criteria also highlight the need for development of better disease biomarkers for diagnosis and activity assessment in PMR. Proposed future work of the group includes a validation study, study of response criteria, longitudinal studies of outcomes, genomic characterization, biomarkers for disease activity and severity, and development of new therapeutics.

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L16. The specificities of pediatric vasculitis classification

Introduction

Vasculitis is characterised by the presence of inflammation in the walls of blood vessels, with resultant tissue ischaemia and necrosis. Certain vasculitides are more common in children whereas some such as cryoglobulinemic vasculitis or giant cell arteritis are never seen in the young age. Estimated overall annual incidence of new cases of vasculitis was 53.3 per 100,000 children under 17 years of age [1]. However, the two most common vasculitides, Kawasaki disease (KD) and IgA vasculitis/Henoch-Schönlein purpura are rather common with figures approaching 100 to 5.5 per 100,000 in children less than 17 years of age, respectively. Reported geographical variations in vasculitis may reflect an environmental influence.

Classification of childhood vasculitis

The definition of vasculitides derives from the Chapel Hill nomenclature criteria (CHCC) and now the CHCC2 [2]. Until the pediatric criteria were developed there was only the ACR criteria for classification. These criteria are not perfect, and adult literature also refers to its problems [3]. The criteria have been based on adult data alone and have never been validated in children. Furthermore, certain vasculitides are specific for pediatrics such as KD and some vasculitides display different disease courses in childhood. In this setting, the pediatricians took a lead and in June 2005, the Paediatric Rheumatology Society (PRES) and the European League against Rheumatism (EULAR) proposed a system of classification for vasculitides that occur in children who are at or below 18 years of age. Specific classification criteria were proposed for the more common childhood vasculitic syndromes [4]. In 2008, the EULAR, PRES and the Paediatric Rheumatology International
IgA vasculitis/Henoch-Schönlein purpura (HSP)

IgA vasculitis/HSP is the most common vasculitis in children. Gardner-Medwin et al. reported an estimated annual incidence of 20.4 per 100,000 children in the UK [1]. It occurs most frequently between the ages of 3 and 10 years [6].

The classification criteria for IgA vasculitis/Henoch-Schönlein purpura include a mandatory finding of purpura with lower limb predominance and the presence of at least one of the following four features:
- diffuse abdominal pain;
- arthralgia or arthritis;
- any biopsy showing predominant IgA deposition;
- renal involvement (any proteinuria and/or hematuria) [4].

If the purpura has an atypical distribution, the demonstration of IgA deposits in a biopsy is required.

Children with IgA vasculitis/HSP and with IgA nephritis have abnormal glycosylation in IgA1 O-linked glycans, an abnormality that facilitates the deposition of IgA in tissues [7]. Skin or renal biopsies demonstrate the deposition of IgA (mainly IgA1) in the wall of dermal capillaries and post-capillary venules and mesangium [8].

The main clinical features of IgA vasculitis/HSP include purpura, arthritis, abdominal pain, gastrointestinal bleeding, and nephritis. Uncommon manifestations of IgA vasculitis/HSP include bullous skin lesions, testicular involvement, seizures, and intussusception [9]. Palpable purpura is the presenting sign in 57–69% of the patients and is more prominent on the lower limbs and buttocks [10]. Renal disease, most often characterized by hematuria and proteinuria, is seen in 20–50% of affected children with 2–5% progressing to end-stage renal failure [11].

No specific laboratory test is available. Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessel walls but is not required in typical presentation of IgA vasculitis/HSP. Renal biopsy is necessary for differential diagnosis and treatment planning.

The extrarenal manifestations of IgA vasculitis/HSP can be managed by symptomatic treatment. Glucocorticoids can decrease the rate of intussusception. However, glucocorticoid therapy does not prevent recurrence of abdominal symptoms, skin involvement, or renal disease [12].

Kawasaki disease

Kawasaki disease (KD) is described as an acute, systemic medium and small vessels vasculitis occurring primarily in children. KD occurs worldwide and affects children of all races, although Asians are at the highest risk [13]. The highest incidence occurs in Japan where it exceeds 120/100,000 [14]. Approximately 80% of children with KD are less than 5 years old and male-to-female ratio of 1.5 to 2 [15].

The classification criteria for KD include:
- fever for 5 days or longer and least four of the following five signs:
  - changes in peripheral extremities or perineal area;
  - polymorphous exanthema;
  - bilateral conjunctival injection;
  - changes of lips and oral cavity: injection of oral and pharyngeal mucosa;
  - cervical lymphadenopathy [4].

If there are coronary aneurysms four criteria are not required [4]. Children with illnesses manifested by fever and at least two of the typical clinical manifestations, so-called incomplete KD, may also develop coronary artery aneurysms [16].

