval. This ultimately results in failure of an atrial impulse to reach the ventricles, when the cycle begins again. After such a block, the cycle begins again. In type II second degree block, the PR and R-R intervals between conducted impulse are constant prior to failure of atrioventricular conduction. Patients that have second degree AV block often have an irregular heart beat and may suffer from bradycardia. In third degree AV block, there is no conduction of the atrial impulse through the AVN and AVB to the ventricular myocardium. Survival in such cases is dependent upon the ventricles developing an “escape rhythm.” There is no correlation between the atrial P wave and the QRS complex generated through the escape mechanism. Patients with third degree AV block generally suffer from bradycardia, which can be quite severe.

In WPW syndrome, an accessory AV pathway bypasses the normal AV conduction axis (Fig. 1c). This results in early activation (or preexcitation) of ventricular myocardium before the normal conduction pathways activate that portion of the myocardium. The appearance of the resulting QRS reflects the relative

amount of myocardium activated through the accessory pathway and the normal conduction tissues, as well as the relative location of the pathway in the heart. The PR interval on the ECG will be abnormally shortened, and the QRS complex, however, is generally abnormally-shaped and wide.

## Therapeutic Principles

At present the only effective treatment for absent or unreliable AV node conduction is a pacemaker. Postnatally acquired complete heart block, whether from genetic mechanisms or not, carries a high risk of Stokes-Adams attacks and sudden death and is an absolute indication for pacing. In contrast, congenital complete heart block carries a low risk of sudden death and pacing decisions are typically based on symptoms. Congenital complete heart block is usually well tolerated in infants if there are no co-existing cardiac structural abnormalities, but the combination of congenital complete heart block and cardiac malformation is very poorly tolerated and is a well documented cause of fetal demise.

Aberrant conduction pathways that result in symptomatic arrhythmias are generally treated by catheterization and ablation, although pharmacologic therapy can also be effective.

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## Atrioventricular Dissociation

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### Synonyms

AVD

### Definition and Characteristics

Atrioventricular dissociation (AVD) is a condition in which the atria and ventricles are activated independently of each other, so that the P waves and the QRS complexes do not have any relationship with each other. In AVD, the ventricular rate (VR) is either the same or faster than the atrial rate (AR), whereas in complete heart block the AR is faster than the VR [1]. In AVD, the atrial pacemaker is usually in the sinus node and produces any atrial sinus rhythms. The ventricular pacemaker may originate from the AV node, bundle of His, bundle branches or peripheral Purkinje tissue. No retrograde ventriculoatrial conduction occurs in AVD. When the AR and VR are similar, but the P wave is not conducting, the rhythm disturbance is known as isorhythmic AVD [2]. When the AR and VR are similar, but occasionally the atria conduct to the ventricles, the rhythm is known as interference AVD. During interference AVD, the atria are driven by a slowed down sinus pacemaker and the ventricles by an accelerated junctional or nodal pacemaker. The impulses from these two independent pacemakers meet or collide, usually in the AV node and interfere with each other's conduction. Incomplete AVD occurs when some of the P waves conduct and capture the ventricles as in interference AVD. AVD is regarded as complete when the atrial rhythm does not conduct and capture the ventricles. Complete AVD can mimic AV block, but the fact that none of the P waves conduct has more to do with the timing of the P waves in relationship to the QRS complexes rather than the presence of AV nodal disease that occurs in AV block. Clinically, most patients with AVD are asymptomatic. Symptoms of AVD are related to bradycardia, tachycardia, AV dyssynchrony, or the loss of "atrial kick" (diastolic filling of the ventricles secondary to atrial contraction). Symptoms of AVD may include exertional dyspnea,

light-headedness, throbbing sensation in the neck, palpitations, fatigue or malaise. On physical examination, a patient may have variable pulse volume or blood pressure, intermittent cannon waves, variable intensity of first heart sound and beat-to-beat variation in systolic murmurs.

### Prevalence

The exact prevalence is not known but deemed to be rare.

### Molecular and Systemic Pathophysiology

A normal cardiac impulse arises from the sinus node and is conducted through the AV junction, the bundle of His, and the bundle branches to the ventricles. The sinus node is the dominant pacemaker because its intrinsic rate (60–100 bpm) is faster than subsidiary pacemakers in the AV junction (40–60 bpm) or the ventricles (30–40 bpm). AVD results from (i) slowing of the dominant pacemaker (sinus node), which allows an escape junctional or ventricular rhythm, or (ii) acceleration of a normally slower (subsidiary) pacemaker, such as a junctional or a ventricular site that activates the ventricles without retrograde atrial capture. In AVD, as P-P intervals are longer (slow atrial rate) than R-R intervals (rapid ventricular rate), the P waves will overtake QRS complexes, and P-R intervals become progressively shorter. The P wave first becomes superimposed on the QRS complexes and then eventually moves progressively away from the QRS complexes. When the P wave falls sufficiently behind the QRS complex, it may find an opportunity to get conducted to the ventricles resulting in an earlier QRS complex known as a ventricular capture beat. Ventricular capture beats commonly occur due to AVD with interference within the AV node [3]. The ventricular or AV nodal impulse cannot be conducted antegradely to the atria, as a result sinus impulses cannot be conducted antegradely to the ventricles. However, as the two pacemakers discharge asynchronously (ventricle pacemaker is faster than atrial), the slower sinus discharge occurs later in relation to nodal or ventricular discharge. Therefore, the sinus P wave falls further and further away from the QRS until the stage is reached when a sinus impulse may eventually reach the AV node when it is no longer refractory. When the above occurs, the sinus wave gets conducted to the ventricle. This momentary activation of the ventricles by sinus impulse during AVD produces capture beats. The captured beat is an early beat that is related to the previous sinus P wave. Conditions that initiate AVD include surgical and anesthesia interventions, cardiac surgery, catecholamine surges, catecholamine blocking drugs, sinus node disease, digoxin toxicity, myocardial infarction,



hyperkalaemia, vagal activation, ventricular tachycardia, ventricular pacing, radiofrequency ablation, sinus bradycardia with escape junctional rhythm and cardiac surgery. Whatever the cause, AVD is usually secondary to some other rhythm disturbances or conditions.

### Diagnostic Principles

The electrocardiogram (ECG) is the most commonly used modality to diagnose AVD. The ECG criteria of AVD are as follows: (i) VR faster than AR; (ii) regular P-P and R-R intervals; (iii) no relationship between P wave and QRS complex; (iv) progressively shorter P-R intervals; (v) ventricular capture beats; (vi) P-R interval of the capture complex often longer than expected; and (vii) ventricular fusion complexes [4].

### Therapeutic Principles

The treatment of AVD depends on the underlying condition and its severity. The hemodynamic status of the patient as well as the underlying pathology are the chief determinants of medical care. For patients who are hemodynamically unstable (e.g., patients with ventricular tachycardia), the usual treatment of choice is direct current cardioversion or intravenous drug therapy.

