Inherited Disorders of Connective Tissue

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Key Points

- Marfan syndrome is an autosomal dominant disease characterized by pleiotropic manifestations involving the cardiovascular, ocular, and skeletal systems. The most common cardiovascular complication in patients with Marfan syndrome is progressive aortic root enlargement initially occurring at the sinuses of Valsalva. Some patients have dissections of the aorta, most often a type I dissection. Mitral valve prolapse is very common in these patients.
- The majority of patients with thoracic aortic aneurysms and dissections who have cystic medial necrosis of the aorta do not have Marfan syndrome.
- Ehlers-Danlos syndrome (EDS) is a heterogeneous group of disorders that are classified together on the basis of skin hyperextensibility, cutaneous fragility, joint laxity, dystrophic scarring, and easy bruising. Spontaneous arterial rupture occurs in type IV EDS.
- Supravalvular aortic stenosis is an autosomal dominant disorder caused by narrowing of the ascending aorta just distal to the coronary ostia.
- Pseudoxanthoma elasticum is an inherited disease caused by progressive calcification of elastic fibers in the connective tissue throughout the body.

This chapter reviews single-gene disorders known or suspected to be the result of mutations in genes that encode for proteins found in the extracellular matrix or connective tissue. Disorders caused by the disruption of connective tissue components by extrinsic factors are addressed elsewhere in this book.

Marfan Syndrome

Marfan syndrome is an autosomal dominant disease characterized by pleiotropic manifestations involving the cardiovascular, ocular, and skeletal systems. The disorder affects all races and ethnic groups and has an estimated incidence in the population of approximately 1 in 3–5000 individuals. The cardinal features of Marfan syndrome (MFS) involve the cardiovascular, ocular, and skeletal systems. The syndrome exhibits marked clinical variability, both among and within families, with essentially complete penetrance. Although MFS is inherited as an autosomal dominant disorder, approximately one third of cases have unaffected parents; in these cases, the syndrome is believed to be caused by sporadic, new mutations in the affected individual.

Clinical Features

Cardiovascular Manifestations

The most common cardiovascular complication in patients with MFS is progressive aortic root enlargement initially occurring at the sinuses of Valsalva.1 Ascending aortic aneurysm can precipitate acute type A aortic dissection, aortic rupture, or aortic regurgitation (AR), leading to premature death prior to the advent of successful preventative therapies. Management of the aortic disease consists of regular imaging to detect and assess the progression of aortic dilation, β-adrenergic receptor antagonist therapy, and prophylactic aortic repair when the dilation reaches a sufficient size to threaten dissection or cause aortic regurgitation. Prior to surgical repair of the aorta, the majority of patients with MFS died prematurely of rupture of the aorta, with an average life expectancy of 45 years.2 The success of current medical and surgical management of the aortic disease in MFS has substantially improved the average life expectancy, extending it up to 70 years.3,4

Aortic Root Dilatation

Aortic root dilatation typically begins with dilatation at the sinuses of Valsalva and progresses to involve the proximal ascending aorta. The rate of enlargement of the proximal aorta varies widely among individuals, and the progressive enlargement is usually asymptomatic. Therefore, regular
assessment of the proximal aorta should be performed annually or more often, depending on the severity of the dilatation and the rate of progression. Transthoracic echocardiography provides precise comparative measurements of aortic root size. Magnetic resonance imaging and transesophageal echocardiography are also useful, particularly in patients with severe thoracic cage abnormalities. Aortography is usually limited to studies made before surgery to define the anatomy [Fig. 121.1]. Aortic valve insufficiency can occur as the aorta dilates. The risk for rupture of the proximal aorta increases with increasing size of the aortic root. The traditional threshold initiating consideration of prophylactic aortic root replacement in patients with MFS has been predicated on aortic size and recommended when the diameter reaches 5.0 cm. The association between increased aneurysm diameter and the risk for dissection or rupture is clearly established, and aneurysms with size greater than 6 cm have a fourfold increase in the cumulative risk of aortic rupture or dissection in patients with MFS. Factors that prompt the recommendation for surgery when the aortic diameter is less than 5.0 cm include rapid growth of the aortic diameter (>1 cm per year), a family history of premature aortic dissection (dissection <5 cm), and the presence of greater than mild AR.

