

Chapter 2

The Molecular Biology and Treatment of Systemic Vasculitis in Children

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Introduction

Systemic vasculitis is characterized by blood vessel inflammation, which may lead to tissue injury from vascular stenosis, occlusion, aneurysm or rupture [1]. Apart from relatively common vasculitides such as Henoch–Schönlein Purpura (HSP) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but when present are associated with significant morbidity and mortality [2, 3]. The cause of the majority of childhood vasculitides is unknown, although it is likely that a complex interaction between environmental factors, such as infections and inherited host responses, triggers the disease and determines the vasculitis phenotype [4]. This chapter summarizes the findings of recent studies relating to the pathogenesis of systemic vasculitis, and considers HSP, KD, antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, polyarteritis nodosa and Takayasu arteritis (TA). Rarer forms of vasculitis are beyond the scope of this chapter, and the reader is referred elsewhere [5]. In addition, we discuss current therapeutic approaches and ongoing challenges in the field of paediatric vasculitis research.

Henoch–Schönlein Purpura

HSP is the most common childhood primary systemic vasculitis [2]. HSP typically affects children between the ages of 3–10 years [6]. Gardner-Medwin et al. reported an estimated annual incidence of 20.4 per 100,000 children in the UK [2].

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Modifications of the classification criteria defining HSP described by Ozen et al. in 2005 [7] have recently been made following a formal validation study [8]. According to the new EULAR/PRINTO/PRES definition, a patient is classified as having HSP in the presence of purpura or petechiae with lower limb predominance (mandatory criterion) plus one out of four of the following criteria [8]:

1. Abdominal pain
2. Histopathology showing typical leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit
3. Arthritis or arthralgia
4. Renal involvement (proteinuria or haematuria or presence of red blood cell casts)

In cases with purpura with atypical distribution, a demonstration of IgA is required at biopsy. This new definition provides sensitivity and specificity for classification of HSP (using other forms of vasculitis as controls) of 100% and 87%, respectively [8].

Pathogenesis

As many as 50% of occurrences in paediatric patients are preceded by an upper respiratory tract infection [4, 9]. Several agents have been implicated, including group A streptococci, varicella, hepatitis B, Epstein–Barr virus, parvovirus B19, *Mycoplasma*, *Campylobacter*, and *Yersinia* [4]. Of note, Masuda et al. showed that nephritis-associated plasmin receptor (NAPlr), a group A streptococcal antigen, may have a pathogenetic role in a subset of patients with HSP nephritis [10]. Among 33 children with biopsy proven HSP nephritis, 30% had segmental or global mesangial deposition of NAPlr antigen, comparing to 3% in other children with non-HSP nephritis glomerular diseases (half of these children had IgA nephropathy) [10]. The exact pathophysiologic mechanism, if any, and the relationship between NAPlr and HSP nephritis need, however, further investigation. So far no single infectious agent has been consistently identified, and it is likely that genetically controlled host responses determine whether or not an individual develops HSP in response to infectious triggers. But despite the fact that the cause of HSP is unknown, it is likely that IgA has a pivotal role in the pathogenesis of the disease, a hypothesis supported by the almost universal deposition of IgA in lesional vascular tissue [11]. Skin or renal biopsies demonstrate the deposition of IgA (mainly IgA1) in the wall of dermal capillaries and post-capillary venules and mesangium [11]. In addition, serum IgA levels have been reported to be increased during the acute phase of the disease, and a proportion of patients have circulating IgA-containing immune complexes and cryoglobulins [12]. Some studies have found IgA antineutrophil cytoplasmic antibodies (IgA-ANCAs) in a proportion of patients with HSP, while others have shown an increase in IgA-rheumatoid factor or IgA-anticardiolipin antibodies [11]. Recently, galactose deficiency of O-linked glycans in the hinge region of IgA1 has

been reported in adults with IgA nephropathy and children with HSP [13]. These aberrantly glycosylated IgA1 proteins form immune complexes that deposit in the mesangium; their binding to mesangial cells stimulates cellular proliferation and overexpression of extracellular matrix components resulting in the typical renal lesions associated with HSP [13]. Recently, Hiasano et al. showed complement activation through both the alternative and lectin pathways in patients with HSP nephritis and demonstrated that this complement activation is promoted in situ in the glomerulus [14]. The formed IgA immune complexes, through the activation of complement, lead to the formation of chemotactic factors (such as C5a), which in turn recruit polymorphonuclear leucocytes to the site of deposition [15, 16]. The polymorphonuclear leucocytes thus recruited by chemotactic factors cause inflammation and necrosis of vessel walls with concomitant thrombosis [11]. This subsequently results in extravasation of erythrocytes from haemorrhage in the affected organs and is manifested histologically as leucocytoclastic vasculitis [11]. The term leucocytoclasia refers to the breakdown of white blood cells in lesional tissue, particularly the characteristic nuclear debris (“nuclear dust”) observed, and is not specific for HSP.

Genetics

Several genetic polymorphisms have been linked with HSP in various population cohorts, often with consistent results across multiple studies (summarized in Table 2.1) [32]. Many of these polymorphisms relate to cytokines or cell adhesion molecules involved in the modulation of inflammatory responses and endothelial cell activation [4, 32]. The connection between HSP and HLA alleles is the most convincing genetic association. In three cohorts from Italy, northwest Spain and Turkey, DRB1*01 and DRB*11 have each been positively associated (OR 1.5–2.5), and DRB*07 negatively associated, with HSP in two of the three studies [17, 18, 33]. HLAB35 was associated with HSP in a Turkish cohort [19], but was only associated with nephritis in a Spanish cohort [20]. Null alleles in either of the complement factor C4 genes (C4A or C4B) have shown associations with HSP in multiple cohorts of different ethnicities [29], but different findings regarding associations with C4A or C4B alleles, association with heterozygosity or only homozygosity for a null allele, and close linkage of the C4 genes to HLA have resulted in debate about the significance of these findings. Polymorphisms in the angiotensin-converting enzyme (ACE) gene have been associated with risk of HSP in two cohorts (OR 2.3–2.7) [24, 25]; several additional studies have focused on association of ACE alleles with risk of nephritis but without consistent findings. A high carriage rate of mutations in MEFV was recently reported in Turkish children with HSP (OR 2.06) [27]. On the whole, however, studies of this nature have been hampered by relatively small patient numbers and thus lack the power to be definitive or necessarily applicable to all racial groups.

Table 2.1 Positive genetic associations in Henoch Schönlein purpura

Molecule/genetic polymorphism	Role of polymorphism	Reference
Human leucocyte antigens (HLAs)	Positivity for HLA-B35 predisposes to renal involvement in a Spanish cohort HLA-B35 predisposes to HSP in a Turkish cohort DRB1*01 and *11 positively associated and DRB*07 negatively associated with risk of HSP	[17–20]
Interleukin-8 (IL-8)	Polymorphism associated with renal involvement	[21]
Interleukin-1 receptor antagonist (IL-1Ra)	Polymorphism predisposes to renal involvement	[22]
Interleukin-1 β (IL-1 β)	Polymorphism predisposes to renal involvement	[23]
Angiotensin converting enzyme (ACE)	Increased risk of HSP	[24, 25]
Vascular endothelial growth factor (VEGF) and its receptor (KDR)	VEGF polymorphisms predispose to renal involvement	[26]
Familial Mediterranean fever genotypes (MEFV gene mutation)	Mutations in MEFV found more commonly in Israeli and Turkish children with HSP	[27, 28]
Complement C4A and C4B	Increased risk of HSP	[29]
PAX2 (paired box gene 2)	Polymorphisms in PAX2 predispose to renal involvement in HSP	[30]
Nitric oxide and associated molecules	Inducible nitric oxide synthase 2A promoter polymorphism predisposes to renal involvement	[31]

