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Vasculitis in children

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Primary systemic vasculitides of the young are relatively rare diseases, but can have a significant morbidity and mortality. The purpose of this review is to provide an overview of the paediatric vasculitides. Vasculitides that predominantly affect children will be considered in more detail than vasculitic diseases that although are seen in children affect adults more commonly, such as the ANCA associated vasculitides. New classification criteria for childhood vasculitis have recently been proposed and are currently undergoing validation. Epidemiological clues continue to implicate infectious triggers in Kawasaki Disease and Henoch Schönlein purpura. Several genetic polymorphisms have now been described in the vasculitides that may be relevant in terms of disease predisposition or development of disease complications. Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents. However new challenges are looming in regards to the role of inflammation in endothelial health and the long term cardiovascular morbidity for children with primary systemic vasculitis. International multicenter collaboration is of utmost importance in order for us to further advance our understanding and improve the treatment and outcome of systemic vasculitis in the young.

Introduction

Primary systemic vasculitis (PSV) of the young is characterised by the presence of inflammation in the walls of blood vessels, with resultant tissue ischaemia and necrosis [1]. Apart from relatively

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common vasculitides such as Henoch-Schőnlein purpura (HSP) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but with a significant attendant morbidity and mortality. Latest developments in the field of paediatric vasculitis include: a) the recent consensus conference for a new international classification of childhood vasculitides b) the identification of various genetic polymorphisms that may be relevant in terms of disease predisposition or development of disease complications, and c) novel therapeutic approaches including the increasing use of biologics in cases where current standardized first line treatment fails to induce or sustain remission.

In addition, with the increased survival of affected patients, new challenges particularly in regard to longer term cardiovascular morbidity in children who survive vasculitis are looming. The purpose of this review is to present an overview of the primary vasculitides that more often affect children, and to review recent areas of both scientific and clinical importance.

New international classification of childhood vasculitis

There has been for many years a need for an acceptable classification of childhood vasculitis. So far there has been much reliance on adult vasculitis classification systems and definitions that are suboptimal for paediatric vasculitides. A recent International Consensus Conference held in Vienna in June 2005 under the auspices of the Pediatric Rheumatology European Society (PReS) resulted in a new proposal for childhood vasculitis classification summarised in Table 1 [2]. These criteria are currently being validated and it is anticipated that this will be an important step in providing a "fit for purpose" classification system to be used in future epidemiological studies and clinical trials of paediatric vasculitis.

Henoch Schönlein Purpura

HSP is the most common form of systemic vasculitis in childhood and predominantly affects small vessels [3]. The presence of palpable purpura in the absence of thrombocytopenia is an essential classification criterion.

Table 1
Proposed classification of childhood vasculitis (adapted from Ozen et al. 2006 [2]).

I.	Predominantly large vessel vasculitis
	Takayasu arteritis
II.	Predominantly medium-sized vessel vasculitis
	Childhood systemic polyarteritis nodosa
	Cutaneous polyarteritis nodosa
	Kawasaki disease
III.	Predominantly small vessel vasculitis
	A. Granulomatous
	Wegener's granulomatosis
	Churg Strauss syndrome
	B. Non-granulomatous
	Microscopic polyangiitis
	Henoch-Schonlein purpura
	Isolated cutaneous leukocyclastic vasculitis
	Hypocomplementaemic urticarial vasculitis
IV.	Other vasculitides
	Behçet's disease
	Vasculitis secondary to infection (including hepatitis B-associated PAN), malignancy and drugs including hypersensitivity vasculitis
	Vasculitis associated with connective tissue disease
	Isolated vasculitis of the CNS
	Cogan's syndrome
	Unclassified

Epidemiology, aetiology and pathogenesis

Although adult cases have been described, HSP typically affects children between the age of 3 to 10 years, with 50% of the cases occurring at or before the age of 5 years old [4]. Gardner-Medwin et al reported an estimated annual incidence of 20.4 per 100,000 children in the UK [5]. Males are most commonly affected, particularly in the autumn and winter, and HSP may follow an intercurrent infection such as an upper respiratory tract infection [3].

Although 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 if IgA in lesional vascular tissue. Serum IgA levels are increased during the acute phase and a proportion of patients have circulating IgA-containing immune complexes and cryoglobulins [6]. Skin or renal biopsies demonstrate the deposition of IgA (mainly IgA1) in the wall of dermal capillaries and post capillary venules and mesangium [6]. Some studies have found IgA antineutrophil cytoplasmic antibodies (IgA-ANCA) in some patients with HSP, whilst others have shown an increase in IgA-rheumatoid factor or IgA-anti-cardiolipin antibodies [6]. 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 [7]. 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 and IgA nephropathy [7].

A wide variety of infectious agents have been reported as potential triggers of HSP including: group A beta-haemolytic streptococcus (GAS, in up to 20–50% of cases); Bartonella henselae; Parvovirus B19; Staphylococcus aureus; Helicobacter pylori; Haemophilus parainfluenza; and Coxsakie virus, amongst others [6].