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## Atrioventricular Junctional Reentrant Tachycardia

► Atrioventricular Nodal Reentrant Tachycardia

## Atrioventricular Nodal Reciprocating Tachycardia

► Atrioventricular Nodal Reentrant Tachycardia

## Atrioventricular Nodal Reentrant Tachycardia

A

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### Synonyms

AVNRT; Atrioventricular nodal reentry; Atrioventricular nodal reciprocating tachycardia; Atrioventricular junctional reentrant tachycardia

### Definition and Characteristics

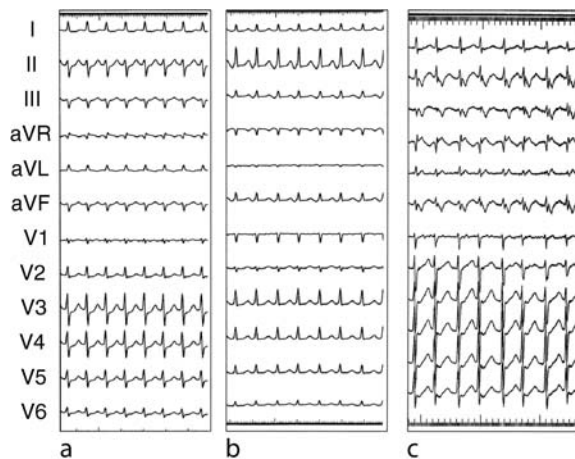
Atrioventricular nodal reentrant tachycardia is the most common form of *paroxysmal* supraventricular tachycardia. AVNRT is more common in women than men (ratio 3:1). Symptoms (palpitations, polyuria, dizziness, presyncope or even syncope) may occur at any age but AVNRT is rare in children (mean age at symptoms onset: 30–43 years; range 5–90 years). Most patients with AVNRT have no structural heart disease. Tachycardia cycle length is extremely variable (600–220 ms) with a mean of 340 ms in the absence of drugs. Predisposing factors are non-specific but stressful situations, exercise or changes in position are frequently reported. The 12-lead resting ECG is usually normal without ventricular preexcitation.

AVNRT is related to the presence of functionally determined dual AV nodal pathways (a slow-conducting one and a fast conducting one) which can be suspected on the 12-lead resting ECG by a short (<0.12 s) P-R interval (non-specific), the occasional presence of two P-R intervals during sinus rhythm or by the presence of double responses (one sinus beat giving two ventricular responses).

AV nodal reentry occurs in three forms [1]: the common, typical form of AVNRT (90%) is called “*slow-fast*” because the anterograde limb of the tachycardia uses the slow pathway and the retrograde limb the fast pathway. In this form, the retrograde P wave during tachycardia occurs simultaneously with the QRS and the ECG demonstrates no P wave or a P wave distorting the terminal part of the QRS complex (rSr’ aspect in lead V1) (Fig. 1a).

The second form of AVNRT (5%) is called “*fast-slow*” or atypical because the anterograde limb of the tachycardia uses the fast pathway and the retrograde limb the slow pathway. Therefore, during tachycardia, the retrograde P wave appears negative in inferior leads and before the QRS (long R-P’ tachycardia) (Fig. 1b).





### Atrioventricular Nodal Reentrant Tachycardia.

**Figure 1** (a) 12-lead resting ECG recorded during *slow-fast AVNRT*: tachycardia is regular, with a ventricular rate of 190 bpm and narrow QRS complexes. P wave is not visible but slight deformation of the terminal part of the QRS complex in lead V1 (rSr' aspect) suggests that the P wave is hidden within the QRS complex. (b) 12-lead resting ECG recorded during *fast-slow AVNRT*: tachycardia is regular, with a ventricular rate of 155 bpm and narrow QRS complexes. P wave is visible before the QRS complex (long R-P tachycardia) and is negative in lead II, III, aVF (retrograde P wave). (c) 12-lead resting ECG recorded during *slow-slow AVNRT*: tachycardia is regular with a ventricular rate of 190 bpm and narrow QRS complexes. P wave is visible after the QRS complex in lead II, III, aVF suggesting a relatively slow retrograde activation of the atrium (differential diagnosis between slow-slow AVNRT and orthodromic AVRT using a concealed accessory pathway).

The third form of AVNRT (5%) is called “*slow-slow*” because one slow pathway is used for anterograde conduction and another slow pathway is used for retrograde conduction (Fig. 1c).

AVNRT may be associated with other forms of tachycardia (orthodromic AVRT using a concealed accessory pathway; atrial flutter or fibrillation; atrial tachycardia; fascicular tachycardia or right ventricular outflow tract tachycardia). Finally, a fourth form of tachycardia may be encountered in association with dual AV nodal conduction: nonreentrant junctional tachycardia related to repetitive double responses. In this particular form of tachycardia two QRS complexes are observed for each P wave which has the morphology of a normal sinus P wave.

### Prevalence

Overall prevalence is unknown because there is no specific ECG marker for AVNRT. AVNRT accounts

for 60–70% of all narrow QRS complex tachycardias referred for investigation or curative treatment with the exception of atrial flutter. Dual AV node conduction may be recorded in many individuals without AVNRT (35–70%) and appears to be non-specific and only related to normal anterior and posterior inputs to the AV node.

### Genes

No specific gene defect or mutation has been described in AVNRT and the vast majority of cases are sporadic. Only one report of familial occurrence of AV nodal duality and AVNRT has been published and this observation has suggested an autosomal dominant genetic defect (dual AV nodal pathways in multiple generation, male-to-male transmission in one family) [2]. Another isolated report has shown dual AV nodal physiology in a pair of identical twin sisters with documented left-sided accessory pathways [3].

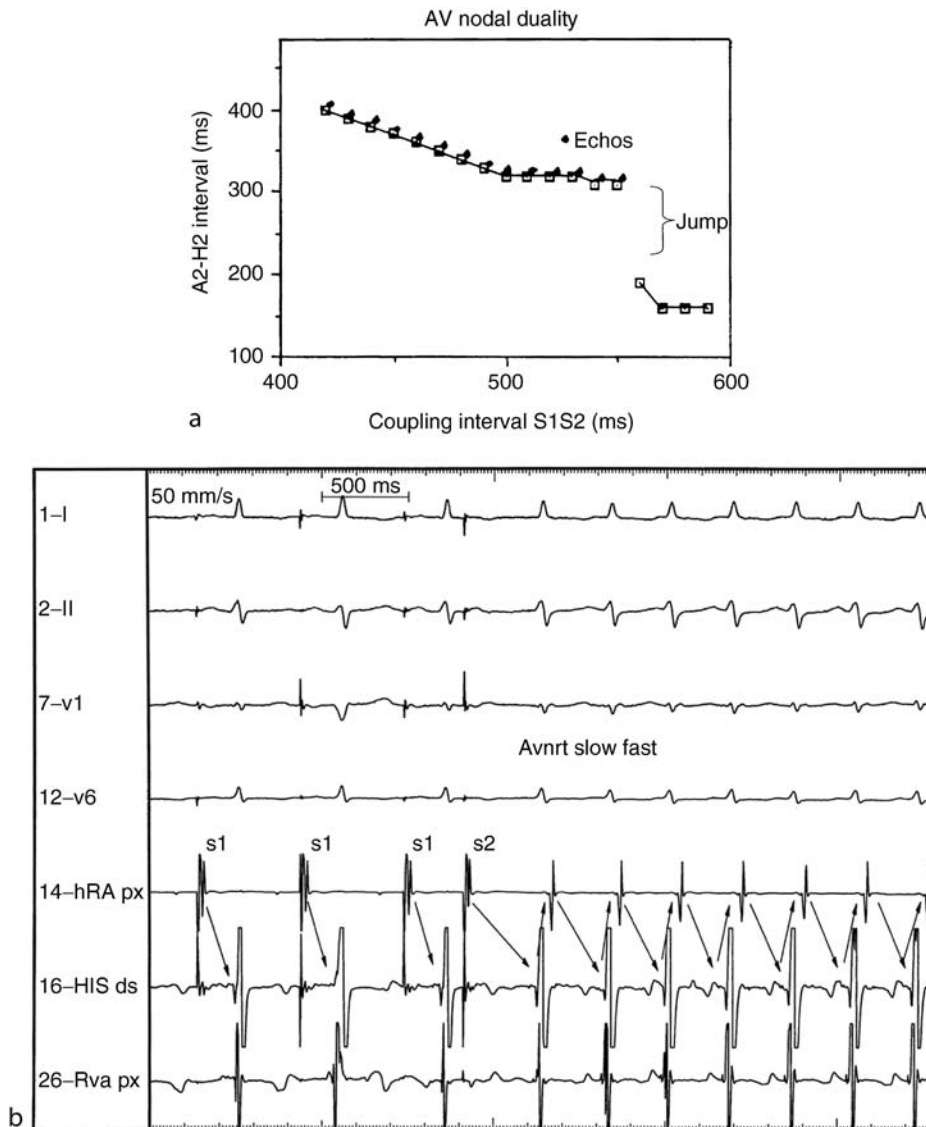
### Molecular and Systemic Pathophysiology