Clinical Features

Skin involvement is typically with purpura, which is generally symmetrical, affecting the lower limbs and buttocks in the majority of cases, the upper extremities being involved less frequently [34]. The abdomen, chest and face are generally unaffected [34]. Angioedema and urticaria can also occur [34]. Around two thirds of the children have joint manifestations at presentation [34]. Three quarters of the children develop abdominal symptoms ranging from mild colic to severe pain with ileus and vomiting [34]. Haematemesis and melena are sometimes observed [34]. Other complications include intestinal perforation and intussusception [34]. Acute pancreatitis is also described, although is a rare complication [34]. Other organs less frequently involved include the central nervous system (cerebral vasculitis), gonads (orchitis may be confused with torsion of the testis) and the lungs (pulmonary haemorrhage) [34]. Reports of HSP nephritis indicate that between 20% and 61% of cases are affected with this complication. Renal involvement can present with varying degrees of severity [34]. This includes isolated microscopic haematuria, proteinuria with microscopic or macroscopic haematuria,

acute nephritic syndrome (haematuria with at least two of hypertension, raised plasma creatinine and oliguria), nephrotic syndrome (usually with microscopic haematuria) or a mixed nephritic–nephrotic picture [34].

Treatment

The large majority of cases of HSP require symptomatic treatment only [34]. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to treat arthralgia associated with HSP [34]. Controversies concerning the use of corticosteroids in the treatment of HSP exist with regard to whether or not they can (1) reduce severity or duration of disease, (2) decrease the risk of glomerulonephritis, and (3) prevent relapses of the disease [35, 36]. Chartapisak et al. recently systematically reviewed all published randomized controlled trials (RCTs) for the prevention or treatment of renal involvement in HSP [37]. Meta-analyses of four RCTs, which evaluated prednisone therapy at presentation of HSP, showed that there was no significant difference in the risk of development or persistence of renal involvement at 1, 3, 6 and 12 months with prednisone compared with placebo or no specific treatment [37]. In the largest of these trials, which enrolled children between January 2001 and January 2005, the primary outcome (urinary protein/creatinine ratio at 1 year) was measured in 290 children [38]. This is the largest study to date showing no significant benefit of prednisone over placebo in preventing persistent renal disease [38]. That said, there could still be a role for early use of corticosteroids in patients with severe extrarenal symptoms such as abdominal pain and arthralgia, as suggested by the findings of a study performed by Ronkainen et al. [36]. Prednisone (1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks) was effective in reducing the intensity of abdominal pain and joint pain [36]. Prednisone did not prevent the development of renal symptoms but was effective in treating them if present; renal symptoms resolved in 61% of the prednisone patients after treatment, compared with 34% of the placebo patients [36]. Of note, Nikibakhsh et al. reported recently on the successful treatment with mycophenolate mofetil (MMF) of recurrent skin, articular and gastrointestinal symptoms in children with who failed to respond to systemic steroid therapy [39].

For patients with rapidly progressive glomerulonephritis with crescentic change on biopsy, uncontrolled data suggest that treatment may comprise aggressive therapy with corticosteroid, cyclophosphamide and possibly plasma exchange [34], as with other causes of crescentic nephritis. Other therapies such as cyclosporin, azathioprine and cyclophosphamide have been reported to be effective [40–42]. As HSP is the most common cause of rapidly progressive glomerulonephritis in childhood, more aggressive therapeutic approaches such as plasma exchange have been employed in some cases [43]. These treatment options, while important in select cases, are not yet supported by RCTs. In addition, there are no robust clinical trials to guide therapy for HSP nephritis that is not rapidly progressive (patients may exhibit less than 50% crescents on renal biopsy, sub-optimal GFR; heavy proteinuria which is not necessarily nephrotic range) [34]. Many would advocate corticosteroids [34].

Others advocate the addition of cyclophosphamide to corticosteroids in HSP nephritis with biopsy showing diffuse proliferative lesions or sclerosis, but with <50% crescentic change with ongoing heavy proteinuria [34]. In patients with greater than 6 months duration of proteinuria, an ACE inhibitor may be indicated to limit secondary glomerular injury, although again the evidence to support this therapy is lacking.

Outcome

The majority of children with HSP make a full and uneventful recovery with no evidence of ongoing significant renal disease [34]. Renal involvement is the most serious long-term complication of HSP [34]. Narchi et al. systematically reviewed all published literature with regards to long-term renal impairment in children with HSP [44]. Persistent renal involvement (hypertension, reduced renal function, nephrotic or nephritic syndrome) occurred in 1.8% of children overall, but the incidence varied with the severity of the kidney disease at presentation, occurring in 5% of children with isolated haematuria and/or proteinuria but in 20% who had acute nephritis and/or nephrotic syndrome in the acute phase [44].

Kawasaki Disease

KD is an acute self-limiting systemic vasculitis predominantly affecting young children [2]. It is distributed worldwide, with a male preponderance, an ethnic bias towards Asian children, some seasonality and occasional epidemics [45–49]. It is the second most common vasculitic illness of childhood and the most common cause of acquired heart disease in children in the UK and the USA [2, 50, 51]. The incidence in Japan is 138/100,000 [52] in children younger than 5 years, whereas in the USA it is 17.1 [53] and in the UK 8.1 [54].

Pathogenesis

The aetiology of KD remains unknown, but currently it is felt that some ubiquitous infectious agent produces an abnormal immunological response in a genetically susceptible subject that results in the characteristic clinical picture [55, 56]. Pronounced seasonality and clustering of KD cases have led to the hunt for infectious agents as a cause [55, 56]. However, so far no single agent has been identified, a fact most recently highlighted by the negative results that emerged from studies examining the potential link between coronavirus infection and KD in Taiwan [57]. One debate regarding the cause of KD has centred around the mechanism of immune

activation: conventional antigen versus superantigen (SAg) [55, 58]. SAgS are a group of proteins that share the ability to stimulate a large proportion of T cells (up to 30% of the T-cell repertoire compared with one in a million T cells for conventional antigens) by binding to a portion of the T-cell receptor β chain (TCRV β) in association with the major histocompatibility complex (MHC) class II molecules with no requirement for antigen processing [59]. SAgS have been identified in a variety of microorganisms, including many of the bacteria and viruses isolated from children with KD [55, 59, 60]. In 1992, Abe et al. were the first to describe the selective expansion of V β 2 and V β 8.1 T cells in KD [61], indicating T-cell V β skewing—the hallmark of a SAg-mediated process. Since then, many similar studies have examined T cell V β repertoires in KD, or examined the prevalence of serological conversion or colonization with SAg-producing organisms [62, 63]. An SAg is also responsible for induction of coronary artery disease in a murine model of KD (discussed in detail in the “In Vivo Experimental Data in KD” section) [55, 59, 60]. However, Rowley et al. recently reported three fatal cases of KD and observed IgA plasma cell infiltration into the vascular wall during the acute phase of the illness [64]. By examining the clonality of this IgA response using reverse transcriptase (RT)-PCR in lesional vascular tissue, these researchers observed that the IgA response was oligoclonal, suggesting a conventional Ag process rather than a SAg-driven one [64]. Although the debate continues regarding the mechanism of initial immune activation, different mechanisms are most likely involved with a final common pathway of immune activation responsible for this clinical syndrome. Regardless of how T cells get activated, the massive immune response characteristic of KD is translated into systemic inflammation manifested clinically as fever and the cardiac features of KD [55].