Coronary artery lesions are responsible for most of the disease-related morbidity and mortality. Aneurysms appear 1 to 4 weeks after the onset of fever and develop in 15–25% of untreated children [17]. All children with known or suspected KD should have an echocardiogram.

Although not included in the criteria, thrombocytosis during the end of the first week of illness is also a classical feature associated with KD.

Standard treatment of KD in the acute phase is with intravenous gamma globulin (IVIG) (2 g/kg single dose in a 10–12-hour infusion) and aspirin (50–80 mg/kg daily divided into four doses) [18]. In resistant patients additional IVIG therapy, and intravenous methylprednisolone (IVMP) or anti-TNF should be considered [19,20].

Polyarteritis nodosa (PAN)

PAN is characterised by necrotizing inflammatory changes in medium- and/or small-sized arteries. The disease is rare in childhood [21].

The classification criteria for childhood PAN require histologic evidence of necrotizing vasculitis in medium- or small-sized arteries or angiographic abnormalities (aneurysm or occlusion) as a mandatory criterion, plus two of the following five [4]:
- muscle tenderness or myalgia;
- skin involvement (livedo reticularis, tender subcutaneous nodules, other vasculitic lesions);
- systemic hypertension;
- mononeuropathy or polyneuropathy;
abnormal urine analysis and/or impaired renal function.

The etiopathogenesis of PAN is unknown, but infections have been implicated. No clear genetic association has been identified, although several reports suggest an association with familial Mediterranean fever (FMF) [22]. Disease manifestations are ranging from the benign cutaneous form to the severe disseminated multi-systemic form [23]. The most common clinical manifestations of PAN include constitutional symptoms (fever, weight loss, malaise), arthralgia, myalgia, mononeuritis multiplex, gastrointestinal disease (ischaemia, infection, haemorrhage or perforation), cardiac disease (ischaemic heart disease), hypertension, livedo reticularis and testicular pain [24].

Laboratory evaluation usually reflects the ongoing systemic inflammation including anemia, leukocytosis, thrombocytosis, and elevated ESR, CRP. Antineutrophil cytoplasmic antibodies (ANCA) are expected to be negative. Biopsy specimens reveal necrotizing inflammation involving the medium-sized or small arteries, with abundant neutrophils, fibrinoid changes, and disruption of the internal elastic lamina. Angiographic changes suggesting PAN include microaneurysms, and/or occlusion or vasculitic changes. A conventional angiography is the gold standard since medium-sized vessels are involved.

The mainstay of therapy for PAN includes steroids and various immunosuppressive medications, depending on disease severity [25]. Severe cases should be treated similar to AAV. 

**Cutaneous polyarteritis nodosa**

Cutaneous PAN is usually limited to skin with possible manifestations in the musculoskeletal system. Cutaneous polyarteritis characterised by the presence of painful subcutaneous nodules, non-purpuric lesions with or without livedo reticularis, with no systemic involvement (except for myalgia, arthralgia, and non-erosive arthritis). ANCA tests are negative and there is often an association with serologic and microbiologic evidence of streptococcal infection [26]. Skin biopsy shows necrotizing, non-granulomatous vasculitis. Treatment for cutaneous PAN is typically much less aggressive [27].

**Antineutrophil cytoplasmic antibody-associated vasculitis**

ANCA-associated vasculitis (AAV) includes granulomatous polyangiitis (GPA)/Wegener granulomatosis (WG), microscopic polyangiitis (MPA), eosinophilic polyangiitis (Churg-Strauss syndrome) (CSS/EPA), and renal-limited vasculitis, the latter probably a variant of MPA [28].

A separate classification has not been suggested for MPA and EPA/CSS in childhood, however, based on the cases in the registry, a validated classification for GPA/WG has been developed. Antineutrophil cytoplasmic antibodies (ANCA) have a crucial role in the pathogenesis of this group of vasculitides. Two types of ANCA have been identified in patients with vasculitis: ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which causes a cytoplasmic immunofluorescence pattern (cANCA) on ethanol fixed neutrophils, and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which results in a perinuclear immunofluorescence pattern (pANCA) [29].

Approximately 82–94% of patients with either GPA/WG or MPA are ANCA positive [30,31]. GPA/WG is primarily associated with PR3-ANCA, while MPA is primarily associated with MPO (myeloperoxidase)-ANCA. In patients with GPA/WG, the sensitivity of PR3-cANCA has been reported to be 28–92%, whereas specificity has been reproducibly high, ranging from 80–100% [29]. ANCA levels will vary during the course of GPA, 43% of patients with an increase in ANCA levels relapsed within 1 year [32].

