Best Practice & Research Clinical Rheumatology 32 (2018) 137–147

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

10

Pediatric forms of vasculitis

Seza Özen*, Hafize Emine Sönmez, Selcan Demir

Department of Pediatrics, Division of Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Keywords:
Primary vasculitides
Childhood vasculitides
Management
Classification

A B S T R A C T

Primary vasculitides that affect children are a challenging and complex group of disorders that may involve any system of the body and lead to significant morbidity and mortality. In recent years, there have been significant advances in the field of childhood vasculitides, including the development of classification criteria and outcome assessment. Although some forms of vasculitis occur in both children and adults, considerable differences exist between childhood and adult vasculitides; we review childhood vasculitides, thus highlighting their differences with the adult forms of the disease. We will also discuss monogenic forms of vasculitis, such as deficiency of adenosine deaminase type 2 (DADA2) and haploinsufficiency of A20 (HA20).

Introduction

Primary vasculitides are a rare group of disorders characterized by inflammation of the blood vessels. The clinical features depend on the size of the vessel involved. Although most forms of primary vasculitis are more common in adults than in children, some types of vasculitis such as Henoch-Schönlein purpura (HSP)/Immunoglobulin A vasculitis (IgAV) and Kawasaki disease (KD) tend to occur predominantly in childhood. In this review, we aim to summarize pediatric vasculitides, with emphasis on the main differences and similarities in clinical features and classification between children and adults.

* Corresponding author. Department of Pediatrics, Division of Rheumatology, Hacettepe University Faculty of Medicine, Ankara, 06100, Turkey.
E-mail address: sezaozen@hacettepe.edu.tr (S. Özen).

https://doi.org/10.1016/j.berh.2018.09.007
1521-6942/

Epidemiological and clinical differences of vasculitides in children

Pediatric vasculitides account for 1%–6% of pediatric diseases [1,2]. A study from the United Kingdom (UK) reported the estimated annual incidence of primary vasculitis to be approximately 23 per 100,000 children [3]. The distribution varies in different ethnic groups [1,2,4]. For example, in the authors' experience, KD and Behçet's disease (BD) are more common in Asian and Turkish children, respectively, although we lack strong precise epidemiological data. In adults, the most common primary vasculitis is giant cell arteritis (GCA), whereas GCA is never seen in childhood [5,6]. Takayasu arteritis (TA) is a large-vessel vasculitis that affects the aorta and/or its major branches. It is rare but may occur even in infancy. The median age of disease onset in children is approximately 11 years [7]. It is more prevalent among Japanese and Asian children [8]. Among pediatric patients with TA, the most common findings are arterial hypertension (82%), headache (31%), fever (29%), dyspnea (23%), and weight loss (22%) [9–11]. Musculoskeletal involvement is more common, and ocular findings are less common in children than in adults [9–11], whereas bruits and claudication are more common in adults than in children [12].

In national registries, IgA-V (HSP) and KD are the most common forms of childhood vasculitis. In most parts of the world, IgA-V (HSP) is the most common type of pediatric vasculitis with an annual incidence of 13–20/100,000 [3,13]. Recently, a French population-based study reported an annual incidence of IgA-V (HSP) of 18.6/100,000 in children [14]. However, in adults, IgA-V (HSP) is less common, with an annual incidence of 0.1–1.8/100,000 [15]. IgA-V (HSP) occurs most commonly between the age of 5 and 15 years in children [15]. Upper respiratory infection may be a predisposing factor in pediatric and adult patients with IgA-V (HSP), whereas malignancy and drug exposure emerge as predisposing factors almost exclusively in adults [16]. There are important clinical differences between pediatric and adult patients. Adult patients tend to have a more severe course of disease, with more significant renal involvement: 8–68% of adult IgA-V (HSP) has been reported to be complicated by chronic renal failure, whereas it occurs in only 1.8–15% of pediatric patients with IgA-V (HSP) [17–19]. Pediatric patients more commonly present with abdominal pain before the appearance of purpuric rash than adult patients with the disease, whereas diarrhea is more common in adult patients with IgA-V (HSP) with abdominal involvement than in pediatric patients [17,20]. However, there are no prominent differences regarding the distribution of purpura, joint involvement, or laboratory findings [21].