In Vivo Experimental Data in KD

Experimental mice develop coronary arteritis in response to intra-peritoneal injections of *Lactobacillus casei* wall extract (LCWE) with the resultant vasculitis being similar to KD in children [65, 66]. Young mice (age 4–5 weeks) are more susceptible to LCWE-induced disease compared with older mice [65–69]. The peripheral immune activation within hours of LCWE injection is followed by local infiltration into cardiac tissue at day 3 with the inflammatory infiltrate comprising mainly T cells [65–69]. This inflammatory response peaks at day 28 post injection and is accompanied by elastin breakdown with disruption of the intima and media, as well as aneurysm formation at day 42 [65–69]. Additionally, an SAg found within LCWE contributes significantly to the development of vascular disease [60]. The common features between this murine model and the human disease include an infectious trigger leading to immune activation; disease susceptibility in the young; a time course similar to that seen clinically in KD; similar pathology of coronary arteritis; and response to intravenous immunoglobulin (IVIG) treatment [55]. The proposed disease model supported by the in vivo experimental data in this mouse model

begins with immune activation by a microbe with superantigenic activity [55]. The SAg found in the LCWE preferentially expands T-lymphocytes expressing TCRV β 2, 4, 6 and 14 positive T cells, and this superantigenic activity is directly correlated with the ability to induce coronary arteritis in mice [60]. Ablation of IFN- γ confirmed that IFN- γ plays an important regulatory role in disease induction in this disease model [55]. Mice with absence of TNF- α activity (blockade of TNF- α) or TNFR1 knockouts) do not develop coronary disease after LCWE stimulation [68]. Of note, the T cells found in affected vessels express SAg-reactive TCRV β families, an unexpected finding considering the usual fate of SAg-activated T cells, which are actively deleted by apoptosis. Moolani et al. have shown that co-stimulation can rescue SAg-stimulated T cells from apoptosis [70]. Furthermore, the coronary endothelium is transformed into a professional antigen-presenting cell (APC) by upregulation of co-stimulatory molecules driven partially by the tissue-specific expression of Toll-like receptor (TLR) [55]. Increased TLR2 expression in conjunction with TLR2 stimulation by the TLR2 ligand in LCWE leads to increased expression of co-stimulatory molecules facilitating rescue of SAg-activated T cells and continued local production of proinflammatory cytokines [71, 72]. This leads to further exacerbation of the inflammation at the coronary vessel wall [55]. IFN- γ and TNF- α are involved in transcriptional regulation of matrix metalloproteinases (MMPs), with TNF- α upregulating, and IFN- γ inhibiting production of MMP-9 [55, 73]. Following that, the enzymatic activity of MMP-9 leads to elastin breakdown and aneurysm formation [73]. Of note, recently Alvira et al. have shown that in the coronary arteritis associated with KD, TGF- β suppresses elastin degradation by inhibiting plasmin-mediated MMP-9 activation [74]. Thus, strategies to block TGF- β , used in those with Marfan syndrome, are unlikely to be beneficial in KD as they lead to worsening of elastin degradation in this murine model of KD [74]. So in summary, a sustained local immune response together with persistent TNF- α production and leucocyte recruitment lead to upregulation of proteolytic activity, elastin degradation, vessel wall damage and the characteristic coronary artery lesions seen in KD [55].

Genetics

Although the clinical syndrome and occurrence of epidemics suggest an infectious cause for KD, a genetic contribution to risk is suggested by the much higher prevalence of the disease in Japan and Korea than elsewhere, and by increased prevalence within families with an increased relative risk to siblings compared to the general population [75]. Recently, a number of polymorphisms have been identified that appear to be linked with disease susceptibility in KD or the risk of coronary artery aneurysms (CAAs). These polymorphisms are summarized in Table 2.2 [4, 81]. In general, candidate gene studies in KD have been difficult to interpret, since most findings have not been replicated. Indeed, conflicting results have been reported for the few genes that have been evaluated in multiple cohorts.

Table 2.2 Genetic polymorphisms associations with Kawasaki disease

Molecule/genetic polymorphism	Role of polymorphism	Reference
Mannose binding lectin	Ambiguous role for MBL influencing risk of coronary artery aneurysms (CAA)	[76]
Angiotensin-converting enzyme (ACE)	ACE I/D polymorphism increases disease susceptibility	[77]
Matrix metalloproteinases (MMP)	MMP-3 6A/6A Polymorphism results in higher frequency of CAA MMP-1, 3, 7, 12 and 13 in the gene cluster on Chr.11q22 results in CAA in US-UK subjects	[78, 79]
Interleukin 1 receptor antagonist (IL-1Ra)	Polymorphism associated with increased disease susceptibility	[80]
Interleukin 18 (IL-18)	Increases disease susceptibility in Taiwan	[81]
Tumour necrosis factor-alpha (TNF- α)	TNF- α -308A associated with increased intravenous immune globulin (IVIG) resistance	[82]
Interleukin-10 (IL10)	IL-10 gene promoter polymorphisms influence risk of CAA	[82]
Vascular endothelial growth factor (VEGF) and its receptor (KDR)	Polymorphisms of both contribute to increased CAA risk	[83]
Chemokines	Chemokine receptor CCR5 and its ligand CCL3L1 influence disease susceptibility	[84]
Nitric oxide and associated molecules	No association of eNOS and iNOS gene polymorphisms to the development of CAL in Japanese KD patients	[85]
Fc γ receptors	No association for Fc γ RIIa-131H/R, Fc γ RIIb-232I/T, Fc γ RIIIa-158V/F and Fc γ RIIIb-NA1/NA2	[86]
Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene	Increases diseases susceptibility and risk of CAA No association with KD and CAA in Taiwanese children	[75, 87]
Caspase 3 (CASP3)	Associated with CAA in Taiwanese children Susceptibility to KD in both Japanese and US subjects of European ancestry	[88, 89]
COL11A2	Susceptibility to disease and CAA	[90]
Inositol 1,4,5-trisphosphate receptor type 3 (ITPR3)	Increased risk of CAA	[91]

Furthermore, a genome-wide linkage study using microsatellite markers in Japanese families identified a number of potential loci [92]. Finer scale studies of the 19q32.2-32.3 region led to identification of a linked group of single-nucleotide polymorphisms (SNPs) in the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene, associated with KD, with an odds ratio of 1.74 [75, 92]. ITPKC mutation was associated with KD not only in Japanese but also in US Caucasian patients, particularly with the risk for developing coronary artery lesions [75, 92]. Additional data

supported a functional significance for one polymorphism identified: SNP (itpkc_3C) led to reduced splicing of the ITPKC gene product and therefore could result in a lower mRNA concentration [75]. Of note, however, Chi et al. subsequently showed no statistically significant association between the ITPKC gene SNP rs28493229 and KD or coronary artery lesions in Taiwanese children [87]. The first genome-wide association study (GWAS) in KD was notable for assessment of population stratification and for replication of GWAS findings in an independent cohort [93]. GWAS of 109 Caucasian patients, followed by SNP genotyping of the 1,116 most significant SNPs in 583 families, then fine mapping of known genes near some of the 40 SNPs that were successfully replicated, led to identification of eight putative novel susceptibility genes [odds ratio (OR) approximately 1.1–1.5] [93].