Composite valve graft replacement is achieved by mobilizing buttons of aortic tissue around the coronary arteries for direct nontension anastomosis to the aortic graft. The operative results, particularly since the mid-1980s, have been excellent, with good 5- and 10-year survival. These patients are maintained on anticoagulants and beta-blockers, and routine bacterial prophylaxis is recommended. One of the most common causes of late death after composite valve graft repair was dissection or rupture of the residual distal aorta, with only one third of these late deaths occurring in patients who initially presented with an extensive type A dissection. In addition, 10% of the patients subsequently required distal aortic surgery. The need for a second repair of the aortic root was rare. These facts highlight the need for frequent serial imaging surveillance of the entire aorta indefinitely in all patients after operation.

Other surgical procedures have been investigated that preserve the patient’s native aortic valve, which are termed “valve-sparing aortic root replacement.” There are two surgical approaches that are distinctly different: the Yacoub procedure is referred to as the “remodeling” technique, and the David procedure is the “reimplantation” technique. Both procedures are options for almost all patients with aortic root aneurysms if the aortic valve is structurally normal. Outcome papers from both Yacoub’s and David’s institutions indicated that the operative mortality rate for either procedure is low, but the need to return to the operating room for bleeding was higher after a Yacoub operation than after a David procedure in Toronto (18% vs. 3%). Therefore, the valve-sparing aortic root replacement now presents patients with MFS with a reasonable alternative to CVG. Survival is excellent using either technique, and complications are rare, but the long-term durability of this repair has not been established. Therefore, patients selecting a valve-sparing procedure must accept the risk of possible additional operations in the future.

FIGURE 121.1. Illustration and aortogram of an aneurysm of the ascending aorta.
Aortic Dissection

Some patients with MFS suffer a dissection through the medial layer of the aortic wall, most often a type I dissection [DeBakey classification], which involves the entire aorta. Less common is type III dissection, which involves the descending thoracic aorta. Dissections involving the ascending aorta can occur in patients who have minimal to no enlargement of the ascending aorta. All forms of dissection are known to occur in the absence of systemic hypertension. Angiography, transesophageal echocardiography, and magnetic resonance imaging are useful techniques for diagnosis of aortic dissection and determination of the extent of an acute dissection. Acute management of an aortic dissection is the same as it is for patients without MFS. Total aortic replacement, which is performed in two stages, is now feasible for patients with chronic type I dissection and fusiform dilatation of the entire aorta.

Mitral Valve Disease

Mitral valve prolapse is present in 70% to 90% of patients with MFS. Progression to mitral valve regurgitation occurs in up to half of these patients, but serious mitral regurgitation develops only in approximately one of every eight patients by the third decade of life. In contrast to aortic root dilatation, which is typically asymptomatic, mitral valve prolapse can be associated with chest pain, palpitations, and lightheadedness. It is now feasible to perform a concomitant composite valve graft replacement of the aortic root and a transaortic mitral valve replacement. Echocardiography with Doppler interrogation and color-flow imaging has been the main diagnostic tool for study of the mitral valve.

The incidence of mitral valve prolapse in children with MFS is the same as it is in adults. Children diagnosed with MFS at a young age exhibit more cardiovascular morbidity associated with mitral valve disease [mitral regurgitation] than with aortic root involvement, although aortic root dilatation may appear early in life.

Skeletal Manifestations

The skeletal features of the disorder include the following: increased height and arm span, anterior chest wall deformities [pectus excavatum or carinatum], long fingers [arachnodactyly] and toes, mild to moderate joint laxity, a narrow, highly arched palate, pes planus [flat feet], protusio acetabulum, and vertebral column abnormalities [scoliosis and thoracic lordosis]. The skeletal manifestations of MFS are the most outwardly striking feature of the disorder and are often the feature that triggers the initial evaluation for possible MFS. Tall stature, due primarily to dolichostenomelia (long, thin legs and arms), is usually present and is reflected in a decreased ratio of upper segment (height minus lower segment) to lower segment (top of pubic ramus to the floor) and an arm span that is greater than the height. The reduced upper-to-lower segment ratio can be further exaggerated by scoliosis and kyphosis. Arachnodactyly (long, thin fingers) is also a common feature and can be demonstrated on examination by a positive thumb sign or wrist sign. Also common are scoliosis, loss of thoracic kyphosis [straight back], and chest wall deformities [pectus excavatum or carinatum]. Such a patient often has a high-arched palate and crowding of the frontal teeth, joint laxity, and flat feet. Less common are congenital contractures in newborn children with MFS.