AV nodal reentry is based on dual (or multiple) AV nodal pathways which are essentially functional. The tachycardia circuit incorporates the compact AV node and the perinodal tissue extending from the apex of Koch's triangle to the coronary sinus os and there is still debate if pure atrial tissue is required for the tachycardia. A lower final common pathway also exists since AVNRT can persist despite 2:1 block in the AV node or in the His bundle. During the common slow-fast form of AVNRT retrograde atrial activation is complex reflecting nonuniform anisotropy but the earliest breakthrough usually occurs at the apex of Koch's triangle in the anterior septum close to the His bundle. In the fast-slow form of AVNRT earliest retrograde activation is seen in the posterior Koch's triangle and in the coronary sinus os region.

### Diagnostic Principles

Diagnosis may be suspected on the 12-lead ECG recorded during tachycardia but is confirmed by invasive electrophysiological techniques. In most patients with AVNRT (>85%), AV dual physiology can be demonstrated during atrial extrastimulus testing: when the coupling interval (A1-A2) of the atrial extrastimulus is progressively shortened, an abrupt increase in A2-H2 is observed in the presence of dual AV nodal conduction (“jump” of more than 50 ms in A2-H2 for a 10 ms decrement in A1-A2 which represents the shift of conduction from the fast to the slow pathway) (Fig. 2a).

The A-H “jump” is frequently associated with the appearance of an atrial echo beat (through the fast



**Atrioventricular Nodal Reentrant Tachycardia. Figure 2** (a) Demonstration of AV nodal duality by extrastimuli applied in the atrium. At 560 ms of coupling interval, a jump in A2-H2 interval is observed (from 190 to 310 ms) together with slow-fast echo beats. (b) Initiation of slow-fast AVNRT by a single atrial extrastimulus S2. A A2-H2 jump is observed after S2 and this critical increase in A-H interval initiates slow-fast AVNRT.

pathway used retrogradely) or with the initiation of a slow-fast AVNRT (Fig. 2b).

Therefore, AVNRT initiation depends on a critical A-H interval in most cases. During tachycardia atrial activation occurs simultaneously with ventricular activation (a mean of 50 ms after His bundle activation) and the earliest atrial depolarization is recorded at the apex of Koch's triangle just above the compact AV node. Differential diagnosis between AVNRT and orthodromic AVRT using a concealed septal accessory pathway may be difficult and is based on timing of retrograde atrial activation, on ventricular stimulus testing and on parahisian pacing techniques. Differentiation of AVNRT

from atrial tachycardia is essentially made using ventricular extrastimuli (V-A-A-V response).

### Therapeutic Principles

1. *Acute Termination of AVNRT*: vagal manoeuvres can frequently terminate tachycardia and patients should be instructed on how to apply these techniques. Intravenous adenosine is highly effective for AVNRT termination and is considered the drug of first choice. Calcium channel blockers (verapamil, diltiazem) and betablockers can also be used. All these drugs affect reentry by slowing or blocking conduction over the slow pathway.

2. **Chronic Management:** betablockers, calcium channel antagonists, amiodarone, digitalis (acting mainly on the slow pathway) or class Ic antiarrhythmic drugs (acting mainly of the fast pathway) may all be effective for prevention of AVNRT but the pharmacologic approach is limited by partial inefficacy, numerous side effects and potential serious adverse reaction. Radiofrequency catheter ablation of the slow pathway is currently the method of first choice for symptomatic patients and should be proposed after the first recurrence [4]. Success rate of radiofrequency catheter ablation is 97–98%, recurrences are rare (2–3%) and the risk of AV block is <0.5%. Slow pathway ablation is conducted on anatomic and electrophysiologic basis and the optimal site is in the lower Koch's triangle just anteriorly to the os of the coronary sinus [5]. Junctional beats are observed during RF application at successful sites. Complete abolition of slow pathway conduction is not mandatory and a simple modification of conduction over the slow pathway is sufficient for clinical cure. Cryo-ablation techniques are currently under development in order to minimize the risk of AV block but recurrence rate is higher and AV block cannot be completely avoided.

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## Atrioventricular Nodal Reentry

### ► Atrioventricular Nodal Reentrant Tachycardia

## Atrioventricular Septal Defects

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### Synonyms

Atrioventricular canal defect; Endocardial cushion defect; Canalis atrioventricularis communis; Persistent atrioventricular ostium

### Definition and Characteristics

*Partial Atrioventricular Septal Defect:* Ostium Primum Defect and cleft in the anterior leaflet of Mitral valve.

*Complete Atrioventricular Septal Defect:* Ostium Primum Defect, Inlet Ventricular Septal Defect and Common Atrioventricular valve consisting of five leaflets [1].

*Classification on the Basis of the Anterior Bridging Leaflet (ABL):* Rastelli Type A with ABL separated into two portions of approximately equal size and attached to the anterior papillary muscle of the respective ventricle; Rastelli Type B with unattached, but separated ABL; Rastelli Type C with unattached, undivided ABL floating above the interventricular septum.

### Prevalence

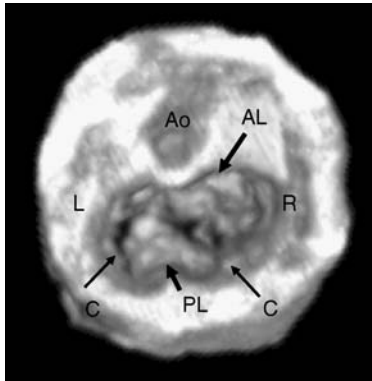
4.4 – 4.8% of congenital heart defects.