In regards to host susceptibility, several genetic polymorphisms relating to HSP and in particular severity and/or risk of renal involvement have recently been described and are summarised in Table 2 (adapted from Brogan, 2007 [8]). On the whole, studies of HSP genetics have been hampered by relatively small patient numbers and thus lack power to be definitive or necessarily applicable to all racial groups.

Clinical manifestations

Peru et al recently described 254 children with HSP, and reported skin involvement in 100%, arthritis in 66%, gastrointestinal involvement in 56%, and renal involvement in 30% [9]. Palpable purpura is the presenting sign in 57–69% of the patients and is more prominent on the lower limbs and buttocks [9]. Local angioedema may precede the development of the purpura. Joint involvement comprises of symmetrical arthritis typically affecting the ankles, feet and knees [9].

The most common gastrointestinal symptom is abdominal pain, occasionally associated with vomiting or bleeding [10]. Intussusception is a serious acute surgical complication occurring in 0.7–13.6 % of patients [10]. Perforations (usually ileal) are also observed, albeit in the minority [11]. Rarer manifestastions include serositis, chylous ascites, and acute pancreatitis [11].

Renal involvement usually manifests as haematuria [12]. The development of renal disease occurs within 4 weeks of HSP onset [13]. Hamdan et al reported a variation in the incidence of nephritis according to age, with cases occurring in 19% of children less than 5 years of age, and in 67% of children 10 years of age and above [14]. The risk of chronic renal failure is related to the initial clinical presentation, being less than 2% in those with haematuria and/or minimal proteinuria to 19% when both nephritic and nephrotic syndromes are found [13]. De Almeida et al reported the development of significant abdominal pain as a significant predictor of nephritis [15].

Other less frequent but serious manifestations include cerebral vasculitis, orchitis , ureteritis and pulmonary haemorrhage [16].

Treatment

The large majority of cases of HSP require symptomatic treatment only. Arthropathy is managed with rest and analgesia. The efficacy of corticosteroids to prevent severe complications or relapse is controversial. Weiss et al performed a meta-analysis based on a comprehensive review of the literature in the Medline database (1956 to January 2007) and the Cochrane Controlled Trials Register of the

Table 2
Genetic polymorphisms studied in Henoch Schonlein Purpura (HSP), Kawasaki disease (KD), Antineutrophil cytoplasmic antibodies associated vasculitis (AAV) and Takayasu arteritis (TA) adapted by Brogan 2007 [8].

Molecule/Genetic polymorphism	KD	HSP	AAV	TA
Mannose binding lectin	Ambiguous role for MBL influencing risk of coronary artery aneurysms (CAA)	MBL and MBL-associated serine protease (MASP-1) detected in glomerular lesions of HSP-	Not studied	Not studied
Angiotensin Converting Enzyme (ACE)	ACE I/D polymorphism increases disease susceptibility	No association of HSP nephritis with polymorphisms in ACE, albeit in studies involving small numbers of children	Not studied	Not studied
Matrix metalloproteinases (MMP)	MMP-3 6A/6A Polymorphism results in higher frequency of CAA	Genetics not studied	Genetics not studied	Genetics not studied
Interleukin 1 receptor antagonist (IL-1Ra)	Polymorphism associated with increased disease susceptibility	Polymorphism predisposes to renal involvement	Not studied	Genetics not studied
Interleukin 1β (IL-1β)	No association found	Polymorphism associated with renal involvement	One study failed to identify associations between IL-1β polymorphisms and WG	Genetics not studied
Interleukin 6 (IL-6)	No association found	No association found	No association found	Increases disease susceptibility
Interleukin 18 (IL-18)	Increases disease susceptibility in Taiwan	Genetics not studied	Genetics not studied	Genetics not studied
Tumour necrosis factor-alpha (TNF-α)	TNF-α-308A associated with increased intravenous immune globulin (IVIG) resistance	TNF-alphaG-308A polymorphism not associated with HSP in Chinese patients	One study failed to identify associations between TNFα polymorphisms and WG	*NFKBIL1*, encoding the I-[kappa]B-like (IKBL) protein increased in Japanese patients
Interleukin-8 (IL-8)	Genetics not studied	Polymorphism associated with renal involvement	Genetics not studied	Genetics not studied
Interleukin-10 (IL10)	IL-10 gene promoter polymorphisms influence risk of CAA	Genetics not studied	IL-10 (−1082) polymorphism associated with WG and MPA	Genetics not studied
Vascular endothelial growth factor (VEGF) and its receptor (KDR)	Polymorphisms of both contribute to increased CAA risk	VEGF polymorphisms predispose to renal involvement	Genetics not studied; VEGF elevated in active WG	Genetics not studied
Chemokines	Chemokine receptor CCR5 and its ligand CCL3L1 influence disease susceptibility	Genetics not studied	Genetics not studied	Genetics not studied; serum levels of MCP-1 elevated in active TD
Familial Mediterranean Fever genotypes (MEFV gene mutation)	Genetics not studied	Mutations in MEFV found more commonly in Israeli and Turkish children with HSP	Genetics not studied	Genetics not studied
Human Leucocyte Antigens (HLA)	No consistent associations	Positivity for HLA-B35 predisposes to renal involvement	No consistent associations	HLA-B52 and B39

