Vasculitis in children

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Abstract

Systemic vasculitis is characterized by blood vessel inflammation which may lead to tissue injury from vascular stenosis, occlusion, aneurysm, and/or rupture. Apart from relatively common vasculitides such as IgA Vasculitis (IgAV; previously referred to as Henoch-Schőnlein Purpura [HSP]) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but are associated with significant morbidity and mortality. The cause of the majority of vasculitides is unknown, although it is likely that a complex interaction between environmental factors such as infections and inherited host responses trigger the disease and determine the vasculitis phenotype. Several genetic polymorphisms in vasculitis have now been described. Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents. Randomized control studies involving predominantly adults have recently recruited children with vasculitis too; but rare disease trial design is required for paediatric specific trials. The SHARE (Single-Hub Access for Pediatric Rheumatology in Europe) project has recently provided guidance on management of rare paediatric rheumatic diseases including the vasculitides. This article provides an overview of paediatric vasculitides with emphasis on presenting features, current insights on aetiopathogenesis and treatment advances.

Keywords child; Henoch-Schőnlein Purpura; IgA Vasculitis; Kawasaki disease; vasculitis

Introduction

Apart from relatively common vasculitides such as IgA Vasculitis, previously referred to as Henoch-Schőnlein Purpura (HSP), and Kawasaki disease (KD), primary systemic vasculitic syndromes are rare in childhood. However, they are associated with significant morbidity and mortality. The general scheme for the classification of paediatric vasculitides is summarized in Table 1. An important advance has been the development and validation of a paediatric vasculitis activity assessment (PVAS) tool that systematically quantifies define disease activity, and is being used as an outcome measure in two ongoing paediatric vasculitis clinical trials, and other research involving children with vasculitis. Treatment regimens continue to improve with the overall intention of reducing cyclophosphamide and glucocorticoid toxicity for children by exploring different immunosuppressive medications including biologic agents.

Most of the current treatment approaches for paediatric vasculitides are based on evidence from small case series, anecdotal observations, or adult studies. Therefore treatment approaches differ substantially internationally, and even between institutions from the same country. Given that vasculitides are rare, traditional large randomised controlled trials may not be feasible. This leaves a gap between evidence and practice and there is an important unmet need for optimized standard management of these rare paediatric diseases. This review summarizes the epidemiology, aetiopathogenesis, presenting clinical features and advances in current management strategies for paediatric vasculitides including reference to soon-to be-published European management guidance.

Predominantly small vessel vasculitis

IgA Vasculitis (HSP)

HSP is the most common childhood primary systemic vasculitis with an estimated annual incidence of 20.4 per 100,000 children in the UK. A child is defined as having HSP in the presence of purpura or petechiae with lower limb predominance (mandatory criterion), plus 1 out of 4 of the following criteria:

1. Abdominal pain
2. Histopathology showing typical leukocytoclastic 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 as a mandatory criterion in research studies, although in routine clinical practice skin biopsy with immunofluorescence is rarely performed. If a skin biopsy is taken from the centre of the necrotic lesion, IgA deposition may be falsely negative due to proteolytic enzymes.

Aetiopathogenesis: about half of occurrences in paediatric patients are preceded by an upper respiratory tract infection. HSP occurrence following occurring vaccination has also been described, although this remains a contentious issue. Several bacteria and viruses have been implicated, including group A *Streptococci*, varicella zoster, hepatitis B, Epstein–Barr virus, parvovirus B19, *Mycoplasma*, *Campylobacter*, and *Yersinia.*

IgA seems to have a pivotal role in the pathogenesis of the disease. There is almost universal deposition of IgA in lesional vascular tissue. IgA immune complexes and activation of complement lead to the formation of chemotactic factors (such as C5a), which in turn recruit polymorphonuclear leucocytes to the site of deposition, resulting in further inflammation and necrosis of vessel walls, with concomitant thrombosis and extravasation of erythrocytes from haemorrhage. The histological endpoint is that of a typical leukocytoclastic vasculitis that refers to the breakdown neutrophils in lesional tissue resulting in the characteristic nuclear debris or "nuclear dust".