Clinical Features

The principal clinical features are fever persisting for 5 days or more, peripheral extremity changes (reddening of the palms and soles, indurative oedema and subsequent desquamation), a polymorphous exanthema, bilateral conjunctival injection/congestion, lips and oral cavity changes (reddening/cracking of lips, strawberry tongue, oral and pharyngeal injection) and cervical lymphadenopathy (acute, non-purulent) [56]. For the diagnosis to be established according to the Diagnostic Guidelines of the Japan Kawasaki Disease Research Committee, five of six criteria should be present [94]. If CAAs are present, fewer features may be necessary for diagnostic purposes [48, 95]. The cardiovascular features are the most important manifestations of the condition with widespread vasculitis affecting predominantly medium-size muscular arteries, especially the coronary arteries [56]. Coronary artery involvement occurs in 15–25% of untreated cases with additional cardiac features in a significant proportion of these, including pericardial effusion, electrocardiographic abnormalities, pericarditis, myocarditis, valvular incompetence, cardiac failure and myocardial infarction [56]. Another clinical sign that maybe relatively specific to KD is the development of erythema and induration at sites of Bacille Calmette–Guérin (BCG) inoculations [46]. Other system involvement can occur, including the gastrointestinal tract, the hepatobiliary tract with hydrops of the gall bladder being well recognised, the central nervous system with seizure and meningeal features, the auditory system with deafness, the skeletal system with arthropathy and the urinary system [56].

Treatment

Early recognition and treatment of KD with aspirin and IVIG have been shown unequivocally by meta-analysis to reduce the occurrence of CAAs [96, 97]. The prevalence of CAA is inversely related to the total dose of IVIG [97], 2 g/kg of IVIG being the optimal dose, usually given as a single infusion [96]. Meta-analysis of

RCTs comparing divided lower doses of IVIG (400 mg/kg/day for 4 consecutive days) versus a single infusion of high-dose IVIG (2 g/kg over 10 h) has clearly shown that even though the 4-day regimen has some benefit, a single dose of 2 g/kg has a greater therapeutic effect in the prevention of CAA [96, 97]. However, IVIG resistance occurs in up to 20% of cases [98]. In those cases most advocate a second dose of IVIG and/or the use of corticosteroids. Regarding corticosteroid use in IVIG resistant to KD, there are apparently conflicting data from clinical trials. Inoue et al. reported on a randomized control trial of 178 KD patients who were assigned to receive IVIG (1 g/kg/day) for two consecutive days, given over 12 h, or IVIG plus prednisolone sodium succinate (2 mg/kg/day) three times daily, given by intravenous (IV) injection until the fever resolved and then orally until the C-reactive protein (CRP) level normalized [98]. Patients in both groups received aspirin (30 mg/kg) and dipyridamole (2 mg/kg/day) [98]. The addition of corticosteroid was associated with reduced CAA compared with IVIG alone: in those receiving IVIG and anti-platelet therapy, 11.4% had CAA at 1 month, compared with 2.2% in those receiving IVIG plus corticosteroids [98]. Also the duration of fever was shorter and CRP decreased more rapidly in the group of patients receiving corticosteroids [98]. In contrast, Newburger et al. in a subsequent multicenter, randomized, double-blind, placebo-controlled trial examined the effect of the addition of a single dose of intravenous methylprednisolone to standard therapy [99]. They found that this corticosteroid regimen did not improve the CAA outcome in these children [99]. These contrasting results suggest that dose and duration of corticosteroids may be critical when considering this as adjunctive therapy in KD. Infliximab, a chimeric monoclonal antibody against TNF- α , has been reported to be effective for the treatment of IVIG-resistant KD [100, 101]. In 13 of 16 patients with failed response to a single dose of IVIG who received infliximab, there was cessation of fever followed by reduction in CRP [100]. More recently, Burns et al. reported on a multi-centre, randomized, prospective trial of second IVIG infusion (2 g/kg) versus infliximab (5 mg/kg) in 24 children with acute KD and fever after initial failed treatment with IVIG [101]. There was cessation of fever within 24 h in 11 of 12 subjects treated with infliximab and in 8 of 12 subjects retreated with IVIG [101]. No significant differences were observed between treatment groups in the change from baseline for laboratory variables, fever or echocardiographic assessment of coronary arteries [101]. These reports are encouraging but further RCTs to establish the optimal management of KD, and in particular IVIG-resistant KD, are needed [102]. In that respect a multi-centre, double-blind, randomized, placebo-controlled trial intended to assess the efficacy of etanercept (a fusion protein combining the TNF receptor 2 and the Fc component of human IgG1) in reducing the IVIG refractory rate during treatment of acute KD is ongoing [103].

In the convalescent phase of the condition, if aneurysms persist, anti-platelet therapy in the form of low-dose aspirin should be continued long term until the aneurysms resolve [56]. In the presence of giant aneurysms (greater than 8 mm), warfarin is recommended in addition to aspirin [104]. Some patients may require coronary angioplasty or a revascularization procedure should ischemic symptoms arise or evidence of obstruction occur [105].

Outcome

The acute mortality of KD in Japan is 1.14 [105]. About 20% of patients who develop CAAs during the acute disease will develop coronary artery stenoses, and the risk is greater with large (giant) aneurysms [105]. However, emerging data suggest that, in spite of seeming recovery, there are long-term cardiovascular sequelae for patients with KD that persist into adult life and that may have important implications [106].

Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

ANCA-associated vasculitides (AAV) are small-vessel vasculitides characterized by necrotizing inflammation of small vessels in association with autoantibodies to neutrophil constituents—in particular, proteinase 3 (PR3) and myeloperoxidase (MPO) [107, 108]. The AAV comprise Wegener's granulomatosis (WG, now also referred to as granulomatous polyangiitis, although for the purposes of this review the term WG is used), microscopic polyangiitis (MPA), including its renal-limited (RL) subset designated as idiopathic necrotizing crescentic glomerulonephritis (iNCGN), and Churg–Strauss syndrome (CSS) [107, 108]. Although rare, AAV do occur in childhood and are associated with significant morbidity and mortality [109].

Pathogenesis

The pathogenesis of AAV is still not fully elucidated, but clinical as well as experimental data strongly suggest a role for autoimmune responses to PR3 and MPO in disease development [110].

In Vitro Studies

The most accepted model of pathogenesis suggests that ANCA activate cytokine-primed neutrophils within the microvasculature, leading to bystander damage to endothelial cells themselves and rapid escalation of inflammation with recruitment of mononuclear cells [111]. Falk et al. demonstrated in 1990 that ANCAs in vitro activate neutrophils to produce reactive oxygen species and release of lytic enzymes [112]. This process requires priming of neutrophils. Priming involves the stimulation of neutrophils with low doses of proinflammatory cytokines that result, among other things, in surface expression of PR3/MPO on the neutrophil membrane but without full neutrophil activation, before their interaction with ANCA [113]. Primed neutrophil activation by ANCA involves interaction with their target antigens on

the neutrophil membrane and also with Fc γ receptors—in particular, Fc γ RIIa and Fc γ RIIIb [113]. In addition, Reumaux et al. showed that ANCA-induced neutrophil activation occurs only when neutrophils are attached to a surface and not when floating in the circulation [114]. Furthermore, Radford et al. demonstrated that ANCA can directly activate neutrophils to become firmly adherent to vessel walls, where they may obstruct flow, initiate tissue damage and contribute to the pathogenesis of vasculitis [115]. These effects can be blocked by antibodies to Fc γ RIIa and by antibodies to CD11b [115]. In more detail, Savage et al. showed that activation of neutrophils by ANCA causes integrin- and cytokine receptor-mediated adherence to cultured endothelial cells and transmigration across the endothelial layer [116]. In addition, activation of neutrophils with ANCA causes a conformational change in beta-2 integrins that enhances ligand binding [116]. A role for adhesion molecules in the interaction between ANCA-activated neutrophils and vessels also is supported by immunohistologic evidence of upregulated adhesion molecules in glomerular lesions in renal biopsy specimens from patients with AAV [117]. In addition to binding to the surface of endothelial cells, both PR3 and MPO are internalized into endothelial cells, where they have different pathologic effects [118]. For example, after internalization, PR3 causes endothelial cell apoptosis, whereas MPO causes generation of intracellular oxidants [118]. These differences in MPO and PR3 interaction with endothelial cells could influence the patterns of tissue injury induced when these antigens react with ANCA at the endothelial cell surface [111]. Furthermore, there is new evidence that after neutrophil activation by ANCA, the neutrophils are driven down an accelerated apoptotic death pathway by reactive oxygen species [119]. These neutrophils develop the morphologic features of apoptosis, but there is dysregulated coordination of cell surface changes that normally accompany apoptosis, including delay in phosphatidylserine expression [119], which could contribute to failure of these apoptotic cells to be recognized and safely removed by phagocytes [119]. Apoptotic neutrophils eventually disintegrate, releasing cytotoxic contents within vascular tissue. This process may explain the leucocytoclasia often seen in vasculitic lesions. Also pertaining to safe clearance of apoptotic neutrophils are two studies showing that apoptotic neutrophils can express proteinase-3 and myeloperoxidase at the cell surface, which can act as an opsonin for ANCA [120, 121]. Both apoptotic and ANCA opsonized apoptotic neutrophils can be phagocytosed by macrophages, but whereas the former induce an anti-inflammatory response from the macrophage release of interleukin-10, the latter are taken up more avidly and are proinflammatory by inducing macrophage release of interleukin-1, interleukin-8 and TNF [120, 121].