PAX2 (Paired box gene 2)	Genetics not studied	Polymorphisms in PAX2 predispose to renal involvement	Genetics not studied	Genetics not studied
Nitric oxide and associated molecules	No association of eNOS and iNOS gene polymorphisms to the development of CAL in Japanese KD patients	Inducible nitric oxide synthetase 2A promoter polymorphism predisposes to renal involvement	Genetics not studied	Genetics not studied
Cell adhesion molecules	Genetics not studied	Patients not carrying the codon ICAM-1 469 K/E genotype are at decreased risk of developing severe gastrointestinal complications	Polymorphism in exon 11 of the CD18 gene associated with MPO ANCA vasculitis; no relevant polymorphisms were identified for ICAM-1, E-selectin, CD11b, or human urokinase plasminogen activator receptor gene	Genetics not studied
α-1-Antitrypsin	Genetics not studied	Isolated case reports of severe multisystemic HSP and α-1-antitrypsin deficiency	An association between PR3-ANCA and the deficient PiZZ phenotype has been described Alpha-1-antitrypsin deficiency is not sufficient in itself to cause ANCA-positive vasculitides, but may act as an amplifying factor	Genetics not studied
Proteinase 3 (PR3)	Genetics not studied	Genetics not studied	Association with the A-564G polymorphism in the proteinase-3 promoter and WG	Genetics not studied
Fcγ receptors	No association for Fcgamma RIIa-131H/R, FcgammaRIIb-232I/T, FcgammaRIIIa-158V/F and FcgammaRIIIb-NA1/NA2	Genetics not studied	Possible association between NA1 allele of FcγRIIIb in patients with WG and renal involvement FcγRII-R131 and FcγRIIIa-F158 may predispose to disease relapse	Genetics not studied
CTLA-4 (cytotoxic T lymphocyte associated antigen-4)	Genetics not studied	Genetics not studied	Polymorphism associated with WG	Genetics not studied
Inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene	Increases diseases susceptibility and risk of CAA	Genetics not studied	Genetics not studied	Genetics not studied

literature regarding corticosteroid therapy of HSP [17]. On the basis of reported outcomes among patients with HSP who were treated at diagnosis with corticosteroids compared with patients treated with supportive care only, odds ratios were calculated for the resolution of abdominal pain, the need for surgical intervention secondary to severe pain or intussusception, the likelihood of HSP recurrence, and the development of transient or persistent renal disease. Two of the studies analysed, evaluated prospectively the effect of corticosteroids on abdominal pain duration by using 14 day symptom diaries [18,19]. In the Huber series a dose of 2 mg/kg/day of prednisolone for 1 week with weaning over weeks 3 and 4 was used [18]. Using median values of total abdominal pain duration, no difference was found between the treatment and the control group. In contrast Ronkainen et al studied 171 patients that were randomised to receive prednisolone at 1 mg/kg/day for 2 weeks with weaning over the following 2 weeks and reported a significant reduction in the intensity and duration of abdominal pain [19].

There are conflicting results from studies examining the role of pre-emptive corticosteroids to prevent the development of nephritis. At the time of writing this review we suggest that the current consensus opinion is that corticosteroids do not prevent the onset of nephritis, but do have a role for the treatment of severe nephritis should it develop [20].

In regards to other immunosuppressive therapy, Cyclosporine A was effective in a retrospective study of HSP nephritis as well as a number of case reports of HSP with nephritic-range proteinuria [21]. Others have suggested good response to combination therapy of steroids with azathioprine or cyclophophamide [21]. Plasma exchange and intravenous immunoglobulin have been effective in individual cases [22]. Most paediatric nephrologists would consider use of an angiotensin converting enzyme inhibitor for proteinuria persisting more than 6 months to limit secondary glomerular injury.

Prognosis of HSP

The majority of children with HSP make a full and uneventful recovery with no evidence of ongoing significant renal disease. However, HSP nephritis is reported to be the cause of ESRF in 1.6–3% of children in the UK [20]. Some instances of hypertension have been reported many years after normalisation of renal function and urinalysis [23]. An increased incidence of pre-eclampsia has also been reported [23]. In view of this, most would advocate monitoring of BP for a minimum of 2 years after normalisation of urinary sediment, although lifelong follow up (annual BP and urinalysis by GP) has been proposed by some for all children with HSP [24].

