

# Update on childhood vasculitides

Tracy V. Ting and Philip J. Hashkes

## Purpose of review

The purpose of this review is to provide an update on the new developments in pediatric vasculitis.

## Recent findings

Because most childhood vasculitides are rare, few large systematic studies have been done. Studies of Henoch–Schönlein purpura have focused on pathogenesis and outcome. Genetic associations and molecular changes occurring during Henoch–Schönlein purpura, including cytokines, and endothelial and nitric oxide metabolism are discussed. Risk factors for renal involvement and poor renal outcome are described. Uncontrolled series of treatment protocols for severe Henoch–Schönlein purpura nephritis are mentioned. Several studies have focused on the pathogenesis of other primary vasculitides, especially polyarteritis nodosa. Series describing the clinical manifestations of childhood vasculitis and case reports of uncommon manifestations of vasculitis in children are presented. The efficacy of new therapies, including the use of thalidomide and biologic modifiers, has been shown in individual childhood cases; however, there are no controlled studies of these agents.

## Summary

Besides studies of Henoch–Schönlein purpura, advances in pediatric vasculitis are few as a result of the rarity of most vasculitides in childhood. Multicenter collaboration is necessary to substantially increase the scientific base of investigating and treating childhood vasculitis.

## Keywords

vasculitis, children, Henoch–Schönlein purpura

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Section of Pediatric Rheumatology, Department of Rheumatic Diseases, Cleveland Clinic Foundation, Ohio, USA

Correspondence to Philip Hashkes, MD, Department of Rheumatic Diseases A50, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA  
Tel: 216 445 8525; fax: 216 445 7569; e-mail: hashkep@ccf.org

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## Abbreviations

<b>ANCA</b>	antineutrophil cytoplasmic antibodies
<b>BD</b>	Behçet disease
<b>FMF</b>	familial Mediterranean fever
<b>HSP</b>	Henoch–Schönlein purpura
<b>IL</b>	interleukin
<b>PAN</b>	polyarteritis nodosa

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## Introduction

Vasculitis is defined as inflammation involving the blood vessel wall. Most types of vasculitis in childhood are rare, with the exception of Henoch–Schönlein purpura (HSP), Kawasaki disease (reviewed separately in this issue), and Takayasu arteritis. Gardner–Medwin *et al.* [1] surveyed the local population in the West Midlands, UK, in 2002 and reported an estimated annual incidence of primary vasculitis of 0.24 per 100,000 children (except HSP and Kawasaki disease), mainly in children of Asian origin. Vasculitides can be classified according to the size or histology of the blood vessel or by clinical manifestations. The Chapel Hill Consensus Conference classification has not been validated in children.

Diagnosis is based on clinical criteria, well defined in some childhood vasculitides (HSP, Kawasaki disease), as well as imaging, and histology. Laboratory tests are usually nonspecific. The utility of antineutrophil cytoplasmic antibodies (ANCA) in children is not clear. In one study the sensitivity of p-ANCA and c-ANCA for microscopic polyangiitis and Wegener granulomatosis was 100%, but the specificity was low. c- and p-ANCA were also found in juvenile rheumatoid arthritis (27% of patients), cystic fibrosis (42%), ulcerative colitis (70%), and autoimmune hepatitis (84%) [2•].

We review the relatively few recent developments in pediatric vasculitis.

## Henoch–Schönlein purpura

HSP, the most common vasculitis in children, classically includes nonthrombocytopenic purpura, abdominal pain, arthritis, and glomerulonephritis.

## Epidemiology, etiology, and pathophysiology

Gardner–Medwin *et al.* [1] found an estimated annual incidence of 20.4 per 100,000 children, with a mode between 4 to 6 years (70.3/100,000). The association of HSP with familial Mediterranean fever (FMF) was supported by Gershoni–Baruch *et al.* [3•], who identified an increased number of FMF gene mutations among Israeli children with HSP. Ten percent were homozygous or had a compound-homozygote FMF genetic defect. Most included the M694V mutation [3•].

HSP is associated with numerous triggers, primarily infectious. Several recent studies have reiterated that upper respiratory tract infections precede HSP in 30 to 50% of cases, often group A *Streptococcus* [4,5•,6]. Masuda *et al.*

[5•] have found increased levels of group A *Streptococcus* antigens in the glomerular mesangium from patients with HSP nephritis compared with other types of glomerular disease. Eisenstein and Navon-Elkan [6] reported the simultaneous occurrence of HSP and rheumatic fever in six patients.