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of vasculitides consisting of granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis), eosinophilic GPA (EGPA) (previously known as Churg–Strauss syndrome, CSS), and microscopic polyangiitis (MPA) [22]. AAV are rare in childhood, with an incidence of 2.4 cases per million per year; GPA is the most common form [3]. GPA occurs around adolescence, with a median disease onset of 11.6 years and an estimated incidence of 0.1 per 100,000 [23]. In adults, GPA has a peak incidence in the sixth decade and is associated with a slight male predominance. The reported frequency of GPA has increased during the past few decades in adults. The annual incidence of GPA is 2.1–15 cases per million in Europe [24]. AAV are associated with significant morbidity, with a higher frequency of relapse, accrue damage in childhood [25]. Pediatric patients with AAV have more fever, more subglottic stenosis, more ischemic abdominal pain, more nasal cartilage damage, and less myalgia and peripheral neuropathy than adult patients with AAV [25]. EGPA is a rare necrotizing vasculitis. In pediatric patients with EGPA, cardiopulmonary involvement such as cardiomyopathy (42% in children versus 24% in adults) and pulmonary infiltrates (88% in children versus 59% in adults) are more common, whereas peripheral neuropathy is less common in these patients than in adult patients with EGPA (39% compared with 69% adult patients) [26]. Approximately 69% of pediatric patients with GPA are anti-PR3 ANCA (c-ANCA) positive, and approximately 21% of them are antimyeloperoxidase (MPO) ANCA (p-ANCA) positive [27]. Almost all the patients with GPA are ANCA positive in the active phase of the disease [28]. The presence of MPO-ANCA in pediatric and adult patients with EGPA is 25% and 38%, respectively [26].

Polyarteritis nodosa (PAN) is a primary systemic necrotizing vasculitis that affects predominantly medium-sized vessels [29]. The actual incidence of the disease is unknown in childhood, but it is estimated to be the third most common vasculitis among children [4]. In adults, it has an annual

incidence of 2-9 cases per million, with a peak age of 25 and 50 years and male predominance [3]. The disease onset age is around 9–10 years in children without gender predominance. When pediatric and adult patients with PAN are compared, weight loss and renal and neurologic involvement are more common in adults than in children, whereas arthralgia/arthritis and skin involvement are more common in children than in adults [30]. Childhood PAN tends to have a more benign course (with less renal and neurologic involvement) than adult-onset PAN [30].

Although KD is a predominantly childhood vasculitis, some very rare case reports of adult patients with KD have been published. It is a self-limiting vasculitis; however, the risk of coronary artery disease significantly increases in untreated cases [31]. It usually affects children under the age of 5 years. It has a higher prevalence among Japanese children with an annual incidence of 360 cases per 100,000, whereas the incidence in the UK is 8.1cases per 100,000 cases per year [3]. A patient may be classified as having KD when she/he has fever lasting for more than 5 days (which cannot be explained by other causes) together with at least four of the following clinical findings: (1) bilateral conjunctival injection, (2) changes in oropharyngeal mucous (fissured lips, strawberry tongue, or injected pharynx), (3) changes in peripheral extremities (erythema, edema of hands and feet, or desquamation), (4) polymorphous rash, and (5) cervical lymphadenopathy [26]. Of note, atypical features such as arthritis, aseptic meningitis, pneumonitis, urethritis, diarrhea, hydrops of gallbladder, and uveitis may occur. Infants tend to have an atypical course with fewer classical signs. Some laboratory findings such as anemia, decreased albumin levels, elevation of alanine aminotransferase, and increased platelet levels after the seventh day may help to detect incomplete cases. Echocardiography should be performed in all patients with three or more suspected findings even if there are not four classical clinical criteria [31].