Other Manifestations

Marfan syndrome can also affect the eye, skeletal, and integument. The lens of the eye is dislocated in approximately 50% of people with MFS [ectopia lentis]. Myopia is common in MFS, but retinal detachment is a rare complication that may be more common if the lenses are surgically removed. Dural ectasia, widening of the dural sac leading to back pain and headaches, occurs in approximately 60% of patients with MFS.11 Spontaneous pneumothoraces, recurrent hernias, and striae atrophicae are also features of the condition.

Diagnosis

The diagnostic criteria for MFS were initially established by an international consortium of clinicians in 1986. These diagnostic criteria were revised in 1997 and are termed the Ghent criteria for diagnosing MFS. The diagnosis is based on findings consistent with MFS involving the cardiovascular, skeletal, and ocular systems. The major criteria reflect findings that are more specific for MFS [aortic root dilatation or dissection, lens dislocation, dural ectasia]. The minor criteria are findings common in patients with MFS but also common in individuals with other connective tissue disorders and in the general population (Table 121.1).

The diagnosis of MFS may be difficult because there is no specific laboratory test for the condition. Instead, it is identified by a composite of clinical findings. The diagnostic evaluation for MFS should be performed by physicians experienced with the condition and should include the following:

- A detailed medical and family history
- A complete physical examination
- A thorough eye examination by an ophthalmologist who uses a slit lamp to look for lens dislocation after fully dilating the pupil
- An echocardiogram [a sound-wave picture of the heart] to look for involvement of the cardiovascular system that is often not evident in a physical examination

The criteria for diagnosis are classified according to how specific to MFS the clinical findings are; the major criteria are clinical features that rarely occur in the general population. Minor criteria are features that are present in individuals with MFS but are also commonly present in the general population. The diagnosis requires that at least two of the major manifestations of the condition be present in patients who do not have affected family members. In families in which MFS is known to occur, only one major criterion is required. The major features necessary for the diagnosis include the following:

- Aortic root enlargement [aortic aneurysm]
- Aortic dissection
- Lens dislocation
- Dural ectasia
- The presence of at least four major skeletal features: (1) chest wall deformities, (2) long, thin arms and (3) legs

Other manifestations include the following:
Diagnosis of MFS is a complicated clinical decision that is based on the presence of both minor and major features. For the index case, there must be major criteria in at least two different organ systems and involvement of a third organ system. Alternatively, if a mutation known to cause MFS in others is detected, one major criterion in an organ system and involvement of a second organ system is sufficient for the diagnosis. For the relative of an individual with MFS, there must be a major criterion in an organ system and involvement of a second organ system. Some of the criteria used to diagnose MFS may arise with age. Therefore, a child may fail to meet the criteria at first but at a later date may have manifestations that definitely meet the criteria. The phenomenon has been termed emerging MFS.

Many conditions or syndromes have features in common with MFS and therefore, require differentiation. Homocystinuria, an autosomal recessive disorder resulting from a deficiency of cystathionine-synthetase, has many features in common with MFS, including scoliosis, dolichostenomelia, pectus deformity, and lens dislocation. Therefore, any patient suspected of having MFS should undergo a plasma amino acid analysis to document the absence of homocystinuria.