The signalling cascades that lead to functional responses such as superoxide release are only beginning to be elucidated. Tyrosine kinases and protein kinase C are known to be involved [122]. Now, mitogen-activated protein kinases that require tyrosine phosphorylation for activation also have been implicated, particularly in TNF-mediated priming [123].

Furthermore, in WG the granulomatous inflammation displays several different morphologies. Within a surrounding inflammatory background, poorly formed epithelioid cell granulomas, scattered histiocytic giant cells of Langhans type or

palisading histiocytes around central necrosis may be seen [124]. The mixed inflammatory infiltrate in WG is composed of lymphocytes, plasma cells, neutrophils, eosinophils, monocytes, macrophages, histiocytes and giant cells [124]. Since INF- γ and T cells play pivotal roles in granuloma formation, alterations of the T-cell and cytokine response could contribute to anomalous autoantigen presentation in ectopic lymphoid-like structures and sustain autoimmunity to PR3 [125]. Skewing of the T-cell phenotype with expansion of the CD4+ and CD8+ T cells lacking CD28 expression is seen in WG [126, 127]. Expansion of CD28 negative T cells is already evident in localized WG and further increases in generalized disease [126, 127]. Abundant IFN- γ , CD26 and Th-1 type CC chemokine receptor CCR5 expression are seen in granulomatous lesions of the respiratory tract in localized WG, but appear less strong in generalized WG [128, 129]. Moreover, a fraction of Th2 type IL-4 producing CCR3+ T cells is present in the circulation and tissue lesions in generalized but not in localized WG [128]. These data suggest that an aberrant Th-1 type response favouring granuloma formation might play a role in initiation of WG [130]. Ectopic presentation of the Wegener's autoantigen PR3 and autoimmunity to PR3 might be sustained within inflammatory lesions and by skewed T-cell and cytokine responses [130]. Progression from localized to generalized WG is associated with the appearance of another subset of Th-2 type cells, which could be a consequence of B-cell expansion and T-cell-dependent PR-3 ANCA production during disease progression [130]. In addition, Th17 cells have been recently described as major effector cells in autoimmune diseases [131]. It has been demonstrated that stimulation of peripheral blood mononuclear cells from PR3-ANCA positive patients with WG with the autoantigen PR3 results in production of interleukin (IL)-17 and not INF- γ , demonstrating that the autoimmune effector cells are Th17 cells [132]. In healthy individuals regulatory T cells (Tregs) control the activity of immune effector cells [131]. There is increasing evidence that the balance between Th17 cells and Fox P3-positive regulatory T cells is disturbed in autoimmune inflammatory conditions [131]. In patients with WG in remission, the percentage of Fox P3-positive Tregs was shown to be increased but the cells were functionally deficient [133].

Taken together, *in vitro* studies support a pathogenic role for the autoimmune responses to PR3 and MPO in AAV. Autoantibodies could be responsible for small-vessel necrotizing vasculitis, whereas dysregulation of T-cell homeostasis may underlie granulomatous inflammation.

In Vivo Studies

Evidence for a pathogenic role of MPO-ANCA in AAV comes from animal models for MPO-ANCA-associated vasculitis [134]. Xiao et al. immunized mice deficient for MPO with mouse MPO and transferred splenocytes from these immunized mice into immunodeficient or normal mice [134]. The recipient mice developed pauci-immune

necrotizing glomerulonephritis and haemorrhagic pulmonary capillaritis, similar to the clinical manifestations and the histopathology of MPO-ANCA-associated vasculitis [134]. In addition, transfer of IgG alone from MPO-immunized mice resulted in pauci-immune focal necrotizing glomerulonephritis in the recipient, demonstrating the pathogenic potential of anti-MPO antibodies [134]. Additional studies showed that both neutrophils expressing MPO and the alternative pathway of complement besides the antibodies are required to induce AAV as recipient mice deficient for factor B and complement C5 did not develop disease [135]. Also in a rat model of MPO-ANCA vasculitis, in which rats were immunized with human MPO, the pathogenic potential of anti-MPO antibodies was demonstrated [136]. Of note, however, no animal models for PR3-ANCA-associated WG have been generated [110].

Microbial Factors as Triggers of AAV

A series of early observations have suggested that infectious episodes may trigger relapses of AAV [137]. Further studies of upper airway involvement in WG showed good responses to treatment with trimethoprim/sulphamethoxazole [138]. Long-term studies demonstrated that chronic nasal carriage of *Staphylococcus aureus* is a major risk factor for relapse in WG in conjunction with persistence of ANCA, and maintenance treatment with trimethoprim/sulphamethoxazole reduced the occurrence of relapses by 60% in patients with WG [139]. Possible mechanisms whereby *S. aureus* could result in flares of WG include SAg production and T- and B-cell activation, direct tropism of *S. aureus* for endothelial cells, with binding and internalization of the organism by endothelial cells or by priming of neutrophils [140].

Recently, two studies have shed new light on the possible role of microbial factors in the pathogenesis of AAV. In the first study, antibodies to complementary PR3 were detected in serum samples from patients with PR3-ANCA-associated vasculitis [141]. Complementary PR3 is a protein translated from the antisense DNA strand encoding PR3. Such a complementary protein is a mirror of the original protein [141]. As such, antibodies to a complementary protein can induce anti-idiotypic antibodies that react with the original protein [141]. Pendergraft et al. immunized mice with complementary PR3, and these mice then developed antibodies to PR3 [141]. This complementary PR3 shows homology with a number of microbial proteins, including proteins from *S. aureus* [141]. This raises the possibility that infection with *S. aureus* could lead to antibodies cross-reacting with complementary PR3, which, in turn, evoke antibodies to PR3 by idiotypic–anti-idiotypic interaction.

A second study describes antibodies to the lysosomal membrane glycoprotein 2 (hLAMP-2) as a sensitive and specific marker for pauci-immune crescentic glomerulonephritis [142]. hLAMP-2 is present on neutrophils and endothelial cells [142]. Anti-hLAMP-2 antibodies, raised in rabbits, were able to activate neutrophils and induce apoptosis of human microvascular endothelial cells [142]. More importantly,

these antibodies induced pauci-immune focal necrotizing glomerulonephritis when injected into rats [142]. Eight out of nine amino acids of the P41–49 immunodominant epitope of hLAMP-2 were shown to be identical to the P72–80 peptide of FimH, an adhesion molecule of fimbriae of Gram negative bacteria [142]. Immunization of rats with FimH resulted in the generation of antibodies cross-reacting with hLAMP-2 and inducing pauci-immune glomerulonephritis [142]. These observations suggest that infection with Gram negative bacteria could result in a loss of tolerance and could lead to AAV.