BD and Cogan syndrome are defined as variable vessel vasculitis [22]. BD is the only variable vessel vasculitis that occurs during childhood. BD manifests with recurrent oral and/or genital aphthous ulcers; additionally, cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions may occur [22]. Children account for 5.4%–7.6% of all patients with BD [32,33]. The disease has high prevalence along the Silk Road, from Japan to the eastern edge of the Mediterranean Sea, including areas of the former Ottoman Empire. The prevalence of BD along the Silk Road is 77–100 cases per 100,000 cases compared to only 0.1–15.9 cases per 100,000 in Western Europe [34–38]. There are differences in BD between pediatric and adult patients. Family history as well as neurologic and gastrointestinal involvement are more common in pediatric patients than in adult patients [39]. Uveitis is more common and more severe in boys than in girls [40–44], and genital ulcers are more common in girls than in boys [41–45].

How to define and classify pediatric vasculitides

Vasculitides are defined according to the predominant size of the involved vessels. With the improvement of knowledge of the etiopathogenesis, the CHCC nomenclature system for defining the different forms of vasculitis was updated in 2012 [22]. The eponyms used in vasculitides were replaced by descriptive names, whenever possible [22]. Thus, Wegener's granulomatosis, CSS, and HSP were renamed as GPA, EGPA, and IgAV, respectively. In addition, new subcategories including single-organ vasculitis (which includes isolated central nervous system vasculitis), vasculitis associated with systemic disease (such as systemic lupus erythematosus), and vasculitis associated with a probable etiology (such as Hepatitis B virus-associated vasculitis) were added to the definition of vasculitides. Furthermore, CHCC 2012 has divided small-vessel vasculitides into two groups depending on the pathogenesis as ANCA-associated vasculitides and those associated with the presence of immune complexes.

Owing to the lack of any pathognomonic tests to diagnose these rare diseases, classification criteria are used to define homogeneous groups of vasculitis for research purposes. In 1990, the American College of Rheumatology (ACR) created a set of classification criteria for adult patients (Table 1) [46,47]. The Ankara 2008 Consensus Conference criteria were endorsed by European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society (EULAR/PRINTO/PRES). These organizations have developed new sets of criteria for childhood vasculitides, including criteria for childhood HSP/IgAV, PAN, GPA, and TA (Table 1) [48,49]. When the current update of the ACR/EULAR criteria for adults with vasculitis is completed (from the

Table 1
Comparison of the American College of Rheumatology (ACR) 1990 [47] and Ankara 2008 (EULAR/PRES/PRINTO) classification criteria [48,49] [a](adapted from Refs. [47–49]).