Mitral valve prolapse occurs in an estimated 4% to 7% of the general adult population. It can occur as an isolated finding or can be inherited within a family, typically in an autosomal dominant manner. Patients with mitral valve prolapse often exhibit thoracic skeletal abnormalities similar to those observed in patients with MFS. These skeletal abnormalities include thoracic kyphosis and pectus deformities. Individuals with skeletal abnormalities and mitral valve prolapse do not meet the diagnostic criteria for MFS. Thoracic aortic aneurysms and aortic dissection can occur in isolated individuals or in familial cases. Aortic dissection with cystic medial necrosis of the aorta has been termed Erdheim’s disease. A number of case reports in the literature have

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**TABLE 121.1. Revised criteria for Marfan’s syndrome**

<table>
<thead>
<tr>
<th>System</th>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Skeletal</td>
<td>Presence of at least four of the following manifestations:</td>
<td>Pectus excavatum of moderate severity</td>
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<tr>
<td></td>
<td>Pectus carinatum</td>
<td>Joint hypermobility</td>
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<tr>
<td></td>
<td>Pectus excavatum requiring surgery</td>
<td>Highly arched palate with crowding of teeth</td>
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<tr>
<td></td>
<td>Reduced upper segment to lower segment ratio or arm span to height ratio greater than 1.05</td>
<td>Hypoplasia, enophthalmos, retrognathia, downsloping palpebral fissures</td>
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<td></td>
<td>Wrist and thumb signs</td>
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<td>Scoliosis &gt;20 degrees or spondylolisthesis</td>
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<tr>
<td></td>
<td>Medial displacement of the medial malleolus, causing pes planus</td>
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<tr>
<td></td>
<td>Prontrusio acetabuli of any degree [ascertained on radiographs]</td>
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<tr>
<td>Ocular</td>
<td>Ectopia lentis [dislocated lens]</td>
<td>Abnormally flat cornea [as measured by keratometry]</td>
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<td></td>
<td></td>
<td>Increased axial length of globe [as measured by ultrasound]</td>
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<td>Hypoplastic iris or hypoplastic dilator muscle causing increased miosis.</td>
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<tr>
<td>Cardiovascular</td>
<td>Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva</td>
<td>Mitral valve prolapse with or without mitral valve regurgitation</td>
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<td></td>
<td>Dissection of the ascending aorta</td>
<td>Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, before the age of 40 years</td>
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<tr>
<td></td>
<td></td>
<td>Calcification of the mitral annulus before the age of 40 years</td>
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<td></td>
<td></td>
<td>Dilatation or dissection of the descending thoracic or abdominal aorta before the age of 50 years</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>None</td>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Skin and integument</td>
<td>None</td>
<td>Apical blebs [ascertained by chest radiography]</td>
</tr>
<tr>
<td>Family/genetic</td>
<td>Lumbarosacral dural ectasia by CT or MRI</td>
<td>Stretch marks not associated with marked weight changes, pregnancy, or repetitive stress</td>
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<tr>
<td>history</td>
<td>Having a parent, child, or sibling who meets these diagnostic criteria independently</td>
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<td></td>
<td>Presence of a mutation in FBN1 known to cause Marfan’s syndrome</td>
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<tr>
<td></td>
<td>Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan’s syndrome in the family</td>
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CT, computed tomography; MRI, magnetic resonance imaging.
documented an autosomal dominant inheritance of aortic dissection in families without other phenotypic manifestations of MFS.

A number of other genetic disorders have some features in common with MFS. The condition that most closely mimics MFS is familial thoracic aortic aneurysms and dissections (FTAAD) [see below]. Stickler’s syndrome [hereditary arthro-ophthalmopathy] is an autosomal dominant disorder characterized by tall stature and skeletal features similar to MFS, retrognathia, midfacial hypoplasia with cleft palate, retinal detachment, and vitreoretinal degeneration. Ehlers-Danlos syndrome type IV is an autosomal dominant disorder associated with skin fragility, skin and joint hypermobility, and arterial and bowel rupture; it is the result of a mutation in the type III collagen gene COL3A1. Arterial rupture typically involves large to middle-sized arteries such as the splenic and renal arteries but rarely involves the aorta. Congenital contractual arachnodactyly is an autosomal dominant disorder with skeletal features in common with MFS [e.g., dolichostenomelia, arachnodactyly, scoliosis, pectus deformity], but in addition, these patients have congenital contractures and a crumpled appearance of the pinna ear.