Ayoub *et al.* [7] reported a possible association of HSP with *Bartonella henselae* infection. Antibodies to *B. henselae* were found in 12 of 18 HSP patients (67%) as opposed to 8 of 57 healthy control subjects (14%;  $P < 0.0001$ ). Other recently reported infectious triggers included hepatitis A [8] and *Hemophilus parainfluenza* [9]. Two cases of HSP following hepatitis B and meningococcal vaccination [10,11], and a case of azithromycin-induced HSP were reported [12]. Unlike previous reports, no evidence of preceding parvovirus B19 infection was found in 28 of 29 children with HSP [13].

Amoli *et al.* [14,15] found an increase in the prevalence of human leukocyte antigen-DRB101 and a decrease in human leukocyte antigen-DRB107 among patients with HSP. They also found an increased prevalence of human leukocyte antigen-B35 and interleukin (IL)-8A allele polymorphism among HSP patients with nephritis [14,15]. The severity of nephritis and renal outcome were influenced by the IL-1 $\beta$  gene polymorphism. Patients with more severe disease carried the 511-T allele [16•]. No associations were found between nitric oxide synthase polymorphisms and HSP [17]. However, another study identified higher levels of serum nitric oxide and urinary nitrate excretion during acute HSP [18]. Endothelial cell involvement as evident by increased endothelin ET-1 and IgA antiendothelial cell antibodies were found during acute HSP [19,20]. Increased levels of adrenomedullin, a vasodilator molecule, were also found during acute HSP [21].

In a Turkish study, increased numbers of apoptotic peripheral neutrophils and lymphocytes were present during the acute phase of disease, indicating that increased apoptosis may have a role in the early control of inflammation in HSP [22•].

### Clinical manifestations

A Thai review of 47 patients with HSP found skin involvement in 100% of patients, gastrointestinal involvement in 75%, renal involvement in 47%, and joint involvement in 43% [23]. A Lithuanian series reported less gastrointestinal (38%) and renal involvement (13%) [4].

Sano *et al.* [24] found that 97% of cases of HSP nephritis appeared within the first 3 months of disease. Risk factors included children older than 4 years, those with gastrointestinal bleeding, purpura lasting more than 1 month, factor XIII activity less than 80% of normal, and/or those treated with factor XIII concentrate.

To differentiate HSP from testicular torsion, Ben-Sira and Laor [25] have described the sonographic features of HSP scrotal disease. These include an enlarged, rounded epididymis with thickened scrotal skin and hydrocele, but with normal-appearing testes.

Eun *et al.* [26•] presented an 8 year-old boy with HSP who developed seizures and changes in mental status. MRI revealed multifocal, high-intensity T2 images. In contrast to other reported cases, irregularities of several middle-size cerebral arteries were found by MR angiography. Rare complications of HSP recently reported included the development of cerebellar and pulmonary hemorrhage [27,28].

Two studies confirmed the benign nature of acute hemorrhagic edema of infancy associated with purpura, edema, and fever in infants younger than 27 months [29•,30].

### Treatment

No new studies were published on the use of corticosteroids for gastrointestinal disease and prevention of glomerulonephritis. Several reports discussed the treatment of severe nephritis. Flynn *et al.* [31] reported that treatment with prednisone and 12 weeks of oral cyclophosphamide resulted in a significant decrease in proteinuria with preservation of renal function in 12 patients with nephrotic-range proteinuria, 10 of whom had crescentic nephritis. Kawasaki *et al.* [32•] reported 56 patients with severe HSP nephritis treated with intravenous methylprednisolone and urokinase pulse therapy. They found 100% renal survival during a follow-up of more than 10 years. A significant decrease in the activity index ( $4.1 \pm 1.9$  to  $2.5 \pm 1.7$ ) was found among 27 patients who underwent pre- and posttherapy renal biopsies. Other series reported the beneficial use of cyclosporin A for nephrotic-range proteinuria (seven patients) [33•] and for steroid-resistant HSP (two patients) [34]. Controlled studies are required before these regimens become standard of care.

Intravenous pulse steroids were used to treat a 15-year-old boy with massive gastrointestinal bleeding with ileus [35]. Another 7-year-old boy with refractory, severe HSP was successfully treated with leukocytapheresis [36]. A recent study showed a lack of efficacy of vitamin E for HSP, despite evidence of oxidative damage and lipid peroxidation [37]. Conservative treatment of ileoileal intussusception in HSP patients is often adequate (three of six patients), but close observation is necessary [38].