In unselected populations of HSP, the overall risk of significant long-term renal impairment is around 2% [24]. Children with isolated haematuria with no proteinuria have a negligible incidence of long-term renal morbidity. Patients who present with isolated microscopic and/or macroscopic haematuria may have microscopic haematuria that persists for many months or years [12]. Recurrence of episodes of macroscopic haematuria may occur following upper respiratory tract infections. The prognosis generally remains good unless there is evidence of significant proteinuria [12]. Where isolated haematuria is associated with proteinuria, the risk of long-term renal dysfunction is around 5% [24]. Children presenting with the acute nephritic syndrome have a less favourable outcome, with a long-term risk of CRF of 10–20% [24]. Those with a mixed nephritic-nephrotic presentation have the worst long-term outlook, with up to 33% developing CRF [24]. Those with more aggressive renal biopsy changes are more likely to have a poorer long-term outlook [24]. Children with significant renal impairment at presentation, and/or persistent proteinuria should undergo regular assessment of their GFR (e.g. at 1, 3 and 5 years post acute episode of HSP) [24].

Practice points

- The majority of children with HSP make a full and uneventful recovery
- However, HSP nephritis is reported to be the cause of ESRF in 1.6–3% of children in the UK
- Steroids do have a role for the treatment of severe abdominal pain in HSP, but intussusception should be excluded
- Corticosteroids do not prevent the onset of nephritis, but do have a role for the treatment of severe nephritis should it develop

Kawasaki disease

Kawasaki disease (KD) is a self-limiting vasculitic syndrome that predominantly affects medium and small sized arteries and can be complicated by the development of coronary artery aneurysms (CAA) in 25% of untreated patients, which falls to 4% with treatment. Sometimes systemic arterial injury occurs in addition to CAA, but rarely is this seen in the absence of CAA.

KD is the leading cause of acquired paediatric heart disease worldwide. CAA can lead to myocardial infarction, and late coronary artery stenosis [25].

Epidemiology, aetiology and pathophysiology

Approximately 85% of children with KD are younger than five years old; patients aged less than 3 months or more than 5 years are encountered less commonly, but are at increased risk for coronary artery aneurysm formation [26]. A higher incidence is noted amongst Japanese children, estimated at 134/100 000 [27]. The incidence in children aged less than five years has doubled during the last decade in the UK and is currently reported to be 8.1/100 000 [28]. While this increase may truly indicate an increasing incidence, better case recognition may partly account for this rising trend.

The hallmark of the KD arteritis is the presence of lesions in various stages of progression within the same patient at any given time [29]. The earliest changes are observed in the endothelium of the musculo-elastic arteries, and more advanced lesions show edema and an inflammatory-cell infiltrate in the subendothelial space [30]. These changes progress to destruction of the media and replacement of the intima and media with fibrous connective tissue, thinning of the media with aneurysm formation, scarring, and stenosis [30]. Coronary-artery rupture is extremely rare but can occur during the subacute phase. Myointimal proliferation and stenosis occur over a period of months to years, and these lesions may remain silent until the moment of acute thrombotic occlusion, often decades after the acute illness [29].

Great challenges still remain in the hunt for the cause of KD. Seasonal variation in KD incidence has been reported [31]. Outbreaks of KD have been linked to weather patterns, with clusters of KD cases occurring in association with precipitation [32]. In addition, the abrupt onset of symptoms that are compatible with infection, and the fairly rapid resolution of the illness in 1–3 weeks, even without treatment and usually without recurrence are clinical features of KD that support an infectious cause. Recently cytoplasmic inclusion antibodies were identified in the ciliated bronchial epithelium of children with fatal acute KD, leading the authors of that study to suggest viral infection as the cause of KD [33]. However the hunt for any single infectious agent has so far not proved fruitful, a fact most recently highlighted by the negative results that emerged from studies examining the potential link between coronavirus infection and KD in Taiwan [34].

The hypothesis that a bacterial toxin causes KD is favoured by some investigators. This theory is based on clinical and immunological similarities between KD and staphylococcal or streptococcal toxin-mediated illnesses, and recently the observation that some children with KD seroconvert for IgM antibodies against a number of bacterial superantigens [35]. This remains an area of controversy, however.

Several polymorphisms relating to KD and in particular disease susceptibility and/or risk of coronary artery aneurysm development have recently been described and are summarised in Table 2. Of note, new insight regarding the cause of the disease is provided by a recent study reporting association of functional polymorphism of inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene with immune activation of KD [36]. ITPKC acts as a negative regulator of T-cell activation and may contribute to immune hyper-reactivity in KD. This finding provides new insights into the mechanisms of immune activation in KD and emphasizes the importance of activated T cells in the pathogenesis of this vasculitis.