Genetic Cause

For many years, it was suspected that the basic defect that causes MFS would lie in a gene that encodes for a protein found in the elastic fiber system. The two major components of the elastic fiber system are an amorphous core, composed of the protein elastin, and closely associated microfibrils (approximately 10 mm in diameter) found on the periphery of the amorphous core [Fig. 121.2]. In addition, microfibrils not associated with elastin exist in many tissues, including the suspensory ligament of the eye. Although microfibrils are composed of many proteins, the primary protein component is fibrillin-1, a large [350 kd] glycoprotein. The gene for fibrillin [FBN1] is large [100 kilobases] and maps to the long arm of chromosome 15 [15q15–21].

Evidence has clearly established the fibrillin gene [FBN1] on chromosome 15 as the gene that causes MFS if it is defective. A number of mutations in FBN1 have been identified in affected individuals and families. Analysis of mutations responsible for MFS indicates that in almost every case the mutations are private—that is, every family or sporadically affected individual has a different mutation. The majority of mutations are missense mutations that alter a single amino acid, but nonsense mutations, small insertions, exon splicing errors, and small intragenic genomic deletions have also been described. A second locus for MFS, termed the MFS2 locus, was mapped to 3p24–25 and mutations in the transforming growth factor-β (TGF-β) receptor type II [TGFBR2] have recently been described in patients with MFS, although the significance of the locus for the phenotype has yet to be determined.11

At present, presymptomatic or prenatal diagnosis of MFS can be performed using linkage analysis to identify polymorphic markers within and closely linked to FBN1 that segregate with the disease in a family. These studies are dependent on the ability to analyze the DNA of a number of individuals in the family to determine the allele that is segregating with the disease. This factor precludes the use of linkage analysis as a diagnostic test in a large number of individuals who are at risk for or are suspected of having MFS. Linkage analysis cannot be used to determine whether an individual has a sporadic case of MFS.

Identification of the causative mutation in FBN1 in a family or an individual is available from some molecular diagnostic laboratories. Detection of a causative mutation is complicated by the fact that almost every affected family or sporadic individual has its own unique mutation in the FBN1 gene. In addition, there are no identified “hot spots” for mutations in FBN1, so the entire coding region of the gene must be screened for the mutations causing the syndrome. Using detection of a mutation to diagnose the condition is also complicated by the fact that FBN1 mutations can lead to a variety of conditions that are related to MFS, including MASS phenotype (myopia, mitral valve prolapse, aortic dilatation, skin and skeletal involvement), familial ectopia lentis, familial Marfan-like habitus, familial thoracic aortic aneurysms and dissections, and Weil-Marchesani syndrome. The variety of phenotypes resulting from FBN1 mutations indicates that identification of a mutation in the FBN1 gene does not predict that an individual has MFS. In addition, the current screening techniques identify FBN1 mutations in at least 70% of patients with classic MFS.13 Therefore, molecular testing for FBN1 mutations is neither sensitive nor specific for MFS, and the diagnosis of the condition continues to require clinical assessment.

Future therapies will be directed at preventing the steps leading from a deficiency of fibrillin-1–containing microfibrils to the observed aortic pathology in the aortic wall characterized by fragmentation and degradation of elastic fibers and loss of smooth muscle cells (SMCs) in the medial layer [termed medial degeneration]; these therapies have begun to be elucidated. Recent characterization of mice after homozygous Fbn1 gene targeting demonstrates that elastogenesis proceeds despite a severe quantitative and qualitative

FIGURE 121.2. Electron microscopic examination of microfibrils (M) around the amorphous core of an elastic fiber (E) in human skin. Larger collagen fibers (C) can be seen.
deficiency of fibrillin-1 microfibrils. Elastic fibers show normal morphology at birth, and fragmentation and loss of elastic fibers is largely a secondary event in these animal models of MFS, with a pathogenetic sequence of loss of connecting filaments that normally serve as a structural interface between elastic lamellae and neighboring SMCs leading to an altered phenotype of the SMC, which includes altered expression of multiple matrix elements, including increased expression of matrix metalloproteinases MMP2 and MMP9. The net result is the initiation of local elastic fiber destruction that correlates temporally and spatially with elastic fiber calcification and infiltration of inflammatory cells into the aortic media. Both increased expression of MMP2 and MMP9 and the presence of inflammatory cells have been demonstrated in the aortic media in aortas of patients with MFS [unpublished data].