**Granulomatous polyangiitis (GPA)/Wegener granulomatosis**

In January 2011, the Boards of Directors of the American College of Rheumatology, the American Society of Nephrology, and the European League Against Rheumatism recommended that the name Wegener’s granulomatosis be changed to granulomatosis with polyangiitis (Wegener’s), abbreviated as GPA [33]. GPA/WG is uncommon in children. It is a necrotizing granulomatous inflammation of small- to medium-sized vessels involving the kidneys and upper and lower respiratory tracts. The male:female ratio was 4:1, and the median age at diagnosis was 14.5 years [34].

The pediatric criteria requires three of the following six criteria to be present for classifying the child as GPA/WG [4]:

- abnormal urinalysis;
- granulomatous inflammation on biopsy;
- nasal-sinus-oral inflammation;
- subglottic, tracheal or endobronchial stenosis;
- abnormal chest X-ray or computed tomography (CT);
- ANCA staining [4].

Patients with GPA/WG frequently present with sinusitis, otitis media, persistent rhinorrhea, purulent/bloody nasal discharge, oral and/or nasal ulcers, nasal crusting, and polychondritis. Patients may also describe earache, both conductive and sensorineural hearing loss, or otorrhea [35]. Nasal and sinus mucosal inflammation can produce sinus pressure and pain, epistaxis, persistent otitis media with effusion or decreased hearing, and cartilage ischemia with nasal septal perforation, resulting in a saddle nose deformity. Pulmonary radiographic abnormalities can include nodules or infiltrates, cavities and ground-glass infiltrates. Renal involvement ranges from microscopic hematuria, proteinuria, to rapidly progressive renal glomerulonephritis.

The biopsy of the respiratory tract will reveal granulomatous inflammation and vasculitis, however, the characteristic renal histology is focal, segmental necrotizing, crescentic glomerulonephritis with few to no immune complexes on immunofluorescence and electron microscopy [36].
Takayasu arteritis (TA) is a disease that affects the aorta, its main branches, and the pulmonary arteries in which granulomatous vasculitis results in stenosis, occlusion, or aneurysms of affected vessels [37,38]. Women are affected in 80–90% of cases, with an age of onset that is usually between 10 and 40 years [39]. It has a worldwide distribution, with the greatest prevalence in Asians [40,41].

The classification criteria for childhood TA requires angiographic abnormalities (conventional, CT, or MR) of the aorta or its main branches (mandatory criterion), plus at least one of the following five features:

- Decreased peripheral artery pulse(s) and/or claudication of extremities;
- Bruits over aorta and/or its major branches;
- Hypertension (related to childhood normative data);
- Blood pressure difference more than 10 mmHg;
- Elevated acute-phase reactants.

The etiology of the disease is unknown. It is presumed to be autoimmune in nature, although genetic (possible major histocompatibility complex linkage) and infectious factors including exposure to tuberculosis have been proposed. Pathologically TA lesions consist of granulomatous changes progressing from the vascular adventitia to the media [42]. Systemic symptoms are common in the early phase of TA, including fatigue, weight loss, and low-grade fever. Vascular symptoms are related to the location and nature of the lesion or lesions and the collateral blood flow. Involvement of the carotid and vertebral arteries causes decreased cerebral blood flow, leading to vertigo, syncope, headaches, convulsions. Visual impairment is a late manifestation and is due to cerebral ischemia [43]. Abdominal pain, diarrhea, and gastrointestinal hemorrhage may result from mesenteric artery ischemia. Chest pain, dyspnea, hemoptysis, and pulmonary hypertension may result from pulmonary artery involvement.

Laboratory changes reflect the inflammatory process but are mostly nonspecific [44]. Acute-phase reactants (ESR and CRP) are usually elevated.

In TA, magnetic resonance angiography (MRA) may be preferred over the other modalities since it detects early signs of large vessel disease, and has the added advantage of potentially revealing evidence of ongoing arterial wall inflammation [45]. Thus, conventional or CT angiography are probably not required in TA. 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 [46].

The mainstay of therapy for TA is glucocorticoids. Cytotoxic therapy (methotrexate, cyclophosphamide and anti-TNF agents) are also used [47]. Surgical intervention may be required to alleviate end-organ ischaemia and hypertension resulting from vascular stenoses [48,49].

In conclusion, we now have validated classification criteria for childhood vasculitidis. It is high time pediatricians start multicenter studies on pathogenesis and treatment in these vasculitides, following the steps of EUVAS.

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Lectures


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L17. What can we expect from the revised Chapel Hill consensus conference nomenclature of vasculitis?

Historical overview of vasculitis nomenclature

The 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides [1] is based on observations and discoveries that