### Prognosis

Kawasaki *et al.* [39] looked at risk factors for developing an “unfavorable” renal outcome, defined as hypertension, proteinuria, and renal failure, in 114 patients followed for 5 to 15 years. They found that patients with

nephritis, decreased factor XIII activity, hypertension, and renal failure at disease onset were at a higher risk for these outcomes. The 15-year renal survival rate was 96% [39]. Garcia-Porrua *et al.* [40] recently confirmed that adults with HSP have a worse renal prognosis than children. Ronkainen *et al.* [41•] found that biopsy findings at onset did not predict the renal outcome. Patients with low- to mid-grade histology had the worst outcomes [41•]. Algoet *et al.* [42] also found that 8 of 12 HSP patients who underwent a renal biopsy 2 to 9 years after disease onset continued to have mesangial IgA deposits despite only minor renal findings in most patients. In an important long-term study (mean follow-up, 24.1 years), Ronkainen *et al.* [43] found that patients with significant glomerulonephritis at onset had a 4.7 risk of developing a poor renal outcome than patients with mild abnormalities. All patients without renal involvement did well. Women were at a 2.5-fold risk for a poor renal outcome, and 70% of the women developed pregnancy complications of hypertension and decreased renal function [43].

### Takayasu arteritis

Takayasu arteritis is the third most common childhood vasculitis. Case reports of unusual clinical manifestations include a child who presented with panuveitis and a child initially thought to have juvenile rheumatoid arthritis [44,45]. Also reported was a 17-year-old woman diagnosed via endovascular biopsy of the infrarenal aorta [46].

The features of pediatric Takayasu arteritis in 142 patients were recently described [47]. The mean age of onset was 11.4 years; 75% were female. The most common clinical and laboratory manifestations were hypertension (88%), cardiomegaly (74%), elevated sedimentation rate (61%), fever (40%), fatigue (40%), palpitations (25%), vomiting (25%), nodules (25%), abdominal pain (19%), arthralgia (19%), claudication (17%), weight loss (17%), and chest pain (11%) [47]. The mean time to diagnose Takayasu arteritis was 19 months, longer than most adult series. The mortality rate was 33% (more than in adults). Similar clinical findings with an 8% mortality rate were seen in 24 Indian children followed for 3 to 72 months [48].

The angiographic findings in 26 children have been described [49]. The most common findings included stenosis in all patients, mainly of the abdominal aorta. Seventeen of 26 (65%) also had aneurysms: fusiform (54%) and saccular (31%). Percutaneous transluminal angioplasty was initially effective in treating stenosis in eight patients [49]. No long-term follow-up was available.

No pediatric studies on the use of methotrexate or newer antitumor necrosis factor agents have been published.

### Polyarteritis nodosa and microscopic polyangiitis

Several studies have explored pathogenic processes in pediatric PAN and microscopic polyangiitis. An association of specific V $\beta$  T-cell receptor families (CD4-12, CD17, and CD8-1) and the development of primary systemic vasculitis, particularly PAN, have recently been described [50•]. Microparticle-containing molecules, indicating endothelial activation, were increased in children with active PAN, microscopic polyangiitis, and Kawasaki disease [51].

Recent studies have found an association of PAN with FMF. Approximately 1% of patients with FMF develop PAN [52]. These patients tend to be younger than children with classic PAN and have a better prognosis. The development of perirenal hematomas is particularly characteristic in these patients [53].

Cheung *et al.* [54] found a decrease in arterial distensibility of the brachial and radial arteries in 13 children with active PAN compared with the distensibility during remission and with normal control subjects.

Bakkaloglu *et al.* [55] examined the utility of p-ANCA testing in children with PAN. They found a 40% sensitivity in classic PAN (6 of 15 children) and positive ANCA in all 10 children with MPO. ANCA levels were useful in following the disease course [55]. Ceruloplasmin levels were significantly elevated in children with active p-ANCA vasculitis compared with children with c-ANCA vasculitis and HSP, particularly in patients with severe renal disease. Ceruloplasmin levels correlated significantly with p-ANCA and antimyeloperoxidase levels, and were decreased during remission [56].

No controlled therapeutic studies were reported in children. Successful treatment with interferon- $\alpha$  was reported in a 9-month-old girl with PAN related to maternally transmitted hepatitis B infection [57].

### Wegener granulomatosis

Wegener granulomatosis is characterized by the presence of upper and lower respiratory tract disease with glomerulonephritis. It is the most common granulomatous vasculitis in children, and it affects medium and small-size vessels.