Another possible avenue for therapy is based on the recent studies that have shown that fibrillin-1 and microfibrils regulate the TGF-β family of growth factors [cytokines] that influence many aspects of cellular performance, including differentiation, proliferation, protein production, and survival. Data in mice demonstrate that a deficiency of fibrillin-1–containing microfibrils results in excessive TGF-β activation and signaling in the developing lung and many other tissues altered in the MFS, including the aortic wall [unpublished data]. These data develop the paradigm that matrix sequestration of cytokines is critical to their regulated activation and signaling, and perturbation of this function can contribute to the pathogenesis of diseases like MFS.

Familial Thoracic Aortic Aneurysms and Dissections

The majority of patients with thoracic aortic aneurysms and dissections who have cystic medial necrosis on pathologic examination of the aorta do not have MFS or other connective tissue disorders, and the cause of the disease remains unknown. There are reports in the literature of familial aggregation of aortic dissection and aneurysms, but reports prior to the 1960s do not specifically address whether the patients had MFS. Hanley and Jones reported the presence of dissecting aortic aneurysms in two sisters and the son of one of them in the absence of the stigmata of MFS. Opitz described three families with aortic disease due to cystic medial necrosis. Nicod and associates described a family in which nine members over two generations had aortic dissecting aneurysms or aortic dilatation. A report describes six families with a dramatic aggregation of thoracic aortic aneurysms and dissections. These families suggest that there is autosomal dominant inheritance of the condition with decreased penetrance and variable expression. In these families, the disease was not linked to FBN1, the defective gene in individuals with MFS. The defect causing the autosomal dominant inheritance of thoracic aortic aneurysms and dissections in the absence of features of MFS has not been identified.

Familial thoracic aortic aneurysms and dissections demonstrate genetic heterogeneity, and linkage studies have identified three thoracic aortic aneurysms and dissections [TAAD] loci at 5q13–14 [TAAD1], 11q23 [FAA1], and 3p24–25 [TAAD2]. The underlying genetic heterogeneity of TAAD is reflected in the phenotypic variation associated with familial TAAD with respect to age of onset, progression, penetrance, and association with additional cardiac and vascular features. Recently, mutations in the TGFBR2 gene have been identified as the cause of disease at the TAAD2 locus, therefore supporting the hypothesis that dysregulation of TGF-β signaling is a mechanism leading to aneurysm formation.

A bicuspid aortic valve and coarctation of the aorta frequently coexist, suggesting that these malformations result from a single developmental diathesis. McKusick and coworkers added a third component; they suggested that medial necrosis is so commonly encountered in patients with either a bicuspid aortic valve or coarctation as to suggest a common underlying defect. McKusick described two patients with bicuspid aortic valves and ascending aortic dilatation and dissection who have medial necrosis on pathologic examination, and he also described a father and son with both aortic disorders. Families with autosomal dominant inheritance of coarctation of the aorta have been described. Two families with familial aggregation of arterial dissections [both aortic and carotid artery dissections] and bicuspid aortic valves have been described. The familial aggregation of thoracic aortic aneurysms and dissection, bicuspid aortic valve, and coarctation of the aorta, along with medial necrosis, suggests a common cause of these defects of the aorta.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome [EDS] [types I through X] comprises a group of heterogeneous disorders that are classified together on the basis of several shared common features: skin hyperextensibility, cutaneous fragility, joint laxity and instability, dystrophic scarring, and easy bruising. There is an increased frequency of mitral valve prolapse in most forms of EDS. The majority of types are inherited in an autosomal dominant manner; the genetic defect is known for only a few.