### Genes

23–60% of patients with AVSD are affected by Trisomy 21 (Down syndrome), where an alteration in the DSCR1 (Down Syndrome Critical Region 1) as a regulatory protein in the Calcium-NFAT-pathways is thought to be responsible for the insufficient fusion of endocardial cushions. In the remaining patients mutations in the AVSD1-locus (1p31-p21) or AVSD2-locus (3p25) can be found.

### Molecular and Systemic Pathophysiology

The septal defects of both partial and complete AVSD lead to increasing left-to-right shunt immediately after birth as pulmonary vascular resistance decreases. After 12 weeks of life, pulmonary (Qp) to systemic (Qs) blood flow ratio reaches its maximum. Frequently an additional volume load is caused by valve regurgitation. Children with partial AVSD may appear normal until adulthood, due to small shunt volume. Depending on the amount of the shunt, infants with complete AVSD



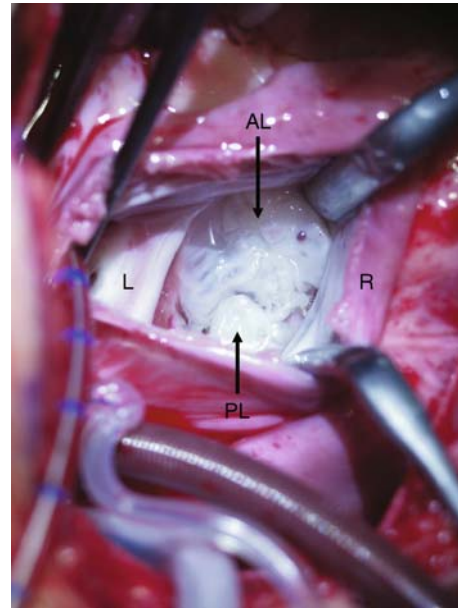
**Atrioventricular Septal Defects. Figure 1**

Three-dimensional echocardiographic view on the atrioventricular valves in atrioventricular septal defect from above: a prominent anterior bridging leaflet (AL), a small posterior bridging leaflet (PL) with the typical “cleft” in between is shown, R = right ventricular side, L = left ventricular side, A = aortic root.

present with signs of congestive heart failure such as dyspnea, growth retardation and tachycardia. Pulmonary vascular disease usually develops after the first year of life as a consequence of near systemic pulmonary pressure levels.

### Diagnostic Principles

Auscultatory findings depend on the nature of the underlying pathophysiology: in partial AVSD they are similar to fossa ovalis defects (pulmonic flow murmur in the second left intercostal space with wide, fixed splitting of the second heart sound) or – as atrioventricular valve regurgitation dominates – an apical holosystolic murmur. In complete AVSD the murmur of atrioventricular valve regurgitation is present, radiating toward the sternum rather than toward the axilla. In pulmonary hypertension the splitting of the second heart sound is narrow and associated with a loud pulmonic component. A loud holosystolic murmur indicating shunt flow across the Ventricular Septal Defect may be heard. ECG shows a prolonged PR interval, right ventricular hypertrophy and a deviation of the frontal plane QRS-axis between  $90^\circ$  and  $-120^\circ$  in 95% of the patients. Echocardiography is diagnostic, revealing absent atrioventricular septum (Fig. 1). In partial AVSD the atrioventricular leaflets appear to originate from the crest of the ventricular septum and usually at the same level. In complete AVSD the inlet-VSD is shown in addition. Colour-Doppler studies outline the regurgitation of the atrioventricular valves (Fig. 2) as well as the direction of atrial and ventricular shunting. Cardiac catheterization is necessary only when non-invasive diagnostic procedures leave significant



**Atrioventricular Septal Defects. Figure 2**

Intraoperative view on the atrioventricular valves: the right atrium is open and the small anterior bridging leaflet (AL) as well as the prominent posterior bridging leaflet (PL) and the cleft is seen.

questions unanswered or when there are concerns about pulmonary vascular disease with elevated resistance.

### Therapeutic Principles

In complete AVSD, corrective surgery is normally indicated in the fourth to sixth month of life. If the infant is developing congestive heart failure, a short term medical treatment with diuretics and fluid restriction can be discussed. Most centres prefer the surgical procedure in these circumstances, consisting of one- or two-patch repair of the septum and reconstruction of the atrioventricular valves. In partial AVSD the decision for corrective surgery is based on the amount of ventricular volume load and mitral regurgitation. Patch closure of the defect and reconstruction of the mitral valve are normally performed between the second and fourth year of life.

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## Atrophia Blanche

- Livedo Vasculopathy

## Atrophia Bulborum Hereditaria

- Norrie Disease

## Atrophia Gyrata

- Gyrate Atrophy of the Choroid and Retina

## Atrophic Polychondritis

- Polychondritis, Atrophic

## Attempted Suicide

- Suicide

## Attention-Deficit Disorder

- Attention-Deficit/Hyperactivity Disorder

## Attention-Deficit/Hyperactivity Disorder

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### Synonyms

ADD; Attention-deficit disorder; HKS; Hyperkinetic syndrome; ADHD

### Definition and Characteristics

Attention-deficit/hyperactivity disorder (ADHD; MIM 143465) is defined as a clinically heterogeneous neurodevelopmental syndrome characterized by inattention, excessive motor activity, and impulsivity. It is the most common behavioral disorder in children with persistence into adulthood which profoundly compromises functioning in multiple areas throughout the life span and can significantly contribute to a variety of health, social, and economic problems. Affected individuals are at increased risk for poor educational and occupational achievement despite normal cognitive and intellectual abilities, low income, underemployment, impaired social skills and relationships, family dysfunction, legal difficulties, and delinquency. On the other hand, high IQ and a highly supportive, well-structured family environment are protective factors against ADHD-related behavioral limitations. While an age-dependent fading may render symptoms not prominent enough to justify diagnosis of ADHD in adulthood, they are frequently associated with clinically significant impairment of cognitive and executive functions as well as stress coping and emotion regulation. As a result, adult ADHD is characterized by high co-morbidity with depression, anxiety disorders, alcohol/drug dependence, and antisocial personality disorders.

### Prevalence

ADHD is a highly prevalent, worldwide disorder estimated to affect 5–10% of children and 3–6% of adults.

### Genes

Twin, adoption, and molecular genetic studies revealed that ADHD is a highly heritable disorder ( $h^2$ : 70–80%) with a multifactorial pattern of inheritance, likely due to several genes of small or moderate effect size [1]. Genom-wide linkage analyses identified several susceptibility loci with maximum LOD scores of 2.1–3.7, for example on chromosome 4q13.2, 5p13, 5q23.3,



6q12, 7p13, 9q33, 11q22, 15q15, 16p13, and 17p11. Finemapping of the region on 4q13.2 identified a common haplotype within the latrophilin 3 (LPHN3) gene which confers susceptibility to ADHD with a relative risk (RR) of  $\sim 1.3$  [2]. Frequency ( $\sim 21\%$ ), extent of linkage disequilibrium ( $\sim 300$  kb), and ancestry of the LPHN3 susceptibility haplotype is consistent with the concept that traits associated with the ADHD phenotype have been subject to positive selection and that ADHD is the extreme of a normal variation exacerbated by adverse environmental circumstances.