Clinical features

KD is an acute childhood illness that usually affects previously healthy infants and children. Diagnostic criteria for complete and incomplete KD, created from epidemiological surveys in Japan are listed below [37]:

Diagnostic criteria for complete KD

(a) Fever of at least 5 days duration + 4/5 criteria below + lack of another known disease process to explain the illness
  (i) Bilateral non-purulent conjunctival injection, with limbic sparing
  (ii) Changes of the mucous membranes of the upper respiratory tract: injected, fissured lips; strawberry tongue
  (iii) Polymorphous rash
  (iv) Changes of the extremities; peripheral oedema, peripheral erythema and periungual desquamation after the second week of illness
  (v) Cervical adenopathy

However, patients with fewer than 5/6 principal features symptoms can be diagnosed with KD when coronary aneurysm or dilatation is recognized by 2-D echocardiography or coronary angiography. Irritability is an important sign, which is virtually universally present, although not included as one of the diagnostic criteria [38]. The exact mechanism of the irritability is unclear, but it may be related to the presence of aseptic meningitis. Another clinical sign not incorporated into the diagnostic criteria, but which is relatively specific to KD, is the development of erythema and induration at sites of BCG immunizations [38]. The mechanism of this clinical sign is cross reactivity of T cells in KD patients between specific epitopes of mycobacterial and human heat shock proteins. With an increasing number of infants receiving the BCG in the UK, it is likely that this sign will become more common, and awareness of it could result in earlier diagnosis and treatment [38].

An important point worthy of emphasis is that the criteria may present sequentially such that a so called "incomplete" case can evolve with time into a "complete" case. Thus the diagnosis of KD must be considered in any child with a febrile exanthematous illness, particularly if it persists longer than four to five days [38].

Other relatively common clinical findings in KD include arthritis, aseptic meningitis, pneumonitis, uveitis, gastroenteritis, meatitis and dysuria, and otitis [26]. Relatively uncommon abnormalities include hydrops of the gallbladder, gastrointestinal ischaemia, jaundice, petechial rash, febrile convulsions, and encephalopathy or ataxia [26]. Cardiac complications other than coronary arterial abnormalities include cardiac tamponade, cardiac failure, myocarditis, and pericarditis [28]. Additional rare complications of KD include macrophage activation syndrome and syndrome of inappropriate anti-diuretic hormone secretion (SIADH) [28].

Treatment

Early recognition and treatment of KD with aspirin and IVIG has been shown unequivocally by meta-analysis to reduce the occurrence of CAA [39]. Moreover, the prevalence of coronary artery abnormalities in KD is highly dependent on total IVIG dose, but independent of aspirin dose [40]. Treated with aspirin alone, 20–40% of children develop CAA [39,40]. Combined therapy with aspirin and high dose IVIG given as a single infusion reduces the occurrence of CAA to 9% at 30 days, and 4% at 60 days after the onset of the illness [39]. The prevalence of CAA is inversely related to the total dose of IVIG [40], 2 g/kg of IVIG being the optimal dose, usually given as a single infusion [39,40]. Meta-analysis of randomised controlled trials comparing divided lower doses of IVIG (400 mg/kg/day for four consecutive days) versus a single infusion of high dose IVIG (2 g/kg over 10 hours) has clearly shown the therapeutic benefits in the prevention of CAA with the latter regimen [39]. One important practical point, however, is that infants who have cardiac compromise may not be able to tolerate the fluid challenge associated with the high dose single infusion, and consideration of divided doses given over several days may be appropriate for this patient group.

IVIG treatment should be started early in the disease, preferably within the first 10 days of the illness [39,40]. Importantly, however, clinicians should not hesitate to give IVIG to patients who present after 10 days if there are signs of persisting inflammation.

Not all patients respond to a single dose of IVIG, and some require a second dose. It has been observed that those children who received IVIG very early in the illness may require a second infusion of IVIG for primary treatment failure or disease recrudescence [41]. Thus, the timing of IVIG administration appears to be important, although this latter point should not dissuade clinicians from giving IVIG before day 5 of fever if the diagnosis of KD is suspected.

One question that remains unanswered is whether the type of IVIG administered is important, perhaps as a result of the presence of antibodies to epitopes derived from different donor pools. That said, although the mechanism of action of IVIG remains unknown recent evidence suggests that the efficacy of IVIG resides within the Fc fragment, and not the Fab component [42].

IVIG resistance occurs in up to 20% of cases [25]. In those cases, most advocate the use of corticosteroids, albeit with apparently conflicting data on which to base this practice. Inoue et al showed in a randomized control trial of 178 KD patients that were assigned to receive IVIG, or IVIG plus corticosteroid. The corticosteroid regimen used in that study was prednisolone sodium succinate 2 mg/kg/day, 3 times daily, given by intravenous (IV) injection until the fever resolved and then orally until the C-reactive protein (CRP) level normalized. Once CRP normalized, prednisolone doses were tapered over 15 days. They found that that the addition of corticosteroid reduced CAA: in those receiving conventional treatment 11.4% had CAA at one month, compared with 2.2% in those receiving conventional treatment plus corticosteroids [43]. 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 [44]. They found that this corticosteroid regimen did not improve the CAA outcome in these children. These contrasting results suggest that dose and duration of corticosteroids may be critical to adjunctive efficacy in KD.