	ACR criteria	Ankara 2008 criteria	Main differences between pediatric-specific criteria and adult criteria
Henoch–Schönlein purpura (HSP)/ Immunoglobulin A vasculitis	≥2 of the following: ● ≤20 years of age at disease onset ● Palpable purpura ● Acute abdominal pain ● Biopsy showing granulocytes in the wall of small arterioles/venules	Purpura or petechia (mandatory) with lower limb predominance plus one of the following: ● Abdominal pain ● Histopathology (predominant IgA deposit in a biopsy) ● Arthritis or arthralgia ● Renal involvement	Palpable purpura became a mandatory criterion. Histopathologic findings were specified as predominance of IgA deposit Arthritis/arthralgia and renal involvement were included.
Granulomatous polyangiitis	≥2 of the following: ● Abnormal urinary sediment (red cell casts or >5 red blood cells per high-power field) ● Abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates) ● Oral ulcers or nasal discharge ● Granulomatous inflammation on biopsy	At least three of the following: ● Histopathology (granulomatous inflammation) ● Upper airway involvement ● Laryngo-tracheo-bronchial stenosis ● Pulmonary involvement (chest X-ray or CT showing the presence of nodules, cavities, or fixed infiltrates) ● ANCA positivity ● Renal involvement	ANCA-positivity was included Computerized tomography findings were included to define pulmonary abnormalities, and more definitive items were added for upper and lower airway involvement
Polyarteritis nodosa	≥3 of the following 10 criteria: ● Granulocyte or mixed leukocyte infiltrate in an arterial wall on biopsy ● Arteriographic abnormalities ● Livedo reticularis ● Myalgia ● Diastolic blood pressure >90 mmHg ● Mono- or polyneuropathy ● Elevated blood urea nitrogen or creatinine ● Testicular pain/tenderness ● Hepatitis B reactants ● Weight loss >4 kg	Histopathology or angiographic abnormalities (mandatory) plus one of the following: ● Skin involvement ● Myalgia/muscle tenderness ● Hypertension ● Peripheral neuropathy ● Renal involvement	The presence of histopathological or angiographic abnormalities became a mandatory criterion. The presence of testicular pain/ tenderness, weight loss, and evidence of hepatitis B infection were removed.
Takayasu arteritis	≥3 of the following: ● Arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal, upper, or lower extremities ● Decreased brachial artery pulse ● Claudication of an extremity >10 mmHg difference in systolic blood pressure between arms ● A bruit over subclavian arteries or the aorta ● Age at disease onset ≤40 years	Angiography (conventional, CT, or MRI) of the aorta or its major branches and pulmonary arteries showing aneurysm/ dilatation, narrowing, occlusion. or thickened arterial wall (mandatory) plus one of the following: ● Pulse deficit or claudication ● Four limbs blood pressure discrepancy >10 mmHg ● Bruits ● Hypertension (>95 percentile for height) ● Elevated acute phase reactants	Angiographic findings became a mandatory criterion Age criterion was removed Hypertension and elevated acute phase reactants were included Pulse deficit and claudication became a single criterion

[a] The table only includes pediatric vasculitides for which validated criteria have been developed. The table excludes giant cell arteritis, Kawasaki disease, and microscopic polyangiitis.

Diagnostic and Classification of Vasculitis Study, DCVAS), some criteria introduced for adults may need to be adapted for use in children.

In pediatric practice, the diagnosis of IgA-V (HSP) is a clinical one; biopsies are rarely performed. However, the presence of IgA in the biopsy sample is specific for the disease. Thus, the presence of predominant IgA deposition in biopsies of affected children is one of the new pediatric criteria for IgA-V (48). The revised pediatric criteria require the presence of palpable purpura (predominantly seen on the lower limbs) together with at least one of the following: abdominal pain, IgA deposition on histology, arthritis/arthralgia, or renal involvement [48]. This criteria set had a higher sensitivity (100% vs. 87.1%) and a similar specificity (87% vs. 87.7%) than the ACR criteria when applied to children [48]. Recently, a group of adult rheumatologists have evaluated the performance of Ankara 2008 pediatric criteria in adult patients with IgA-V (HSP) and found a higher sensitivity and specificity (99.2% vs. 86.8% and 86.0% vs. 81%) than the original ACR criteria for HSP [50].

The most significant changes in the Ankara 2008 criteria for childhood PAN were as follows: (1) histopathology or angiographic abnormalities became a mandatory criterion and (2) some criteria such as the presence of testicular pain/tenderness, weight loss, and hepatitis B reactants were removed because of their low specificity [48].

For GPA, the major differences between the pediatric Ankara 2008 criteria and the 1990 ACR adult criteria were the inclusion of ANCA positivity, the addition of computerized tomography abnormalities to pulmonary findings, and more definitive items for upper and lower airway involvement. The sensitivity and specificity of the Ankara 2008 criteria for childhood GPA were 93.3% and 99.2%, respectively [48]. For TA, the most marked changes in Ankara 2008 criteria were as follows: (1) angiography findings became a mandatory criterion, (2) age limitation was removed, (3) hypertension and elevated acute phase reactants were included, and (4) pulse deficit and claudication became a single criterion. With these changes, the sensitivity of Ankara 2008 criteria for childhood TA increased to 100% and the specificity to 99.9% [48].