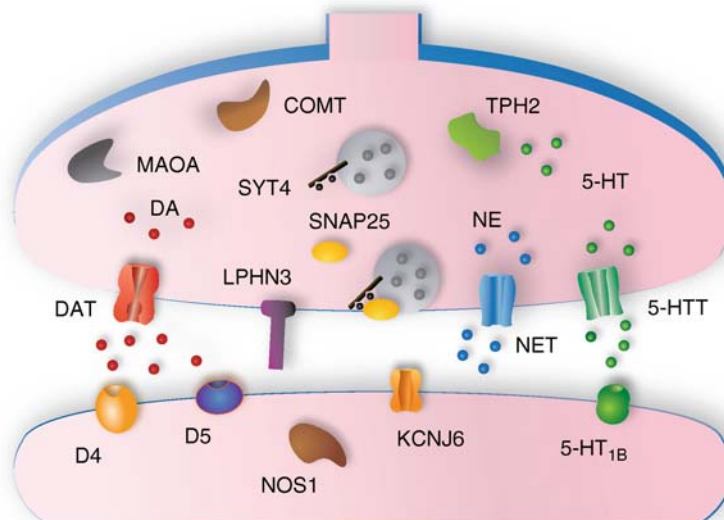
With focus on relevance to pathophysiological and pharmacotherapeutic mechanisms, the candidate gene approach has also been utilized in case-control or family-based studies. Investigations concentrated on genes which modulate synaptic transmission and, on the basis of the pooled odds ratios of 1.19–1.45 across studies, association with ADHD was detected for genes encoding key modulators of the dopaminergic and serotonergic signalling pathways, such as the dopamine 4 receptor (DRD4), dopamine 5 receptor (DRD5), dopamine transporter (DAT, SLC6A4), serotonin 1B receptor (HTR1B), serotonin transporter (5-HTT, SLC6A4), tryptophan hydroxylase 2 (TPH2),

and synaptosomal-associated protein 25 (SNAP25) (see Fig. 1) [3].

Moreover, gene targeting approaches, e.g. generation of a DAT knockout mouse, provide informative insight into pathophysiological mechanisms of locomotor hyperactivity and effects of psychostimulant drugs, such as methylphenidate or cocaine. Finally, complex interactions are to be expected between environmental factors and multiple genes each with a small to moderate influence on different traits. Perinatal complications, low socio-economic status, disruptive family environment and other psychosocial adversity have been identified as predisposing environmental risk factors. While prenatal and parental risk factors may be critical mediators of influences on the risk, the association between these variables and ADHD is generally indirect.

### Molecular and Systemic Pathophysiology

Converging evidence from animal and human studies including structural and functional neuroimaging implicates dysregulation of prefrontal–striatal–thalamic–cerebellar excitatory and inhibitory circuits with broadening to a multi-pathway framework in the



**Attention-Deficit/Hyperactivity Disorder. Figure 1** Proteins (*genes*) that are known or suspected to be altered in function or amounts in attention-deficit/hyperactivity disorder (ADHD). Dopamine 4 receptor (D4, *DRD4*), dopamine 5 receptor (D5, *DRD5*), dopamine transporter (DAT, *SLC6A4*), serotonin 1B receptor (5-HT<sub>1B</sub>, *HTR1B*), serotonin transporter (5-HTT, *SLC6A4*), monoamine oxidase A (*MAOA*), catechol-O-methyltransferase (*COMT*), nitric oxide synthase 1 (*NOS1*), and tryptophan hydroxylase 2 (*TPH2*) are key modulators of dopaminergic and serotonergic signalling pathways. DAT, NET, and 5-HTT are targets for psychostimulant drugs, methylphenidate and d-amphetamine, the non-stimulant atomoxetine, and antidepressants. Synaptosomal-associated protein 25 (*SNAP25*), synaptotagmine 4 (*SYT4*), and latrophilin 3 (*LPHN3*) are critically important in the regulation of neurotransmitter release. DAT, SYT4, and potassium channel, inwardly rectifying, subfamily J, member 6 (*KCNJ6*) knockout mouse have provided insight into pathophysiological mechanisms of locomotor hyperactivity and effects of psychostimulant drugs.

pathophysiology of ADHD. It is widely accepted that ADHD is the common final behavioral consequence of an array of dysfunctions in each of several independent systems, such as cognitive, motivational, and executive pathways, as well as circuitries of stress adaptation and emotion regulation. Executive functions, which consist of a set of higher order thought processes required for adaptive and future-oriented behavior (e.g. deliberate suppression of a response to achieve a later, internally represented goal) and are controlled by frontal-subcortical circuits, include behavioral inhibition, working memory, attention set-shifting, interference control, planning, and sustained attention. Impairment of executive functions with failure of inhibitory control; dysregulation of brain systems mediating reward and response cost; and deficits in arousal, activation, and effortful control, are central to the pattern of neuropsychological deficits. Deficits in arousal and effort lead to state-dependent cognitive deficits and underscore the view of an impairment in regulating cognitive functions rather than core deficits in any single function. Inattention but not hyperactivity/impulsivity is associated with deficits in executive functioning and poor academic achievement, whereas hyperactivity/impulsivity appears to be more closely related to dysfunctions of reward mechanisms.

Functional neuroimaging studies have assessed the degree of brain activation associated with neuropsychological tasks of attention and disinhibition. The findings are consistent with the structural studies indicating delays in brain maturation processes and locating abnormalities of brain activation in patients with ADHD in fronto-subcortical–cerebellar circuits [4]. Since the spectrum of ADHD features is not explained by a single neuropsychological deficit, disorder-associated impairments are heterogeneous and this complexity corresponds with causal heterogeneity. Despite recognition of ADHD as a neurodevelopmental condition, only few causal explanations have considered the two-way interactions between pre-existing abnormal functioning and biological, cognitive, emotional, motor and social developmental processes, and their contribution to the expression of the clinical phenotype.

The notion that dysregulation of dopamine, norepinephrine, and serotonin signalling pathways underlies ADHD was initially suggested by the action of therapeutically effective compounds (e.g. methylphenidate, atomoxetine, citalopram), which increase the synaptic availability of these neurotransmitters, and by animals showing that lesions in or genetic modification of these pathways (as well as cholinergic, glutamatergic, and GABAergic signalling) create animal models of ADHD. Neuroimaging showed that methylphenidate exerts some of its therapeutic effects by binding to DAT located in subcortical structures abundant with dopaminergic terminals and synapses

such as the striatum. Several but not all studies using radiolabelled ligands indicated an increase of DAT binding in adults with ADHD.

### Diagnostic Principles

Although classification systems such as DSM-IV and ICD-10 provide structured, criterion-based diagnoses for ADHD, they have several limitations. The diagnostic items, although well-described, largely fail to provide developmentally sensitive definitions and to assist differentiation of ADHD symptoms from developmentally healthy levels of inattention, hyperactivity, and impulsivity. During the diagnostic assessment, data from multiple informants (e.g. parent and teacher; parent and teenage child; adult with ADHD and spouse) are acquired but categorical classification systems provide no guidelines to integrate this information.