Treatment with cyclophosphamide, cyclosporine, and plasma exchange may also be warranted for those with ongoing disease activity despite IVIG and corticosteroids [12,26]. More recently infliximab has been reported to be effective for the treatment of IVIG resistant KD. In 13/16 patients, there was cessation of fever followed by reduction in CRP [45], and these important preliminary observations are supported by our own (unpublished) observations of infliximab efficacy in IVIG resistant KD.

Prognosis

KD has emerged as the most common cause of acquired heart disease in children in the developed world. CAA can remain silent until the third or even fourth decade of life. Prognosis is better when the aneurysms are small (<8 mm) and fusiform [46].

The overall outlook of children with KD is good, with the 1–2% acute mortality rate due to myocardial infarction having been reduced further by alertness of the clinicians to the diagnosis and prompt treatment [28]. Nonetheless the disease may eventually contribute to the burden of adult cardiovascular disease, an area of active ongoing research.

Practice points

- A functional polymorphism of inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene has been linked to immune activation of KD, but the genetic contribution is polygenic and remains to be fully defined
- The features of KD may present sequentially and should be sought in the history as well as on examination
- Early recognition and treatment of KD with aspirin and IVIG has been shown unequivocally to reduce the occurrence of CAA
- IVIG should be administered at a dose of 2 g/kg usually given as a single infusion
- In cases of IVIG resistance the use of corticosteroids has been advocated
- Infliximab may also be effective in IVIG resistant KD, and is actively being studied

Polyarteritis nodosa, microscopic polyangiitis and cutaneous polyarteritis

Classification of polyarteritis in children

The proposed new classification criteria recognise three subtypes of polyarteritis: systemic polyarteritis nodosa (PAN); cutaneous polyarteritis; and microscopic polyangiitis.

Systemic PAN is characterised by necrotizing inflammatory changes in medium and/or small sized arteries. The disease is rare in childhood [47], and although the epidemiology is poorly defined PAN occurs more commonly in children than the ANCA associated vasculitides. Although any organ can be affected, PAN most commonly involves the skin, joints, peripheral nerves, gastrointestinal (GI) tract, and kidney [47]. Disease manifestations are diverse and complex, ranging from the benign cutaneous form to the severe disseminated multi-systemic form [48]. PAN is also observed as a complication of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [49].

In the literature, PAN has often been described along with microscopic polyangiitis (MPA), the latter previously referred to as microscopic polyarteritis. According to the new classification criteria of childhood vasculitis, PAN is defined as vasculitis causing necrotizing inflammation of medium-sized or small-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules [2]. Conversely, MPA causes necrotizing vasculitis with few or no immune deposits (pauci-immune) affecting small vessels (capillaries, venules, arterioles) [2]. Necrotizing glomerulonephritis and pulmonary capillaritis often occur in MPA [50], typically with MPO-ANCA positivity.

Pathogenesis of PAN and MPA

Several studies have explored the pathogenic processes in paediatric PAN and MPA, but the pathogenesis is still poorly defined. It is likely that MPA is somewhat distinct from PAN in terms of pathogenesis, the former falling into the category of ANCA associated vasculitis. Systemic PAN and cutaneous PAN are less distinct in terms of pathogenesis, however.

An infectious aetiology for PAN has been considered for years. Early observers considered streptococci or Staphylococcus aureus to be likely candidates [51]. It has been reported that Hepatitis B surface antigenaemia (with immune complex formation) is associated with approximately 20% of patients with PAN [52], although in the UK this is rarely seen in children.

Viruses other than hepatitis B, such as hepatitis A and C, human immunodeficiency virus (HIV), cytomegalovirus (CMV), human T-cell lymphotropic virus-1 (HTLV-1), and parvovirus, have been reported to have etiologic associations with PAN, but none have been repeatedly isolated from patients with PAN [49]. ANCA appear to play a significant role in causing endothelial injury [53], particularly in MPA. ANCA are present in the minority of children with PAN, however, and if found would prompt many clinicians to consider a diagnosis of MPA rather than classic PAN. That said, in some paediatric series approximately 15 % of patients with classic PAN were positive for P-ANCA [47]. In contrast, patients with MPA, 40% are positive for C-ANCA (with anti-proteinase 3, PR3-ANCA), 50% are positive for P-ANCA (MPO-ANCA), and only 10% are negative for ANCA [53].

Other pathogenic mechanisms are likely to be involved in PAN. For example, superantigens may play a role in some cases [54]. Additionally an association of Familial Mediterranean Fever and the development of PAN is recognized in some ethnic groups [55].

Clinical features

A recent multicenter study of PAN in children and adolescents reported that 30% of polyarteritis cases in children were classified as cutaneous PAN, 4.6% PAN associated with Hepatitis B surface antigen (HBsAg), 8.1% MPA associated with ANCA and 57.2% systemic PAN [47]. Patients with systemic PAN had multi-systemic involvement usually affecting the skin, kidneys, peripheral nerves, muscle and gastrointestinal tract [47]. Symptoms of weight loss, myalgia, pyrexia were common. In contrast, cutaneous PAN only affected the skin although arthralgias and myalgia were occasionally associated [48].