KD classification criteria were not validated in the Ankara 2008 Consensus Conference. Patients are classified as KD according to American Heart Association (AHA) criteria as follows: unexplained fever lasting for more than 5 days together with at least four of the following clinical findings: (1) bilateral conjunctival injection, (2) changes in oropharyngeal mucous (fissured lips, strawberry tongue, or injected pharynx), (3) changes in peripheral extremities (erythema, edema of the hands and feet, or desquamation), (4) polymorphous rash, and (5) cervical lymphadenopathy [31].

An international expert consensus group (the pediatric BD [PEDBD] group) has suggested a new set of criteria to classify pediatric BD [51]. A child can be classified as having BD when presenting with three or more of the following criteria: (1) oral aphthosis ($\geq$3 attacks per year), (2) genital aphthosis (typically with scars), (3) skin involvement (necrotic folliculitis, acneiform lesions, or erythema nodosum), (4) neurologic involvement (except isolated headaches), (5) ocular manifestations (anterior uveitis, posterior uveitis, or retinal vasculitis), and (6) vascular features (venous thrombosis, arterial thrombosis, or arterial aneurysms) [51]. Recently, two centers from Turkey and Israel evaluated the performance of the new pediatric criteria and found them to have a sensitivity of 73.5% and a specificity of 98.9% for childhood BD [52].

Outcome and management of pediatric vasculitides

Disease activity and damage are the most important domains to determine the disease outcome. PRES Pediatric Vasculitis Working Party has validated an activity score, called the Pediatric Vasculitis Activity Score (PVAS) [53]. This score has been modified from the activity score for adults (Birmingham Vasculitis Activity Score, BVAS) and comprises the sum of the new or worsening clinical characteristics in nine organs/systems [53]. To date, the Vasculitis Damage Index (VDI) has not been validated in children, although a preliminary version has been produced and tested [54]. Some items such as puberty delay and growth retardation of children have been included in the preliminary pediatric version of the VDI [54].

Apart from the epidemiological, clinical, and classification differences, the outcomes in children are also different from those in adults. IgA-V (HSP) is usually a self-limiting form of vasculitis. However, gastrointestinal involvement during the early phase of the disease and renal involvement during the

later stage are risk factors for a worse long-term outcome. Furthermore, older children have a more severe course with worse renal outcomes and more relapses than younger children [55,56]. Adults with IgA-V (HSP) have worse renal outcomes than children with the disease [17–19].

With regard to the other vasculitides, Belostotsky et al. [57] reported that the mortality rate of pediatric patients with GPA was 12% during a 17 year period. Zwerina et al. [26] demonstrated that EGPA has a higher mortality rate in children than in adults (19% in children versus 5% in adults). Childhood PAN has a benign course, with mortality rates of 1–4% in children [29,58] compared to those of 24.9% in adults [59]. Eleftheriou et al. [7] found that the mortality rate for pediatric TA was 27% in the UK.

In untreated cases of KD, coronary involvement is present in up to 25% of cases. Recently, Lin et al. [60] demonstrated that the severity of coronary artery involvement during the first month of disease was the most important predictor for late coronary outcomes. However, in patients who were given appropriate treatment within the first 10 days of fever, the incidence of coronary artery lesions decreased from approximately 25%–5%.

Long-term morbidities such as Cushing's syndrome and osteopenia, due to glucocorticoid therapy, are common in pediatric BD [45]. The data regarding long-term outcomes of childhood BD are limited, and the outcome mainly depends on organ involvement.