Clinical Features

The form of EDS with major vascular complications is EDS type IV, which is characterized by severe, life-threatening cardiovascular complications, along with gastrointestinal complications. Unlike patients with other forms of EDS, patients with EDS type IV do not have overly extensible skin. Instead, they typically have skin that is thin and translucent, often with a visible venous pattern over the chest, abdomen, and extremities. In addition, EDS type IV patients have a particular facial appearance characterized by thin lips; a thin, delicate nose; and prominent eyes. The hallmark of EDS type IV is the catastrophic internal complications that involve the rupture of arteries, the colon, and the gravid uterus. These complications can occur sequentially in an individual. Spontaneous arterial rupture is more common than aneurysm formation or dissection. Vascular complications can occur at almost any arterial site and can result in the formation of an arteriovenous fistula. The most common site of arterial bleeding is the abdominal cavity as the result of the rupture of a visceral vessel or, less commonly, the aorta. Also frequently reported is carotid-cavernous sinus fistula formation, which can result in exophthalmos.
Although it is not usual, some patients with EDS type IV form abdominal aneurysms. Arterial rupture accounts for most of the deaths of EDS type IV patients, and death typically occurs before 40 years of age. Vascular surgery is commonly complicated by the fact that these patients’ tissues are extremely friable and do not hold sutures well. Therefore, bleeding should be managed conservatively whenever possible. Angiography is associated with a high rate of complications and should be avoided. Rupture of internal organs, primarily of the colon, occurs in these patients. In addition, affected women may experience life-threatening complications during pregnancy, typically near the time of delivery or in the postpartum period. Complications associated with pregnancy include rupture of the gravid uterus, rupture of arteries or internal organs, postpartum hemorrhage, and vaginal lacerations.

Genetic Causes
The genetic defect that causes EDS type IV is heterozygous mutations in the gene that encodes the peptide chains of type III collagen, the COL3A1 gene found on chromosome 2. As a result of the mutation, the connective tissue contains less type III collagen, which plays an important role in maintaining the structural integrity of blood vessels, skin, and internal organs.

A diagnostic test is available to confirm the diagnosis of EDS type IV. This test requires the culture of dermal fibroblasts explanted from a skin biopsy. These cells are metabolically labeled to analyze the synthesis and secretion of type III collagen. In individuals with EDS type IV, this biochemical analysis typically shows abnormal migration and reduced secretion of type III collagen by the cultured dermal fibroblasts. Reduced levels of the amino propeptide of type III collagen are found in the serum of affected individuals, and such a determination has been proposed as a diagnostic test, but it is not currently used.

Supravalvular Aortic Stenosis

Clinical Features
Supravalvular aortic stenosis is an autosomal dominant disorder characterized primarily by the narrowing of the ascending aorta originating at the sinotubular junction just distal to the coronary ostia. The lesion is typically shaped like an hourglass but can also be characterized by diffuse hypoplasia of the entire ascending aorta. Although the lesion is progressive, it is often asymptomatic. Vascular surgery is corrective for symptomatic lesions. The disease can also affect other vascular sites, including the pulmonary arteries and, rarely, the coronary or carotid arteries.

The disorder is inherited in an autosomal dominant manner. Although true penetrance of supravalvular aortic stenosis is uncertain, recent studies indicate that it is close to 100%. There is extensive variability of expression of the disorder within families; some family members have significant disease that requires surgical repair and others have only minimal disease, with or without peripheral pulmonary artery stenosis. Rarely, an isolated family member exhibits only pulmonary artery stenosis. Sporadic occurrences of the disease do occur, but their cause is unclear. Supravalvular aortic stenosis is a feature of Williams syndrome (see subsequent section).

Genetic Causes
A defect in the elastin gene, located on chromosome 7, has been identified as the cause of supravalvular aortic stenosis. Initial linkage studies mapped the disorder to a region of chromosome 7, where the elastin gene is located. Several mutations in the elastin gene have been identified in individuals with supravalvular aortic stenosis. At present, there is no evidence of genetic heterogeneity in this disorder; all cases reported have been linked to the elastin gene.

Williams syndrome is characterized by multiple anomalies that affect the vascular tissue, connective tissue, and tissues of the central nervous system. Features of the disorder include mental retardation (mean IQ of 53 to 58), abnormal facies, growth deficiency, infantile hypercalcemia, hoarse voice, premature aging of the skin, joint laxity, diverticulosis of the bladder and colon, and congenital heart defects, particularly supravalvular aortic stenosis with or without peripheral pulmonary artery stenosis. Williams syndrome typically occurs sporadically, although there are rare reports of familial cases. Williams syndrome is a contiguous-gene syndrome caused by hemizygosity for a chromosomal deletion at 7q11.22 that includes the elastin gene. In all patients reported on, there is complete deletion of one elastin allele, along with segments of the chromosome adjacent to the elastin gene. This deletion is believed to be the cause of the supravalvular aortic stenosis and connective tissue deficiencies in affected individuals.