A series of 17 pediatric patients with Wegener granulomatosis (age range, 2 weeks to 14 years) was recently reported [58]. The children's ages were lower than in previous pediatric series. Clinical manifestations were similar to adult cases, with nasal and sinus involvement in 100%, respiratory in 87%, arthralgia in 53%, ocular in 53%, skin in 53%, gastrointestinal in 41%, and central nervous system in 12%. Renal involvement was seen in 53% (less than in other series), whereas subglottic ste-

nosis was more frequent (41%). The follow-up period was unclear, but one patient died, one was in drug-free remission, and other patients were stable while receiving treatment.

Unusual manifestations of Wegener granulomatosis, including intracranial bleeding in a 4-year-old girl and pseudo tumor orbitae in a 7-year-old girl were recently reported [59,60].

The adult therapeutic regimens, including corticosteroids and cyclophosphamide for induction and methotrexate for maintenance, have not been validated in children.

### Behçet disease

Behçet disease (BD) is a small-vessel immune complex vasculitis typically involving the oral and genital mucous membranes, eyes, and skin, and often involving the musculoskeletal, central nervous, and gastrointestinal systems.

### Epidemiology

BD is more frequent in East Asia and the Mediterranean. Researchers in Korea and Turkey have reported that less than 10% of BD cases start in childhood (149 of 1697 patients) [61,62]. A multinational study has found a significantly greater familial aggregation in families with pediatric cases of BD (12.3%) than adult BD (2.2%) [63]. Another study reported that siblings were affected in 33% of families with childhood BD (4 of 12 patients) [62].

### Clinical manifestations

The International Study Group diagnostic criteria for BD in 1989 have not been validated in children [64]. In a series from Israel comparing pediatric with adult BD, children had uveitis more often, but less genital ulcerations, vascular thrombosis, arthralgia, and central nervous system involvement [65]. The spectrum of BD-related eye involvement was described in 36 Turkish children. Panuveitis was the most common form, but more than 80% also had retinal vasculitis and/or infiltrates. Unlike earlier series, more than 50% of the children had complications, including blindness in 17%, despite aggressive immunosuppression given to 75% of the children [66•].

Case reports of pediatric BD included a 13-year-old boy with abdominal aortic aneurysm and superior sagittal sinus thrombosis [67], two cases of cerebral venous thrombosis [68], and fatal hemoptysis in a 10-year-old child [69].

### Treatment

Current therapy includes colchicine, corticosteroids, and various immunosuppressive medications [70]. Two papers reported the efficacy of thalidomide for mucous

membrane and enteric features of pediatric BD [71,72]. However, symptoms of peripheral neuropathy were present in four of five children treated with thalidomide, and was irreversible in one patient [71]. Infliximab was effective in a 15-year-old girl with severe mucous membrane ulcers [73]. Cord blood stem cell transplantation in a 10-year-old girl with a myelodysplastic syndrome was also effective in curing her BD [74].

### Central nervous system vasculitis

A comprehensive review by Benseler and Schneider [75••] was recently published in this journal. Benseler *et al.* [76] reviewed the predictors of primary central nervous system vasculitis progression in 62 children. High-risk factors included significant neurocognitive dysfunction and severe headache at onset, MR findings of multifocal parenchyma lesions with bilateral areas of infarction, and MR angiographic findings of multiple stenoses, with bilateral and peripheral vessel involvement. Isolated stroke features were associated with a low risk of progression [76].

### Secondary vasculitis

Several cases of the development of vasculitis secondary to other diseases have been reported. A 16-year-old girl with congenital cyanotic heart disease was diagnosed with infectious endocarditis after presenting with systemic vasculitis and glomerulonephritis [77]. A 16-year-old girl with systemic lupus erythematosus was found to have mononeuritis multiplex 4 years after diagnosis. Nerve biopsy confirmed vasculitis [78]. An 11-year-old girl with pre-B-cell acute lymphoblastic leukemia presented with cutaneous lymphocytic vasculitis that resolved after chemotherapy [79]. A 9-year-old girl with systemic juvenile rheumatoid arthritis treated with etanercept developed purpura that resolved after etanercept discontinuation. Purpura did not recur after gradual reintroduction of etanercept [80].

### Conclusion

There are still significant gaps in the understanding and treatment of pediatric vasculitis. We are dependent, to a large degree, on the adult knowledge and experience. A concerted multicenter, international effort is needed to develop an independent understanding of the unique pathogenesis, clinical features, and therapeutic modalities of pediatric vasculitis.

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