Treatment approaches

Pediatric treatment approaches mainly depend on the recommendations published for adult patients, together with small case series and personal experiences of managing pediatric cases. The SHARE initiative (Single-Hub Access for pediatric Rheumatology in Europe) [61] has been developing evidence-based recommendations for the treatment of pediatric vasculitides (manuscript in preparation). Treatment of IgA-V (HSP) is mainly conservative; studies show that early steroid treatment does not prevent renal involvement [62]. However, in the presence of severe gastrointestinal or skin involvement, systemic glucocorticoids may be required [33]. We hope that the SHARE initiative will provide clinicians with a more standardized approach in IgA-V (HSP) treatment in the future.

Management of AAV in childhood mainly depends on clinical trials conducted in adults [68]. The recommendations endorsed by EULAR have been reviewed elsewhere.

KD is one of the most common vasculitides occurring during childhood. Recently, the AHA updated its guideline for the management and follow-up of KD [26]. It is currently recommended that the measurement of coronary artery size should be made and compared with Z scores to provide a more quantitative assessment [31]. Patients should be treated with a single dose of 2 g/kg intravenous immunoglobulin (IVIG) together with acetylsalicylic acid (ASA). However, the standard dose of ASA at initiation is still controversial [31]. Patients can be classified as IVIG resistant, in the presence of persistent or recrudescent fever for at least 36 h after the end of the first IVIG infusion [31]. Patients with IVIG resistance may be treated with a second dose of IVIG, high-dose pulse steroids, tumor necrosis factor (TNF) inhibitors, cyclosporine A, or anakinra [31]. Patients should be evaluated by a cardiologist at 4–6 weeks after discharge and during the first year. If there is no coronary involvement, routine cardiology follow-up is not indicated after the first year, but patients should be assessed for cardiovascular risk factors [31]. Risk scoring systems to predict IVIG resistance have been suggested [63–65]; however, these scores have not been as successful in patients of Western ethnicity [66,67]. The Kobayashi score [63–65] remains the most widely used scoring system. In the presence of high risk, patients should be treated with corticosteroids combined with IVIG and ASA [31]. Recently, a phase I/IIa trial in children with KD demonstrated the safety and tolerability of anakinra in KD [68].

Classic treatment of PAN usually follows practice in adults [69]. We still lack evidence-based data for the treatment of PAN in childhood. The ongoing “MYPAN trial” is a multicenter, open-label, randomized controlled trial conducted to compare the efficacy of cyclophosphamide with mycophenolate mofetil (a potentially less toxic therapy) for the induction of remission in pediatric forms of PAN.

EULAR recommendations for adult patients with TA have already been established [70], but we lack randomized controlled trials for the treatment of pediatric patients with TA. Promising results with tocilizumab have been published in pediatric patients with TA as a single-center experience [71].

A new group of vasculitides in childhood: the monogenic vasculitides

Deficiency of adenosine deaminase type 2

Recently, a new monogenic disorder, mimicking PAN, has been described: deficiency of adenosine deaminase 2 (DADA2) [72,73]. This is an autosomal recessive inherited disease that manifests with early-onset stroke and vasculopathy, elevated acute phase reactants, fever, peripheral neuropathy, mild immunodeficiency, and fluctuating low titers of antibodies [72,73]. Loss-of-function mutations in the *cat eye syndrome chromosome region candidate 1 (CECR1)* gene, which encodes adenosine deaminase 2 (ADA2), are associated with the disease [72,73]. Deficiency of ADA2 leads to endothelial damage and reduction in the anti-inflammatory macrophage population [72,73]. However, the pathogenesis of the disease remains unclear. The presence of early-onset stroke, parental consanguinity or familial cases, or unresponsiveness to conventional treatment should be seen as red flags in patients with presumed PAN, which should prompt a genetic analysis for mutations in *CECR1*. ADA2 enzyme activity is significantly reduced in affected individuals compared to that in healthy controls [74]. ADA2 enzyme replacement therapy may be a treatment option in the future; however, current treatment is usually with TNF inhibitors [72,75].