Genetics

A number of candidate gene association studies have identified variants associated with an increased incidence of AAV [143]. Most of the genes described so far encode proteins involved in the immune response and are summarized in Table 2.3. Of note, the genes with variants most strongly associated with AAV, the MHC and *PTPN22* genes, also have variants associated with other autoimmune diseases, including rheumatoid arthritis, type 1 diabetes and systemic lupus erythematosus (SLE) [143]. This suggests that genetic risk factors common to other autoimmune diseases also apply to AAV. Different variants within each gene may be associated with different polymorphisms—for example, SLE associates with the IL-2RA SNP rs11594656, while AAV is associated with rs4129506 [143]. A GWAS of AAV is currently ongoing and may be enlightening in that respect.

Furthermore, Ciavatta et al., in an attempt to uncover a potential transcriptional regulatory mechanism for PR3 and MPO disrupted in patients with ANCA vasculitis, examined the PR3 and MPO loci in neutrophils from ANCA patients and healthy control individuals for epigenetic modifications associated with gene silencing [173]. They demonstrated that levels of the chromatin modification H3K27me3, which is associated with gene silencing, were depleted at PR3 and MPO loci in ANCA patients compared with healthy controls [173]. Interestingly, in both patients and controls, DNA was unmethylated at a CpG island in PR3, whereas in healthy controls, DNA was methylated at a CpG island in MPO [173]. Consistent with decreased levels of H3K27me3, JMJD3, the demethylase specific for H3K27me3, was preferentially expressed in ANCA patients versus healthy controls [173]. In addition, the mechanism for recruiting the H3K27 methyltransferase enhancer of zeste homolog 2 (EZH2) to PR3 and MPO loci was shown to be mediated by RUNX3. RUNX3 message was decreased in patients compared with healthy controls, and may also be under epigenetic control [173]. DNA methylation was increased at the RUNX3 promoter in ANCA patients [173]. These data indicate that epigenetic modifications associated with gene silencing are perturbed at ANCA autoantigen-encoding genes, potentially contributing to inappropriate expression of PR3 and MPO in ANCA patients [173].

Table 2.3 Positive genetic association studies in antineutrophil cytoplasmic antibody-associated systemic vasculitis

Molecule/genetic polymorphism	Disease	Reference
HLA DPB1*0401	WG	[144]
HLA DPB1*0401	WG	[145]
HLA B50	WG	[146]
HLA DR9	WG	[146]
HLA DQw7	WG, MPA	[147]
HLA DR3	WG, MPA	[147]
HLA DR1	WG	[148]
HLA DR4	WG, MPA, CSS, RL	[149]
HLA DR6	WG, MPA, CSS, RL	[149]
HLA DRB4	CSS	[150]
HLA DRB3	CSS	[150]
HLA DRB4	CSS	[151]
HLA DRB3	CSS	[151]
PTPN22-620W	WG	[152]
PTPN22-620W	WG, MPA, CSS	[153]
IL-2RA rs41295061	WG, MPA, CSS	[154]
CTLA4 -318T	WG	[155]
CTLA4 +49G	WG, MPA, CSS, RL	[156]
CTLA4 rs3087243	WG, MPA, CSS	[153]
PRTN3 -564G	WG	[157]
AAT Z allele	WG, MPA, RL	[158]
AAT Z allele	WG, MPA, RL	[159]
AAT Z allele	WG	[160]
AAT Z allele	WG	[161]
AAT Z allele	WG	[162]
C3F	WG, MPA	[163]
CD18 Ava II	MPO positive	[164]
IL-10 microsatellite	WG	[165]
IL-10 (-1082) AA genotype	WG, MPA	[166]
IL-10 haplotype	CSS	[167]
LILRA2 intron 6 AA genotype	MPA	[168]
CD226 rs763361	WG	[169]
FCGR2A R131 RR genotype with FCGR3A F158 FF	WG	[170]
FCGR3B copy number high	WG, MPA, CSS	[171]
FCGR3B copy number low	WG	[171]
FCGR3B copy number low	MPA	[171]
FCGR3B copy number low	WG	[172]

Clinical Features

WG typically affects the upper and lower respiratory tract and is associated with glomerulonephritis, although the disease can affect any organ system in the body [34]. From a clinical perspective, it may be useful to think of WG as having two forms: a predominantly granulomatous form with mainly localized disease with a

chronic course; and a florid, acute small vessel vasculitic form characterized by severe pulmonary haemorrhage and/or rapidly progressive vasculitis or other severe vasculitic manifestation [34]. These two broad presentations may coexist or present sequentially in individual patients. Symptoms and signs of upper respiratory tract involvement include epistaxis, otalgia and hearing loss (conductive and sensorineural) [34]. Nasal septal involvement with cartilaginous collapse results in the characteristic saddle nose deformity, although this may not be present at initial presentation [34]. Chronic sinusitis may be observed. Glottic and subglottic polyps and/or large- and medium-sized airway stenoses can result from granulomatous inflammation [34]. Lower respiratory tract manifestations also include granulomatous pulmonary nodules with or without central cavitation and pulmonary haemorrhages that can be relatively asymptomatic but result in evanescent pulmonary shadows on chest X-ray, or catastrophic pulmonary haemorrhage from pulmonary capillaritis associated with respiratory failure and high mortality [34].

The typical renal lesion is a focal segmental necrotizing glomerulonephritis, with pauci-immune crescentic glomerular changes [34]. Clinical manifestations include hypertension, significant proteinuria, nephritic and nephrotic syndrome, and ultimately the protean clinical features renal failure [34]. Other manifestations include orbital involvement with granuloma, retinal vasculitis, peripheral gangrene with tissue loss, and vasculitis of the skin, gut, heart, central nervous system and/or peripheral nerves (mononeuritis multiplex), salivary glands, gonads and breast [34]. Non-specific symptoms such as malaise, fever, weight loss or growth failure, arthralgia and arthritis are relatively common [34].

Treatment of AAV

Renal morbidity and mortality is a major concern in the AAV, hence therapy aimed at preservation of renal function is a recurring theme for the treatment of AAV in adults and children [174]. Treatment for paediatric AAV is broadly similar to the approach in adults, with corticosteroids, cyclophosphamide (usually 6–10 intravenous doses at 500–1,000 mg/m² [2] per dose given 3–4 weekly; alternatively given orally at 2 mg/kg/day for 2–3 months), plasma exchange (particularly for pulmonary capillaritis and/or rapidly progressive glomerulonephritis–“pulmonary-renal syndrome”) routinely employed to induce remission [3, 175]. Intravenous pulsed cyclophosphamide is increasingly favoured over oral continuous cyclophosphamide in adults because of reduced cumulative dose and less neutropenic sepsis [176, 177] and is thus increasingly used to treat children with AAV as well, albeit without good paediatric evidence. This is followed by low-dose corticosteroids and azathioprine (1.5–3 mg/kg/day) to maintain remission [3, 178]. Anti-platelet doses of aspirin (1–5 mg/kg/day) are empirically employed on the basis of the increased risk of thrombosis associated with the disease process [179]. Methotrexate may have a role for induction of remission in patients with limited WG [180], but is less commonly used as an induction agent in children with AAV. Co-trimoxazole is commonly

added for the treatment of WG, particularly in those with upper respiratory tract involvement, serving both as prophylaxis against opportunistic infection and as a possible disease-modifying agent [139]. Recommendations regarding duration of maintenance therapy are based on adult trial data, suggesting that the strongest predictor of relapse is withdrawal of therapy, and hence maintenance therapy should be continued for several years [174]. As a general therapeutic measure, prophylaxis against osteoporosis, gastrointestinal ulceration and infection (bacterial, protozoal and fungal) is standard for treatment for AAV [174].