While basically descriptive and theoretical, three symptom-based subtypes of ADHD have been accepted: mainly inattentive, mainly hyperactive–impulsive, or both combined. Evidence for the validity and clinical use of these subtypes is mixed and the ongoing controversy about whether a purely inattentive disorder exists that could be causally different, is motivating the search for neurobiological construct-based and quantifiable intermediate traits, termed endophenotypes, that lie in the pathway from genes to behavior predicting an individual's disease risk [5]. Intermediate phenotypes may be neuromorphological, neurophysiological or neuropsychological in nature. Criteria whether or not an endophenotype relates to genetic causes of ADHD are that the endophenotype should itself be heritable, co-segregate with ADHD within families, and the endophenotype found in affected family members should also be found in non-affected family members at a higher rate than in the general population. Deconstructing ADHD into its underlying neurobiological component processes not only facilitates genetic analysis but also offers alternative ways of describing and classifying those with the disorder and reduce the heterogeneity associated with categorical classification.

### Therapeutic Principles

Pharmacological treatments of ADHD are psychostimulant drugs, methylphenidate (including long-acting formulations) and d-amphetamine, and the non-stimulant atomoxetine, which enhance neurotransmission of dopamine and norepinephrine [1]. Emotional dysregulation and comorbid depression is frequently treated with antidepressants, such as sertraline or venlafaxine. Psychosocial interventions are used for children and cognitive–behavior therapy is helpful against symptoms and associated features of ADHD particularly in adults. After pharmacological treatment has been initiated, assessment of residual dysfunctions

leads to subsequent implementation of psychosocial and behavioral treatment strategies.

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## AT-V1

►Nijmegen Breakage Syndrome

## AT-V2

►Nijmegen Breakage Syndrome

## Atypical HUS

►Hemolytic Uremic Syndrome

## Atypical Phenylketonuria

►Tetrahydrobiopterin Deficiencies

## Atypical PKU

►Hyperphenylalaninemia

## Austin Disease

►Multiple Sulfatase Deficiency

## Autism Spectrum Disorders

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### Synonyms

Pervasive development disorders; PDD; ASD

### Definition and Characteristics

Autism spectrum disorders (ASD) are diagnosed on the basis of a triad of behavioral impairments: impaired social interaction, impaired verbal and non verbal communication skills and restricted, repetitive and stereotyped patterns of behavior. Autism is not a single entity, but rather a constellation of conditions ranging from a severe form, called autistic disorder, to a milder form, Asperger syndrome. ASD also include pervasive developmental disorder not otherwise specified (PDD-NOS), and very severe disorders like Rett syndrome and childhood disintegrative disorder. ASD can be associated with other genetic disorders, chromosomal anomalies, but in the majority of the cases, the cause of ASD remains unknown (Fig. 1a).

### Prevalence

60–116:10,000 in ASD; 13–39:10,000 in autistic disorder; 3–10:10,000 in Asperger syndrome; 31:10,000 in PDD-NOS; 1:10,000 in Rett syndrome; 0.2:10,000 in childhood disintegrative disorders. For autistic disorder the male:female ratio is 4:1; For individuals with normal to high IQ, including those with Asperger syndrome, the male:female ratio may be closer to 10:1.

### Genes

Genes associated with ASD fall into three categories: genes causing syndromes associated with ASD, genes

altered by chromosomal abnormalities, and genes mutated in idiopathic ASD [1].

*Syndromes Associated with ASD (only the Most Frequent are Indicated):* ► **Fragile X syndrome:** CGG triplet expansion in FMR1 (Xq28) encoding FMRP a protein regulating translation at the synapse.

► **Rett syndrome:** (mostly *de novo*) point mutations in *MECP2* (Xq28) encoding the methyl binding protein MECP2 regulating gene expression by remodelling chromatin.

► **Tuberous sclerosis:** point mutations in *TSC1* (9q34) or *TSC2* (16p13) encoding the tumour suppressor proteins TSC1 or TSC2.

► **Neurofibromatosis:** point mutations in *NF1* (17q11) encoding the tumour suppressor protein NF1.

► **Cowden syndrome:** (mostly *de novo*) point mutations in *PTEN* (10q23) encoding the tumour suppressor protein PTEN. *PTEN* mutations seem to be restricted to 3 patients with macrocephaly.

*Chromosomal Rearrangements:* A large number of chromosomal rearrangements have been associated with ASD, but the most frequent anomalies are the 15q11–13 duplication and the 22q13 deletion.

**Chromosome 15q11–13 duplication:** The most frequent chromosomal rearrangement in ASD ( $\approx 1\text{--}2\%$ ) is a tandem duplication of a maternal 4–5 Mb region corresponding to 15q11–q13, or supernumerary pseudo-dicentric, inverted, and duplicated regions of chromosome 15. The ASD phenotype of 15q11–13 duplication is characterized by epilepsies, hypotonia and motor coordination problems combined with moderate to severe mental retardation and speech delay or absence of speech.

**Chromosome 22q13 deletion:** The *de novo* deletion can vary from 130 kb to 9 Mb, but always include SHANK3 (see below).

*Single Gene Associated with ASD:* NLGN3/NLGN4: point mutations or deletions of neuroligins NLGN3 (Xq13)/NLGN4 (Xp22) encoding the postsynaptic cell adhesion molecules NLGN3 and NLGN4.

**SHANK3:** deletions of chromosome 22q13 or point mutations in SHANK3 (22q13) encoding the synaptic scaffolding protein SHANK3. Mutations in SHANK3/22q13 seem to be restricted to patients presenting with neonatal hypotonia and absence or severely delayed speech.

**NRXN1:** a *de novo* deletion of neurexin NRXN1 (2p16) was identified in two sisters with ASD. NRXN1 encodes a presynaptic cell adhesion molecule, which binds to the postsynaptic neuroligins.

## Molecular and Systemic Pathophysiology

ASD can be associated with a broad range of anomalies affecting different physiological processes such