Autoinflammatory interferonopathies presenting with vasculopathy

STING-associated vasculitis of infancy (SAVI) is an autoinflammatory disease, caused by gain-of-function mutations in the *TMEM173* gene [76]. SAVI manifests with severe vasculopathy and interstitial lung disease [76]. Patients present with vasculitic lesions such as violaceous plaques and/or nodules prominent in cold-sensitive acral areas. Gangrene and infarcts of fingers and toes leading to tissue loss are the most remarkable skin involvements of the disease [76]. Skin biopsies of patients show marked vascular inflammation, limited to capillaries without any sign of medium- or large-vessel vasculitis. In addition, microthrombotic vascular changes may be observed in some biopsy samples [76]. Janus kinase (JAK) inhibitors may be a promising therapeutic alternative. A Baricitinib (JAK1 and JAK2 inhibitor) trial is underway [77].

Haploinsufficiency of A20

Haploinsufficiency of A20 (HA20) is a newly described monogenic autoinflammatory syndrome that mimics BD [78]. This disease is caused by high-penetrance heterozygous mutations in *TNF α-induced protein 3* (*TNFAIP3/A20*), which encodes the nuclear factor kappa-B (NF-κB) regulatory protein [78]. A20 suppresses NF-kB signals, and this subsequently leads to increased expression of inflammatory cytokines through its deubiquitinase activity, and a loss-of-function mutation in this gene leads to an increase in inflammatory processes, especially NF-kB signaling [78]. Sixteen patients have been described with early-onset recurrent oral, genital, and/or gastrointestinal ulcers. There is no standard treatment for the disease. Published cases were treated with TNF inhibitors, anti-IL1 receptor (anakinra), or anti-IL6 receptor (tocilizumab) [78–80].

Association of primary immune deficiencies and vasculitides in childhood

Systemic vasculitides related to immunodeficiency have already been reported, including Wiskott–Aldrich syndrome (WAS) and interleukin-12 receptor beta-1 (IL-12Rβ1) deficiency [81,82]. In 2016, a new monogenic autosomal dominant immune dysregulatory disease, called COPA Syndrome, was described. Patients manifest with arthritis, renal disease, and interstitial lung disease with pulmonary hemorrhage, resembling AAV [83]. Recently, we described a patient with a hypomorphic mutation in the *recombination-activating (RAG)* 1 gene, presenting with a severe PAN-like disease [84]. This patient had pulmonary hemorrhage, digital necrosis, and finger amputation. The tissue biopsy of the patient was compatible with PAN. In patients with atypical presentations of vasculitis, genetic defects and immune deficiencies should be considered, especially if there is consanguinity.

Current initiatives in pediatric vasculitis

The pediatric field is improving the recognition and management of patients with vasculitis. International registries such as the PRINTO vasculitis registry have served as the basis for the childhood classification criteria and to define the characteristics of these diseases. Another international registry, ARCHIVE, has served for validation studies and for defining treatment strategies [85].

A number of collaborative studies are currently underway to improve our understanding of the diagnosis, biomarkers, and treatment [86]. Furthermore, through international collaborations, pediatricians have provided management recommendations for two childhood vasculitides: KD and IgA Vasculitis (HSP) (submitted work). Pediatricians have led the work in defining characteristics of some rare vasculitides of childhood, such as the pediatric central nervous system vasculitides, pediatric BD, and vasculitis mimics due to single-gene defects.

Conclusion

Vasculitides in children present distinct features. Collaboration among pediatricians has enabled better characterization of these diseases. Multicenter studies may lead us to classify, treat, and manage this challenging disease group; indeed, new pediatric initiatives are emerging as outlined above.

Summary

New data emerging in childhood vasculitides suggest that the vasculitic syndromes display differences in epidemiology and clinical aspects. These differences and the lack of validation of the adult criteria have led pediatricians to develop separate classification criteria for childhood vasculitides. The adult vasculitis activity score has been adapted for use in pediatric studies with the term “pediatric vasculitis activity score (PVAS).”