As the use of cyclophosphamide contributes to morbidity and mortality [3, 174] with infection playing a prominent role [181], and disease relapses occur in 50% of the patients with AAV as drugs are reduced or withdrawn, newer immunosuppressive agents and immunomodulatory strategies are being explored in both adults and children [3, 174]. Such treatments include MMF and rituximab, which have already been reported to be effective at inducing or maintaining remission in adults with AAV [182, 183]. Of interest, two recent randomized control trials reported on the efficacy of rituximab compared to cyclophosphamide to induce remission in adults with AAV [184, 185]. Jones et al. report on the results of a randomized trial of rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXIVAS) and Stone et al. report on the results of the rituximab in ANCA-associated vasculitis (RAVE) trial [184, 185]. Similar conclusions are reached in the two studies [184, 185]. Both trials showed that rituximab was efficacious in inducing a remission, as compared with intravenous cyclophosphamide (in the RITUXIVAS trial) or oral cyclophosphamide (in the RAVE trial) [184, 185]. There are, however, a number of important differences between the two trials. In the RITUXIVAS trial, patients who were randomly assigned to the rituximab group also received at least two doses of intravenous cyclophosphamide, whereas in the RAVE trial, patients randomly assigned to the rituximab group did not receive any cyclophosphamide [184, 185]. The trials were similar in that all patients in both trials received both intravenous and oral glucocorticoid therapy [184, 185]. Investigators in the RITUXIVAS trial reported sustained remission for 12 months, whereas outcome data from the RAVE trial were reported only on the 6-month remission-induction period [184, 185]. The RAVE trial data were confounded by the use of glucocorticoid therapy for 5 of the 6 months of follow-up [185]. In addition, both trials raised concerns about the substantial complications from the use of rituximab and other immunomodulating agents in ANCA-associated disease [184, 185]. Fewer adverse events would have been expected in patients treated with rituximab as compared with cyclophosphamide. Unfortunately, in the RAVE trial the rate of adverse events was equivalent in the two study groups [185]. Similarly, in the RITUXIVAS study, 6 of 33 patients in the rituximab group died, as did 2 of 11 patients in the control group [184]. The RAVE trial also showed an unexpectedly elevated number of malignant conditions detected over a relatively short treatment period [185]. These studies suggest that rituximab might be considered as an option for first-line therapy for induction of remission of ANCA-associated disease. It remains unclear whether rituximab should be used with glucocorticoids alone or in combination with intravenous cyclophosphamide.

Biologic therapy is also increasingly used to treat children with small vessel vasculitis, including AAV and ANCA negative vasculitides [186]. Agents used include rituximab (previously mentioned), anti-TNF- α (etanercept, infliximab, and adalimumab), and anakinra (recombinant interleukin 1 receptor antagonist) [186]. These therapies are mainly reserved for those children who have failed standard treatment, or in those patients where cumulative cyclophosphamide and/or corticosteroid toxicity is of particular concern [186]. Of note is the European vasculitis study group (EUVAS) MYCYC trial (UK and Europe), which is comparing induction therapy of WG and MPA using cyclophosphamide (standard therapy) versus MMF (experimental therapy). This is the first EUVAS trial to include children as well as adults and is actively recruiting patients under the age of 17 years in the UK. For a full list of the past and present EUVAS trials for AAV, the reader is directed to: <http://www.vasculitis.org/>.

Outcome

The AAV still carry considerable disease-related morbidity and mortality, particularly due to progressive renal failure or aggressive respiratory involvement, and therapy-related complications such as sepsis. The mortality for paediatric WG from one recent paediatric series was 12% over a 17-year period of study inclusion [187]. The largest paediatric series of WG reported 40% of cases with chronic renal impairment at 33 months follow up despite therapy [188]. For MPA in children, mortality during paediatric follow up is reportedly less than 14% [189]. For CSS in children, the most recent series quotes a related mortality of 18%, all attributed to disease rather than therapy [190].

Polyarteritis Nodosa

Systemic polyarteritis nodosa (PAN) is rare in childhood. Although the epidemiology is poorly defined, PAN occurs more commonly in children than in adults, as well as being more common than the AAV [56]. Disease manifestations are diverse and complex, ranging from the benign cutaneous form to the severe disseminated multi-systemic form [56].

Pathogenesis

The immunopathogenesis leading to vascular injury in PAN is probably heterogeneous [56]. Based on animal models, the mechanism of vascular inflammation

implicated most often is induction by immune complexes [56]. In addition, there are some data supporting a role for hepatitis B in some patients [191] and reports of a higher frequency of exposure to parvovirus B19 and cytomegalovirus in PAN patients compared to control populations [192, 193]. HIV has also been implicated and PAN-like illnesses have additionally been reported in association with cancers and haematological malignancies [194, 195]. However, associations between PAN and these infections or other conditions are rare in childhood. Streptococcal infection may be an important trigger [195], and indirect evidence suggests that bacterial SAGs may play a role in some cases [56]. In terms of pathogenetic mechanisms, it seems likely that the immunological processes involved are similar to those in other systemic vasculitides and include immune complexes, complement, possibly autoantibodies, cell adhesion molecules, cytokines, growth factors, chemokines, neutrophils and T cells [196, 197]. Of note, immunohistochemical studies performed on biopsied perineural and muscle vessels from homogeneous populations of PAN patients showed that inflammatory infiltrates consist mainly of macrophages and T lymphocytes, particularly of the CD8+ subset [198]. To date, there is no reliable animal model of the disease. The PAN-like disease in cynomolgus macaques, which is very similar to the human disease, occurs only sporadically [199, 200]. Snyder et al. described a PAN-like illness arising spontaneously in beagle dogs, but to date this animal model has not provided insight to the pathogenesis of PAN in humans [201].

Furthermore, it is assumed that there are probably genetic predisposing factors that may make individuals vulnerable to develop PAN, as have also been considered for other vasculitides [202–204]. An example of this is the link with familial Mediterranean fever [56, 205]. Yalcinkaya et al. have recently reported on the prevalence of FMF mutations in 29 children with PAN showing that 38% of the patients were carriers of MEFV mutations [205].

Clinical Features

The new EULAR/PRINTO/PRES classification criteria for PAN are as follows: histopathological evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormality (aneurysm, stenosis or occlusion) as a mandatory criterion, plus one of the following five—skin involvement, myalgia or muscle tenderness, hypertension, peripheral neuropathy and renal involvement [8]. The main clinical features of PAN are malaise, fever, weight loss, skin rash, myalgia, abdominal pain and arthropathy [56]. Additional features include ischemic heart and testicular pain; renal manifestations such as haematuria, proteinuria and hypertension; and neurologic features such as focal defects, haemiplegia, visual loss, mononeuritis multiplex and organic psychosis. Livido reticularis is also a characteristic feature, and occasionally subcutaneous nodules overlying affected arteries are present.

Treatment

For many years, the treatment of PAN has involved the administration of high-dose steroid with an additional cytotoxic agent such as cyclophosphamide to induce remission [56, 206–208]. Empirically, aspirin has also been given as an anti-platelet agent by some clinicians [209]. Once remission is achieved maintenance therapy with daily or alternate day prednisolone and oral azathioprine is frequently utilized for about 18 months. Adjunctive plasma exchange can be used in life-threatening situations [210]. Biologic agents such as infliximab and rituximab are increasingly used [185, 211–215]. Treatment for cutaneous PAN is typically much less aggressive. Agents commonly utilized include low-dose prednisolone, anti-platelet agents, colchicine, hydroxychloroquine or azathioprine [56]. However, in a few cases cutaneous PAN may progress over time to the systemic form of the disease and therefore require more aggressive therapy [56].

