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 Henoch–Schönlein Purpura (HSP) and Kawasaki disease (KD), most of the primary vasculitic syndromes are rare in childhood, but are associated with significant morbidity and mortality. Classification criteria for childhood vasculitis and a disease activity scoring tool have recently been proposed and validated. 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 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. We provide an overview of paediatric vasculitides with emphasis on presenting features, current insights on aetiopathogenesis and treatment advances.

Keywords child; Henoch–Schönlein Purpura; Kawasaki disease; vasculitis

Introduction

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. Until recently classifications in childhood vasculitis have been based on modifications of those used in adult populations. In 2005 the vasculitis working group of the Paediatric Rheumatology European Society (PRES) proposed preliminary classification criteria for some of the most common childhood vasculitides. Subsequently, with support from the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trials Organisation (PRINTO) and PRES, established a formal statistical validation process with a large-scale data collection that culminated the final 2008 Ankara Consensus Conference. The general scheme for the classification of paediatric vasculitides is summarized in Table 1. Another important advancement in the field of paediatric vasculitis has been the development and validation of a paediatric vasculitis activity assessment (PVAS) tool that we anticipate will robustly and objectively define disease activity as a vasculitis outcome measures for use in clinical trials and research involving children with vasculitis. Treatment regimens continue to improve, with the use of different immunosuppressive medications and newer therapeutic approaches such as biologic agents. This review summarizes the epidemiology, aetiopathogenesis, presenting clinical features and advances in current management strategies for paediatric vasculitides.

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Predominantly small vessel vasculitis

Henoch–Schönlein Purpura (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. According to the 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:

- Abdominal pain
- Histopathology showing typical leucocytoclastic vasculitis with predominant IgA deposit; or proliferative glomerulonephritis with predominant IgA deposit
- Arthritis or arthralgia
- 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, although in routine clinical practice skin biopsy with immunofluorescence is rarely performed. Another caveat regarding this point is that if the skin biopsy is taken in the centre of the necrotic lesion, IgA deposition may be falsely negative due to the presence of proteolytic enzymes.

Aetiopathogenesis: as many as 50% 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 infectious agents have been implicated, including group A Streptococci, varicella, hepatitis B, Epstein–Barr virus, parvovirus B19, *Mycoplasma*, *Campylobacter*, and *Yersinia.*

It is suggested 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. 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. 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

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Classification of childhood vasculitides

Predominantly small vessel vasculitis
Granulomatous:
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

typical leukocytoclastic vasculitis that refers to the breakdown neutrophils in lesional tissue resulting in the characteristic nuclear debris or "nuclear dust".

Several genetic polymorphisms have been linked to HSP in various population cohorts. On the whole however, studies of this nature have been hampered by relatively small patient numbers and lack of power to be definitive or necessarily applicable to all racial groups.

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. Angioedema and urticaria can also occur. Around two thirds of children have joint manifestations at presentation with the knees and ankles most frequently involved; articular symptoms tend to resolve without the development of 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 is also described, although is a rare complication.

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). Ureteric obstruction has been reported. Recurrence of symptoms occurs in around one-third of cases, generally within four months of resolution of the original symptoms.

Reports of HSP nephritis indicate that between 20 to 61% of cases are affected with this complication. 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 diagnostic renal biopsy in children with HSP are:

- Nephritic/nephrotic presentation (urgent)
- Raised creatinine, hypertension or oliguria (urgent)
- Heavy proteinuria (Ua:Ucr persistently more than 100 mg/mmol) on an early morning urine sample at 4 weeks. Serum albumin not necessarily in the nephrotic range.
- Persistent proteinuria (not declining) after 4 weeks
- Impaired renal function (GFR less than 80 ml/min/1.73^2).

Management: the large majority of cases of HSP require symptomatic treatment only. Arthropathy is managed with rest and analgesia. Detailed management of renal disease is discussed below:

Treatment to prevent renal disease: Chartapisak et al. recently systematically reviewed all published randomized controlled trials for the prevention or treatment of renal involvement in HSP. Meta-analyses of four randomized controlled trials (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 one, three, six and twelve months with prednisone compared with placebo or no specific treatment. Thus it is becoming clearer that prophylactic corticosteroid does not prevent the onset of HSP nephritis. That said, there could still be a role for early use of corticosteroids in patients with severe extrarenal symptoms and in those with renal involvement as suggested by the findings of a study performed by Ronkainen et al.

Treatment of rapidly progressive glomerulonephritis: there are good data indicating that crescents in more than50% of glomeruli and nephrotic range proteinuria carry an unfavourable prognosis, thus highlighting the need for an effective intervention. Unfortunately, to date, there is only one randomized-controlled trial evaluating the benefit of treatment, which shows no difference in outcome using cyclophosphamide versus supportive therapy alone For patients with rapidly progressive glomerulonephritis (RPGN) with crescentic change on biopsy, uncontrolled data suggest that treatment may comprise aggressive therapy with corticosteroid, cyclophosphamide and possibly plasma exchange as for other causes of crescentic nephritis. Other therapies such as ciclosporin, azathioprine and cyclophosphamide have

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