Cutaneous features of PAN (including systemic or predominantly cutaneous forms) include ulceration, gangrene, urticaria, livedo racemosa with tender or painful and inflammatory nodules within the livedo, and bullae [48].

Selective visceral arteriography in PAN

Selective visceral digital subtraction arteriography (DSA) still plays an important role in the diagnostic work-up of children with suspected PAN. Despite suggestions that non-invasive arteriography may replace DSA in some clinical situations, the former lacks sensitivity for some of the more subtle changes associated with smaller order vessels seen in children with PAN, and it is recognised that magnetic resonance angiography overestimates vascular stenotic lesions [56].

Brogan et al described the selective renal DSA findings in children with systemic PAN [57]. 40% of children had aneurysms mostly affecting small and medium-sized arteries and the presence of these was significantly associated with renal impairment and hypertension. Non-aneurysmal changes were detected more commonly on renal angiography than aneurysms in the PAN group.

Treatment of PAN

There are no paediatric randomised controlled trials to guide therapy of PAN in children. Induction of remission of systemic PAN is with high doses of corticosteroids and cyclophosphamide (the latter given usually as IV monthly doses for 6 months) [58], in combination with antiplatelet doses of aspirin. Adjunctive plasma exchange undoubtedly still plays an important role in some children for gaining rapid disease control where life or critical organs are threatened [22].

Following successful induction of remission, azathioprine at 2 mg/kg once a day is instituted, combined with low dose daily or alternate day prednisolone [59]. Total treatment duration is for a minimum of 18 months, usually 2–3 years. Although relapse can occur during the maintenance phase, this occurs much less commonly than in other vasculitides such as Wegener's granulomatosis.

Recently successful treatment of systemic PAN with infliximab or rituximab have been reported [60,61]. We are increasingly using these biologics for the treatment of PAN which has not responded to the conventional approach described above with promising preliminary results [62].

Treatment for cutaneous PAN is typically much less aggressive. Agents commonly utilised include low dose prednisolone, anti-platelet agents, colchicine, hydroxychloroquine, or azathioprine. Dapsone is not a preferred choice of the author because of risk of haemolytic anaemia. Use of cyclophosphamide is rarely justified for cutaneous PAN. An important differential diagnosis for cutaneous PAN in children and adults is the entity referred to as occlusive vasculopathy (also known as "livedoid vasculopathy"). This is an important differential diagnosis because the latter respond more readily to anti-platelet or anti-coagulant therapy rather than immunosuppression [63].

Prognosis of PAN

Prognosis for individuals with PAN varies with a better outcome in childhood disease compared to adult onset disease where the mortality rate can be as high as 20–30% despite aggressive therapy [47]. The most recently published mortality for PAN in children at Great Ormond St Hospital is approximately 10% [64]. Although the medium term prognosis is good, it is not yet clear if survivors of PAN in childhood are prone to premature atherosclerosis later in life, an area of ongoing research [65].

ANCA associated vasculitis (AAV)

The AAV do occur in children, but less commonly than PAN and are dealt with in more detail elsewhere in this edition of the Journal. What follows therefore will be necessarily brief. These include WG, MPA, Churg-Strauss Syndrome (CSS), and so-called renal-limited vasculitis, the latter probably a variant of MPA. AAV in children share many of the features of the adult diseases although clearly the consequences of damage caused by AAV such as renal failure have important and different implications for growing children. Of the AAV occurring in children WG and MPA are seen much more commonly

than CSS, although CSS does occur in children and the clinical features of the paediatric disease have recently been extensively described [66].

There is a perception that some children with WG may present with more localised disease than adults, particularly sub-glottic disease [67]. However, another relatively recent large paediatric series revealed that the spectrum of disease presentation for all intents and purposes was similar to that in adult series, with both localised and florid multi-systemic vasculitic presentations described [68].

The genetic contribution to AAV (Table 2) and environmental factors predisposing to AAV are likely to be similar in children and adults and are discussed elsewhere in this edition of the Journal. The pathogenesis of paediatric AAV has also very recently been extensively reviewed elsewhere [8].

Treatment for paediatric AAV is broadly similar to the approach in adults, with corticosteroids, cyclophosphamide, plasma exchange (particularly for pulmonary capillaritis and/or rapidly progressive glomerulonephritis), and anti-platelet doses of daily aspirin routinely employed. Co-trimoxazole is routinely added for the treatment of WG, serving both as prophylaxis against opportunistic infection, and as a disease modifying agent.