Pseudoxanthoma Elasticum

Clinical Features
Pseudoxanthoma elasticum (PXE) is an inherited disorder characterized by progressive calcification of elastic fibers in the connective tissue throughout the body. The primary clinical manifestations of the disorder affect the skin, eyes, and cardiovascular system. The estimated prevalence of the disorder is approximately 1 in 100,000.

The skin lesions are pathognomonic for the disorder (Fig. 121.3). Initially, the lesions typically appear at areas of flexure when the affected individual is a teenager. Yellow-orange, popular skin lesions are characteristic. The retinopathy associated with the disorder is characterized by a peau d’orange pigmentation of the retina. Although retinal hemorrhages can occur and typically involve the macula, they rarely lead to total blindness.

The cardiovascular complications are caused primarily by calcification of the elastic media in the arterial system, a process that has been proposed to lead to secondary disruption of the intima and atheromatous plaque formation. Primarily the peripheral arteries are affected, leading to claudication that begins in the third to fourth decade of life. Because the occlusions are slowly progressive, collateral circulation can form and is encouraged by a regular exercise...
program early in life. The major arteries and the coronary arteries are less commonly involved, but premature coronary artery disease does occur in a few patients with PXE. Strokes, gastrointestinal hemorrhaging, and hypertension are additional clinical features that result from vascular involvement. Mitral valve prolapse and endocardial calcification are observed in some patients with PXE.

Diagnosis

The precise diagnostic criteria for PXE have not been established. At present, diagnosis is based on the characteristic skin changes and the findings of calcification of elastic fibers on biopsy of affected tissue. Ultrasound has been proposed as a diagnostic test, based on calcification of the vasculature of internal organs.

Genetic Cause

Pseudoxanthoma elasticum is usually inherited as an autosomal recessive disorder. However, it can also be inherited in an autosomal dominant manner. Delayed onset of symptoms and variable expression of the disorder make adequate assessment of family members difficult. For unclear reasons, females are more commonly affected than males, with an approximate ratio of 2:1. A genome-wide screen was done of 38 families with two or more affected siblings and established that the gene causing PXE is located on chromosome 16p13.1. The defective gene at this location is the \( ABCC6 \), which encoded for the cellular transport protein ABC\( \text{C} \text{C}6 / \text{MRP}6 \), giving evidence that PXE is a systemic metabolic disorder rather than a purely structural disorder of connective tissue. The ABC (adenosine triphosphate [ATP]-binding cassette) proteins are transmembrane proteins that have diverse physiologic functions. Numerous mutations of \( ABCC6 \) have been described and compound heterozygous mutations are common. The allelic heterogeneity of the disorder complicates the use of genetic testing for diagnosis of the condition. It is also interesting to note that the most common PXE mutation, \( R1141X \), seen in 20% of cases, is associated with a fourfold increase in the prevalence of premature coronary artery disease.

Cutis Laxa

Cutis laxa is a rare connective tissue disorder that can be inherited in an autosomal dominant or recessive manner. The disorder is characterized by genetic heterogeneity and clinical variability. The primary diagnostic feature is loose, hypextensible skin with decreased elasticity. The redundant skin leads to a premature aged appearance. Other manifestations associated with the skin findings including pulmonary emphysema, bladder diverticula, pulmonary artery stenosis, and pyloric stenosis. Some patients with recessively inherited cutis laxa may exhibit tortuous arteries, arterial aneurysms, and fibromuscular renal artery dysplasia.

Histologic examination of the skin reveals marked fragmentation or diminution of elastic fibers. Two groups have reported that autosomal dominant cutis laxa is associated with mutations in the \( ELN \) gene. These mutations differ from those observed in patients with supravalvular aortic stenosis, in which the mutations are predicted to lead to haploinsufficiency for \( ELN \). The \( ELN \) mutations reported in patients with cutis laxa predict loss of the functional carboxyl terminus of the tropoelastin molecule. In addition, homozygous mutations in fibulin-5 (\( FBLN5 \), also known as \( EVEC \) or \( DANCE \)) have been identified as a cause for a recessive form of cutis laxa.

References