Outcome

Ozen et al. reported on a retrospective series of childhood PAN and improved outcome compared to that reported in adults with only 1 (1.1%) death and 2 (2.2%) patients with end-stage renal disease among 110 patients [195]. Of note, however, in that series 30% of patients were classified as having cutaneous PAN, which typically has a more benign course than systemic PAN [195].

Takayasu Arteritis

TA is a predominantly large vessel vasculitis with a worldwide distribution, although the disease is most common in Asia [216]. Onset of TA is most common during the third decade of life but has been well reported in young children [216].

Pathogenesis

Even though the precise factors responsible for the arterial damage in TA are unknown, it is believed that genetically linked immune responses to unidentified antigens may incite autoimmune damage by cell-mediated or humoral pathways, resulting in the disease and its relapses [216]. In the acute phase of TA, the inflammatory lesions originate in the vasa vasorum and are characterized by perivascular cuffing mainly composed of $\gamma\delta$ T lymphocytes, cytotoxic lymphocytes and T helper cells [217]. Luminal stenosis of adventitial small arteries due to intimal thickening is relatively common [217]. In the chronic stage of TA, intimal fibrosis is often accompanied by well-formed fibrous atherosclerotic plaques and calcification [217].

Furthermore, autoantibodies against aortic endothelial cells have been proposed as a key factor in the pathogenesis of TA [218, 219]. Chauhan et al. reported that patients with TA show circulating anti-aortic endothelial cell antibodies (AAECAs) directed against 60–65 kDa heat-shock proteins (HSPs 60/65) [218, 219]. Sera from AAECA-positive patients with TA were found to induce apoptosis of aortic endothelial cells, suggesting that these antibodies may have a role in the disease pathogenesis [218]. Lastly, while previous reports have suggested a link between TA and tuberculosis, additional studies have not supported this association [220].

Genetics

Familial occurrence of the disease has been extensively reported, leading to a hypothesis for a hereditary basis [221]. The genetic association of TA with HLAB52, and particularly B*5201 that has been observed, with high estimated OR (4.7–10.2), in multiple cohorts of diverse ethnicity (East Asia, South Asia and Mexico) [222]. In addition, a hypothesis was made, based on a Japanese cohort, that an even stronger association can be identified, considering HLA alleles that share the motif of glutamate at position 63 and serine at position 67, which characterizes B*3902 as well as B*5201 [223]. Data supporting this hypothesis were recently reported using a Mexican cohort [222]. Candidate gene studies have also reported associations with interleukin (IL)-12, IL-2 and IL-6 gene polymorphisms in a Turkish cohort but have not been replicated [4, 32].

Clinical Features

Clinical diagnosis of TA is commonly challenging for the clinician. It is estimated that one-third of children present with inactive, so-called burnt-out stage of disease, in which clinical features represent vascular sequelae rather than active vasculitis [216]. The natural history and the time from onset of symptoms to diagnosis are variable. The clinical spectrum at presentation of children with TA differs from that of adults; however, hypertension is the most common symptom in both groups [216]. Cakar et al. recently reported in a series of 19 children with TA that the most common complaints at presentation were headache (84%), abdominal pain (37%), claudication of extremities (32%), fever (26%) and weight loss (10%) [224]. One child presented with visual loss. Examination on admission revealed hypertension (89%), absent pulses (58%) and arterial bruits (42%) in the same cohort [224].

Treatment

Corticosteroids are still the mainstay of treatment for TA [4, 216]. In addition, MTX, azathioprine, MMF and cyclophosphamide have been used in children [4, 216].

Ozen et al. described six children with TA, and treatment with steroid and cyclophosphamide induction followed by MTX was suggested as effective and safe for childhood TA with widespread disease [225]. Anti-TNF therapy may be beneficial [226]. Surgical intervention is frequently required to alleviate end-organ ischemia and hypertension resulting from vascular stenoses [216].

Outcome

The mortality rate in children has been reported as high as 35% [216]. The outcome depends on the vessel involvement and on the severity of hypertension [216].

Novel Biomarkers for Vasculitis Disease Activity: Tracking Endothelial Injury and Repair

Initially considered as a single cell lining of the vascular tree, the endothelium has recently emerged as a dynamic interface responsive to environmental stimuli [227]. As a result, alteration of the endothelium generates a repertoire of biological responses playing a key role in the control of vascular homeostasis such as haemostasis, inflammation or angiogenesis [228]. As a consequence, the endothelium not only displays altered functions but also loses its integrity. Endothelial microparticles (EMPs) released from activated or apoptotic endothelial cells and whole endothelial cells, circulating endothelial cells (CECs), detached from injured vessels constitute a fundamental feature of these injurious responses affecting the vessel wall [229–231]. In response to injury, regenerative mechanisms are activated to restore endothelium integrity [232]. In the past, endothelial repair was considered to solely involve adjacent endothelial cells able to replicate locally and replace the lost cells. Since the original study by Asahara et al., it has become obvious that the recruitment of endothelial progenitor cells (EPCs) represents an additional mechanism for vascular repair [232]. These stem cells are mobilized from the bone marrow and are able to differentiate into mature cells, restoring endothelial integrity at sites of vascular injury [232]. This spectrum of endothelial responses can be considered in a dynamic triad “activation/injury/repair”, which has critically transformed our understanding of endothelial biology.

CECs and EMPs are sensitive biomarkers of vascular injury for monitoring disease activity and response to therapy in children with vasculitis [233]. In addition, preliminary data show altered endothelial repair responses in children with systemic vasculitis, suggesting an unfavourable balance of endothelial injury and repair in childhood vasculitis [234].

Does Vasculitis in Childhood Predispose to Accelerated Atherosclerosis?

Several key aspects of the long-term outcome of vasculitis in the young remain of ongoing concern. Histological findings seen in KD arteries at sites of previous aneurysmal lesions long after disease resolution appear to be indistinguishable from atherosclerosis [235]. Dhillon et al. studied vascular responses to reactive hyperemia in the brachial artery using high-resolution ultrasound [106]. Flow-mediated dilation (an endothelial-dependent response) was reduced in KD patients compared with control subjects many years after the illness, even in patients without detectable early coronary artery involvement. In addition, Cheung et al. studied a cohort of patients with KD with or without coronary aneurysms compared to healthy controls and demonstrated reduced arterial distensibility (an independent risk factor for cardiovascular morbidity and mortality in adults), as assessed using ultrasound pulse wave velocity in the brachio-radial arterial segments and carotid IMT [236]. Similar findings have also been documented in children with PAN [237]. Thus, the long-term outlook for patients with systemic vasculitis must remain guarded at the present time.

Conclusions and Future Directions

A series of significant short- and long-term challenges are looming in the field of paediatric vasculitis research. The development of biomarkers that allow reliable non-invasive monitoring of disease activity and guide therapeutic decisions is of great clinical importance [233, 238]. Furthermore, several key aspects of the long-term cardiovascular risk for children who have systemic vasculitis are described [239]. The emergence of new therapies for the treatment of vasculitis in children provides a real opportunity to limit cyclophosphamide and corticosteroid exposure in the young. These include MMF [182, 183, 240, 241] and biologic agents such as rituximab [184, 185, 187], anti-TNF- α [187, 242] and thalidomide analogues such as lenalidomide [243], amongst others. None of these agents yet has an evidence base to justify their routine use in paediatric vasculitis, although many are increasingly used in this context in individual cases. It is likely that in the future clinical trials in the young will attempt to focus on these agents as alternatives to cyclophosphamide and azathioprine for induction of and/or maintenance of remission of systemic vasculitis. These sorts of trials will require international collaboration if meaningful patient numbers are to be realized, and this remains an important challenge for vasculitis research in children.

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