Newer treatments for the induction of remission of AAV in children include Mycophenolate mofetil (MMF) or rituximab. For the first time, children are now included in a EUVAS trial of MMF versus cyclophosphamide for the induction of remission of AAV which hopefully will provide a less toxic but equally effective agent to replace cyclophosphamide in the future (www.vasculitis.org). We are increasingly using rituximab for children with WG that is frequently relapsing or fails to respond initially to conventional induction therapy, and the results are very promising albeit anecdotal [62]. In the paediatric community we have not yet embraced the approach of protocol rituximab therapy every six months (irrespective of peripheral B cell return) for WG, and approach that is beginning to be used in some adult vasculitis treatment protocols.

Prognosis of AAV in children

Despite the development of newer immunosuppressive agents and immunomodulatory therapies, AAV still carries considerable disease related morbidity and mortality mainly due to progressive renal failure or aggressive respiratory involvement. Flares of WG occur in up to 75% as treatment is weaned [68] and significant treatment-related infection is observed in approximately 20–40% [68] significant long-term renal impairment still occurs in 17–40%. The mortality for paediatric WG from one recent paediatric series was 12% [67].

Prognosis for MPA in children is similar to that of PAN in terms of mortality, albeit with a higher long-term renal morbidity of 30% relating to pauci-immune crescentic nephritis [69]. For CSS in children, the most recent series quotes a relatively mortality of 18%, all attributed to disease rather than therapy [66].

Takayasu arteritis

Takayasu arteritis (TA) is a predominantly large vessel vasculitis with a worldwide distribution, although the disease is most common in Asia [70]. Onset of TA is most common during the third decade of life [70]. Park et al reported that in a series of 108 Korean patients with TA, only 7% were under 10 years of age, and 19% were 10–20 years old at onset of disease [71]. Females are affected more often than males. The pathogenesis of TA is reviewed elsewhere in this journal, and the (comparatively limited) genetic associations so far studied that may be associated with TA are summarized in Table 2.

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%) [72]. One child presented with visual loss. Examination on admission revealed hypertension (89%), absent pulses (58%), and arterial bruits (42%) [72].

Conventional DSA remains an important tool in the initial evaluation of paediatric TA. Increasingly, however, magnetic resonance angiography (MRA) can be useful in detection of early signs of large-vessel disease, and has the added advantage of potentially revealing evidence of ongoing large arterial wall inflammation [73]. One caveat, however, is that MRA may result in false positive diagnoses for TA

based on aortic signs in young children. In our experience two pre-school children referred to us with the presumptive diagnosis of TA on the basis of aortic caliber variation observed on MRA turned out to have alternative diagnoses, and with normal aortic anatomy on subsequent formal digital subtraction arteriography.

In the Cakar series, angiography revealed stenosis as the most common type of lesion, followed by occlusion, dilatation, and aneurysms [72]. The most commonly involved vessels were the renal, subclavian and carotid arteries, whilst previous series had reported the innominate and subclavian arteries (93% of cases) followed by aorta (65%) as the most frequently involved vessels [72]. Positron emission tomography (PET) scanning with radioactive-labeled 18-fluorodeoxyglucose (FDG) has been shown to be useful in monitoring disease activity and response to treatment in preliminary studies [74]. Presence or absence of FDG uptake correlates well with clinical state and MRA findings.

In terms of therapy, as in adults with TA progress has been hampered by lack of good clinical trials on which to base firm recommendations. Corticosteroids are still the mainstay of treatment for TA [75]. In addition, MTX, azathioprine, MMF, and cyclophosphamide have been used in children [75]. Cyclophosphamide has been used for children with severe TA refractory to other immunosuppressive drugs [75]. Ozen, *et al* described 6 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 [76]. Anti-TNF therapy might be beneficial in TA, and a high rate of response to TNF inhibitors has been reported [77]. This important topic is considered in more detail elsewhere in this journal. Besides medical therapy, surgical intervention is frequently required to alleviate end-organ ischemia and hypertension resulting from vascular stenoses [78].

Summary

Primary systemic vasculitides are relatively rare conditions in children, but carry significant morbidity and mortality despite newer diagnostic modalities and treatments. Our understanding of the disease pathogenesis has advanced but there is still much to learn. Significant short and long-term challenges are looming. These include establishing international research networks and databases to obtain adequate patient numbers enabling powering of paediatric studies; validation of classification criteria suitable for the paediatric vasculitides (currently underway); the development of tools such as biomarkers to allow reliable non-invasive monitoring of disease activity; and the development of robust core outcome variables that can be used to assess outcomes in clinical trials. Lastly, there remains the question regarding longer term cardiovascular morbidity in children who survive vasculitis. Ultimately it must be anticipated that advances in our understanding of the environmental triggers and host responses will shape future novel therapeutic approaches to PSV in the young.

Research agenda

- Development of clinical outcome variables and biomarkers to allow reliable non-invasive monitoring of disease activity
- Further advance our understanding of the environmental triggers and host responses resulting in vasculitis of the young
- Optimise current vasculitis treatment protocols and develop novel therapeutic approaches
- Investigate the longer term cardiovascular morbidity in children who survive vasculitis

Conflict of interest

The authors declare no conflict of interest.

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