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Classification of childhood vasculitides

Predominantly small vessel vasculitis
Granulomatous:
Granulomatosis with Polyangiitis (GPA) [formerly Wegener granulomatosis (WG)]
Churg Strauss syndrome (CSS)
Non granulomatous:
Microscopic polyangiitis
Henoch Schönlein Purpura (HSP)
Isolated cutaneous leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis
Predominantly medium-sized vessel vasculitis
Childhood polyarteritis nodosa (PAN)
Cutaneous polyarteritis
Kawasaki disease
Predominantly large vessel vasculitis
Takayasu arteritis (TA)
Other vasculitides
Behçet's disease
Vasculitis secondary to infection (including Hepatitis B associated PAN), malignancies and drugs, including hypersensitivity vasculitis
Vasculitis associated with other connective tissue diseases
Isolated vasculitis of the CNS (Childhood Primary Angiitis of the Central Nervous System: cPACNS)
Cogan's syndrome
Unclassified

Table 1

Whilst associations between known genetic polymorphisms have been reported cohort studies have been hampered by relatively small patient numbers and lack of power to be definitive or necessarily applicable to all racial groups.

Clinical features: purpura generally is symmetrical, affecting the lower limbs and buttocks. The upper extremities are less frequently involved. Angioedema and urticaria can also occur. Around two thirds of children have joint manifestations at presentation. Knees and ankles are most frequently involved; these tend to resolve without permanent articular damage.

Three-quarters of children develop abdominal symptoms ranging from mild colic to severe pain with ileus and vomiting. Haematemesis and melaena are sometimes observed, due to mesenteric vasculitis. Other serious complications include intestinal perforation and intussusception. The latter may be difficult to distinguish from abdominal colic, and the incidence of intussusception is significant enough to warrant exclusion by ultrasound where suspected. Acute pancreatitis may, rarely, occur.

Reports of HSP nephritis indicate that between 20 and 61% of cases are affected. Renal involvement is normally manifest between a few days and a few weeks after first clinical presentation, but can occur up to 2 months or (rarely) more from presentation. Renal involvement can present with varying degrees of severity. 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.

The renal lesion of HSP nephritis is characteristically a focal and segmental proliferative glomerulonephritis with IgA deposition. Severe cases with rapidly progressive glomerulonephritis can demonstrate crescentic glomerular changes on renal biopsy. Indications for discussion with a paediatric nephrologist for consideration of diagnostic renal biopsy in children with HSP are:

- Nephritic/nephrotic presentation (urgent)
- Raised creatinine, hypertension or oliguria (urgent)
- Heavy proteinuria ($U_{albumin}$:$U_{creatinine}$ persistently more than 100 mg/mmol) on an early morning urine sample at 4 weeks
- Persistent proteinuria (not declining) after 4 weeks
- Impaired renal function (GFR less than 80 ml/minute/1.73m^2)

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). Recurrence of symptoms occurs in around one third of cases, generally within four months of resolution of the original symptoms.

Management: there is surprisingly little robust evidence to guide the management of HSP. Early morbidity in the disease is due to GI involvement; late morbidity and the most important overall determinant of poor outcome is renal involvement.

In children the management of HSP is mainly conservative because the extra renal manifestations are usually self-limiting. Arthritis responds well to non-steroidal anti-inflammatory drugs (NSAIDs). Severe skin lesions and gastrointestinal involvement could require a short course of an oral corticosteroid. Controlled studies have shown that corticosteroids do not prevent renal disease. Despite this, patients with severe renal involvement usually do require corticosteroids combined with other immunosuppressive agents, and sometimes anti-proteinuric and antihypertensive agents.

Summary of the SHARE guidelines for HSP: the SHARE (Single Hub Access for pediatric Rheumatology in Europe) initiative provides consensus guidance for the management of vasculitides. Consensus guidance is due for imminent publication.

Children with microscopic haematuria without renal dysfunction or proteinuria, and those with non-persistent mild-moderate proteinuria usually do not require any specific therapeutic intervention other than a "watchful waiting approach" since the prognosis is excellent. Those with more severe proteinuria and/or impaired glomerular filtration, and those with persistent proteinuria should be reviewed by a paediatric nephrologist, and a renal biopsy is usually recommended. Treatment thereafter includes first line therapy with corticosteroids: oral for all; and initially intravenous pulsed methylprednisolone for those with more severe renal involvement.

For the severest cases, intravenous cyclophosphamide is usually required (sometimes with plasma exchange under expert guidance) as additional first line treatment combined

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