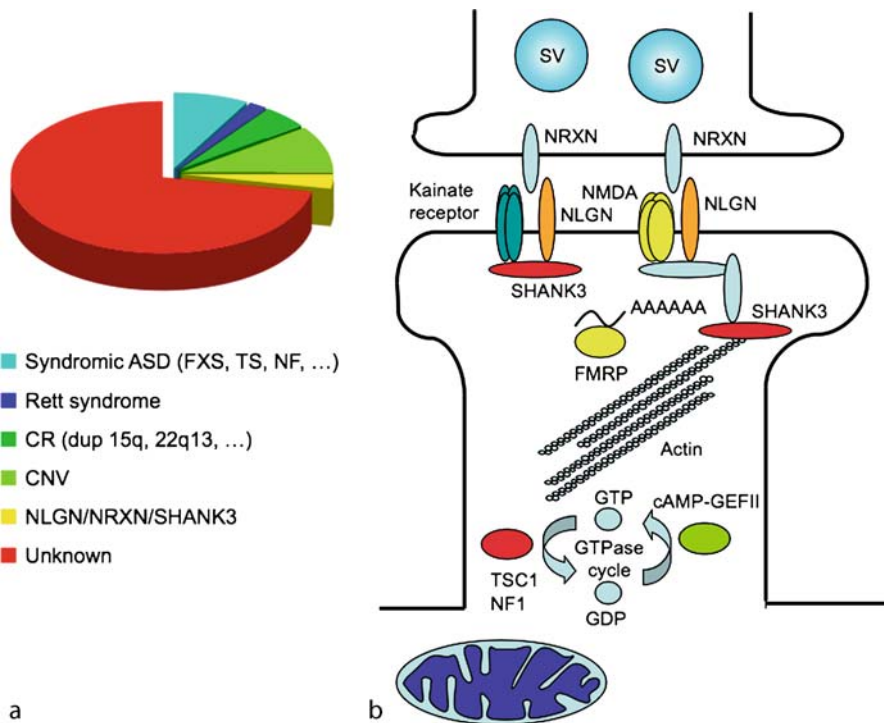
as chromatin remodelling (MECP2), synaptic gene regulation (FMRP), actin skeleton dynamics (TSC1/TSC2, NF1), cell growth (PTEN) and calcium signaling (CACNA1C). Although the mutated genes are numerous and diverse, they might all affect the same downstream pathways at the origin of ASD. One such pathway may include the synaptic protein NLGN, NRXN and SHANK3 (Fig. 1b). NLGN and NRXN are synaptic cell adhesion proteins and crucial factors for the validation and maintenance of functional synapses. SHANK3 is the gene causing the neurological phenotype of the 22q13 deletion syndrome and encodes a postsynaptic scaffolding protein, which binds to the NLGN. Mutations in NLGN3, NLGN4, NRXN1 and SHANK3 were identified in apparent monogenic form of ASD [2–4]. The mutations of the NLGN and SHANK3 were found to cause abnormal synaptogenesis and SHANK3 clustering in neuronal cell cultures. Interestingly, at least in humans, this synaptic pathway is sensitive to gene dosage since mutations, or loss of one copy, of NRXN1 or SHANK3 are associated with autism, whereas the presence of an extra copy of SHANK3 might be associated to Asperger syndrome [3,4]. Although mutations within NLGN/NRXN/SHANK3 concern a limited number of patients, these results strongly suggest that this synaptic pathway – crucial for the appropriate functional validation of the synapse, as well as a correct balance between glutamatergic and GABAergic synapses – is a core component of ASD.

## Diagnostic Principles

Due to the genetic heterogeneity of ASD and the absence of biomarker, the diagnostic protocol should include a full clinical assessment, including neurologic and genetic assessment, along with cognitive and language testing. If present, syndromes associated with ASD should be carefully examined at the clinical and molecular level by genetic test of the causative genes. For research purpose, structured interviews are used such as the Autism Diagnosis Interview–Revised (ADI–R), the 3di (Developmental, Dimensional and Diagnostic Interview), and the DISCO (Diagnostic Interview for Social and Communication Disorders). Parental reports may be supplemented by standardized observational assessments such as the Autism Diagnostic Observation Schedule (ADOS) or the Childhood Autism Rating Scale (CARS).

At the genetics level, *de novo* copy number variants (CNVs) seem to be frequent ( $\approx 10\%$ ) in ASD and can be detected using DNA arrays [3, 5]. In addition, the synaptic genes NLGN3, NLGN4, SHANK3 and NRXN1 could also be screened for mutations. However, mutations in these genes affect a limited number





**Autism Spectrum Disorders. Figure 1** The heterogeneity of ASD and synaptic proteins associated with the disorder. **a.** A broad estimation of the cause of ASD. ASD includes  $\approx 8\%$  of known genetic syndromes (e.g. Fragile X Syndrome (FXS), Tuberous sclerosis (TS), Neurofibromatosis (NF)),  $\approx 2\%$  of Rett syndrome,  $\approx 5\%$  of chromosomal rearrangements (CR),  $\approx 10\%$  of copy number variants (CNVs),  $\approx 3\%$  of mutations in the NLGN/NRXN/SHANK3 pathway, and  $\approx 72\%$  of unknown causes. These numbers are only a broad estimation since epidemiological data concerning the causes of ASD are missing. In addition, the percentage may vary for sporadic or familial cases and if the affected individual has dysmorphic features. **b.** The synaptic genes associated with ASD. Synaptic vesicles (SV) and neurexins (NRXN) are present at the presynaptic side of a glutamate synapse. At the postsynaptic side, the NLGN and the glutamate receptors bind to scaffolding proteins of the postsynaptic density (PSD) such as SHANK3. The FMRP controls the translation of several synaptic proteins. TSC1 and NF1 are regulating the actin dynamics and the morphology of the neuron.

of individuals ( $\approx 3\%$  of ASD) and their functional consequences are still difficult to interpret since they can be associated with a range of severities.

At the biochemical level, a high level of serotonin and a decrease of melatonin were repeatedly reported in ASD. The low level of melatonin was shown to be often the consequence of a primary enzyme deficiency of ASMT/HIOMT, the last enzyme of the melatonin synthesis pathway. When melatonin levels are low, individuals with ASD may benefit from melatonin treatment for reducing their sleep problems.

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## Autoimmune Cardiomyopathy

► Myocarditis, Autoimmune



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## **Autoimmune Cholangitis**

- ▶ Cholangitis, Autoimmune

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## **Autoimmune Chronic Active Hepatitis**

- ▶ Hepatitis, Autoimmune

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## **Autoimmune Hemolytic Anemia**

- ▶ Anemia, Hemolytic Autoimmune

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## **Autoimmune Hepatitis**

- ▶ Hepatitis, Autoimmune

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## **Autoimmune Hypophysitis**

- ▶ Hypophysitis, Autoimmune

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## **Autoimmune Inner Ear Disease**

- ▶ Inner Ear Disease, Autoimmune

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## **Autoimmune Liver Disease**

- ▶ Hepatitis, Autoimmune

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## **Autoimmune Myasthenia Gravis**

- ▶ Myasthenia Gravis

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## **Autoimmune Myocarditis**

- ▶ Myocarditis, Autoimmune

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## **Autoimmune Neuromyotonia**

- ▶ Neuromyotonia, Autoimmune and Idiopathic

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## **Autoimmune Pancreatitis**

- ▶ Pancreatitis, Autoimmune

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## **Autoimmune Polyendocrinopathy- Candidiasis-ectodermal Dystrophy**

- ▶ Multiple Endocrine Abnormalities

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## **Autoimmune Polyendocrinopathy Ectodermal Dystrophy**

- ▶ Polyendocrinopathy      Ectodermal      Dystrophy,  
Autoimmune

## Autoimmune Polyendocrinopathy Syndrome

► Polyendocrinopathy      Ectodermal      Dystrophy, Autoimmune

## Autoimmune Thrombocytopenic Purpura

► Thrombocytopenic Purpura, Idiopathic

## Autoimmunity-Immunodeficiency Syndrome, X-linked

► Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Autonomously Functioning Thyroid Nodules

► Hyperthyroidism due to Thyroid Autonomy

## Autosomal Dominant Cerebellar Ataxia

► Ataxias, Spinocerebellar

## Autosomal Dominant Cutis Laxa

► Cutis Laxa

## Autosomal Dominant Distal Myopathy

► Distal Myopathy, Autosomal Dominant

## Autosomal Dominant GTP Cyclohydrolase I [adGTPCH] Deficiency

► Tetrahydrobiopterin Deficiencies

## Autosomal Dominant Hypocalcaemia with Hypercalciuria

► Hypocalcaemia with Hypercalciuria, Autosomal Dominant

## Autosomal Dominant Hypophosphatemic Rickets

► Osteomalacia  
► Rickets, Autosomal Dominant Hypophosphatemic

## Autosomal Dominant Ichthyosis Vulgaris

► Ichthyosis Vulgaris

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## **Autosomal Dominant Mandibulofacial Dysostosis**

- ▶ Treacher Collins Syndrome

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## **Autosomal Dominant Polycystic Kidney Disease**

- ▶ Polycystic Disease (Kidney)

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## **Autosomal Dominant Muscular Dystrophy, Emery-Dreifuss**

- ▶ Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

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## **Autosomal Dominant Pseudohypoaldosteronism**

- ▶ Pseudohypoaldosteronism, Autosomal Dominant
- ▶ Hypotension, Hereditary

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## **Autosomal Dominant Myopathy with Congenital Joint Contractures**

- ▶ Myosin Heavy Chain IIa Myopathy, Autosomal Dominant (E706K)

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## **Autosomal Recessive Pseudohypoaldosteronism**

- ▶ Pseudohypoaldosteronism, Autosomal Recessive

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## **Autosomal Dominant Myosin Heavy Chain IIa Myopathy**

- ▶ Myosin Heavy Chain IIa Myopathy, Autosomal Dominant (E706K)

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## **Autosomal Recessive Congenital Ichthyosis**

- ▶ Lamellar Ichthyosis

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## **Autosomal Dominant Optic Atrophy Kjer Type**

- ▶ Optic Atrophy, Autosomal Dominant, Kjer Type

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## **Autosomal Recessive Cutis Laxa Type 1**

- ▶ Cutis Laxa

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## **Autosomal Dominant Osteopetrosis Type II**

- ▶ Albers-Schönberg Disease

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## **Autosomal Recessive Cutis Laxa Type 2**

- ▶ Cutis Laxa

## Autosomal Recessive Endosteal Hyperostosis

- Van Buchem Disease and Sclerosteosis

## Autosomal Recessive Medullary Cystic Disease

- Nephronophthisis

## Autosomal Recessive Polycystic Kidney Disease

- Polycystic Disease (Kidney)

## Autosomal Recessive Pseudohypoaldosteronism

- Hypotension, Hereditary

## Autosomal Recessive Sepiapterin Reductase Deficiency

- Tetrahydrobiopterin Deficiencies

## AV Accessory Pathways

- Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## AV Fistula

- Arteriovenous Fistula

## AV Shunt

- Arteriovenous Fistula

## Avascular Bone Necrosis

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### Synonyms

Osteonecrosis; Ischemic necrosis; Aseptic necrosis

### Definition and Characteristics

Pathological process characterized by deficient oxygen supply to the bone leading to bone tissue death, with possible epiphyseal fracture, and early osteoarthritis. Joint destruction eventually occurs within three to five years. The femoral head is most commonly clinically affected. Other sites include the knee, the humeral head, and less frequently the small bones of the wrist and the foot. Bilateral involvement is found in many patients at the time of diagnosis which is usually made between ages 30 and 60 years. Male to female ratio is 7:3 [1].

### Prevalence

300,000–600,000 cases of avascular necrosis (AVN) of the femoral head have been estimated in the USA. The incidence is approximately 15,000 new patients diagnosed per year.

### Genes

COL2A1 mutations in inherited familial osteonecrosis of the femoral head have been described in three Taiwanese families [2].

### Molecular and Systemic Pathophysiology

Avascular bone necrosis results from decreased blood flow within the bone as a result of traumatic or non-traumatic conditions. Traumatic causes include injury, fracture or dislocation leading to interruption of vascular supply to the bone. Non-traumatic conditions are associated with the administration of corticosteroids, excessive alcohol use, smoking, SLE, antiphospholipid antibodies, hemoglobinopathies (sickle-cell anemia, polycythaemia), acute leukaemias, storage disorders (Gaucher disease), hyperbaric events, radiation therapy, HIV infection, heritable thrombophilia (antithrombin or factor V Leiden genes mutations), hypofibrinolysis (variant plasminogen activator inhibitor-1 genotype) or it can be idiopathic. Although the pathogenesis of non-traumatic osteonecrosis is not well defined, it appears to involve vascular damage, occlusion of intra-osseous capillaries, increased local pressure, bone and cell death or defective bone repair [1]. Avascular necrosis generally develops in yellow marrow. In few conditions (hemoglobinopathies, storage disorders) it may develop in red marrow. There is a genetic predisposition for individuals exposed to the two leading etiologic associations for AVN: corticosteroids and alcohol [3]. In steroid-induced osteonecrosis, possible mechanisms involve alterations in circulating lipids resulting in fat embolism, intra-medullary fat-cell hypertrophy with compression of local capillaries, or changes in venous endothelial cells, leading to stasis, increased intraosseous pressure (mainly in weight-bearing bones), and eventual

necrosis. In alcohol-induced osteonecrosis, fat emboli, venous stasis and increased cortisol levels have been implicated as etiologic factors [1].

### Diagnostic Principles

Pain (often non-specific) is the most common presenting symptom. [1]. Magnetic resonance imaging (MRI) is the most accurate non invasive test for detecting AVN at early stages with sensitivities and specificities approaching 100%. The “double line sign” observed on T2- weighted images occurs at the interface between viable and non-viable tissue and is pathognomonic of AVN. This double line appears as a single low intensity band on T1- weighted images (Fig. 1) [4].

Plain radiography lacks sensitivity in the early stage of the disease and is generally diagnostic only after the development of the “crescent sign” at the ischemic interface. Bone scintigraphy can detect AVN before radiographic changes when there is increased vascularity [5].

### Therapeutic Principles

The choice of treatment depends on four factors: (i) the bone involved, (ii) the stage of disease, (iii) the size of the necrotic lesion, and (iv) the morbidity of the proposed treatment. Symptomatic joints should be put at rest. Joint-preserving procedures are indicated for the earlier stages of AVN and include core decompression with or without bone grafting (vascularized and non-vascularized) and osteotomy. Core decompression relieves pain by decreasing



**Avascular Bone Necrosis. Figure 1** Coronal T1- (left panel) and T2-weighted (right panel) Spin Echo Images of the right femoral head of an asymptomatic patient with previous hip dislocation show femoral head necrosis characterized by a rim of low signal intensity (black arrow) on T1-weighted and low (black arrow) and high signal intensity (white arrow) on T2-weighted images. The signal of the infarct is similar to that of fat because it contains mummified necrotic fatty marrow.



intra-osseous pressure and stimulating neovascularization and is used to treat early stages of AVN of the femoral head when the size of the lesion is small (less than 30% femoral head involvement). Osteotomy is an option for patients with discrete necrotic lesion that can be shifted away from the weight-bearing area of the joint. Arthroplasty procedures are indicated after loss of congruity or involvement of the acetabulum. Limited femoral head resurfacing is used to treat femoral head lesions before involvement of the acetabulum. Total hip arthroplasty must be left for late stages of the disease when the acetabulum is involved [5].

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## AVD

- Atrioventricular Dissociation

## AVED

- Ataxia due to Vitamin E Deficiency
- Vitamin E Deficiency

## “Avellino” Corneal Dystrophy

- Corneal Dystrophy, Granular Type II

## AVF

- Arteriovenous Fistula

## AVNRT

- Atrioventricular Nodal Reentrant Tachycardia
- Arrhythmia, Cardiac in Adults with Congenital Heart Disease

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