Treatment strategies mainly depend on adult experience and recommendations because most of these diseases are very rare in childhood. Pediatricians have led the work on monogenic vasculitides because these new diseases often have a childhood onset. Among the new monogenic diseases, ADA2 deficiency and “STING associated vasculopathy of infancy” have been particularly important in our practice.

Funding

No funding support was received.

Conflicts of interest

The authors declare no conflict of interest.

Practice points

- Systemic vasculitides are a group of disorders that occur during childhood characterized by inflammation of vessel walls, with an increased risk of morbidity and mortality. Thus, early diagnosis and multidisciplinary assessment are very important.
- There are differences in the forms of the disease between children and adults in terms of epidemiology, type of vasculitis, and clinical features.
- Monogenic forms of vasculitis should be considered in children with vasculitis of early onset or with an atypical course, especially if there is parental consanguinity.

Research agenda

- Further epidemiologic studies are needed to define the true incidence and prevalence of these rare diseases.
- We still lack randomized controlled trials in many types of childhood vasculitis.
- Multicenter studies and collaboration may guide us in improving the outcome in these patients.
- Understanding the pathogenesis of the new monogenic forms of vasculitis will not only help us in better management of these patients but also shed light on our understanding of the more common forms of vasculitis.

References

[1] Bowyer S, Roettcher P. Pediatric rheumatology clinic populations in the United States: results of a 3 year survey. Pediatric Rheumatology Database Research Group. J Rheumatol 1996;23(11):1968–74.
[2] Malleson PN, Fung MY, Rosenberg AM. The incidence of pediatric rheumatic diseases: results from the Canadian pediatric rheumatology association disease registry. J Rheumatol 1996;23(11):1981–7.
[3] Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 2002;360(9341):1197–202.
[4] Ozen S, Bakkaloglu A, Dusunsel R, Soylemezoglu O, Ozaltin F, Poyrazoglu H, et al. Childhood vasculitides in Turkey: a nationwide survey. Clin Rheumatol 2007;26(2):196–200.
[5] Baldursson O, Steinsson K, Björnsson J, Lie JT. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. Arthritis Rheum 1994;37(7):1007–12.
[6] Rajala SA, Ahvenainen JE, Mattila KJ, Saarni MI. Incidence and survival rate in cases of biopsy-proven temporal arteritis. Scand J Rheumatol 1993;22(6):289–91.
[7] Eleftheriou D, Varnier G, Dolezalova P, McMahon AM, Al-Obaidi M, Brogan PA. Takayasu arteritis in childhood: retrospective experience from a tertiary referral centre in the United Kingdom. Arthritis Res Ther 2015;17:36.
[8] Jain S, Sharma N, Singh S, Bali HK, Kumar L, K Sharma B. Takayasu arteritis in children and young indians. Int J Cardiol 2000;75(Suppl. 1):S153–7.
[9] Brunner J, Feldman BM, Tyrrell PN, Kuemmerle-Deschner JB, Zimmerhackl LB, Gassner I I, et al. Takayasu arteritis in children and adolescents. Rheumatology (Oxford) 2010;49(10):1806–14.
[10] Morales E, Pineda C, Martinez-Lavin M. Takayasu's arteritis in children. J Rheumatol 1991;18(7):1081–4.
[11] Watson L, Brogan P, Peart I, Landes C, Barnes N, Cleary G. Diagnosis and assessment of disease activity in takayasu arteritis: a childhood case illustrating the challenge. Case Rep Rheumatol 2014;2014:603171.
[12] Chun YS, Park SJ, Park IK, Chung H, Lee J. The clinical and ocular manifestations of Takayasu arteritis. Retina 2001;21(2):132–40.
[13] Yang YH, Hung CF, Hsu CR, Wang LC, Chuang YH, Lin YT, et al. A nationwide survey on epidemiological characteristics of childhood Henoch-Schonlein purpura in Taiwan. Rheumatology (Oxford) 2005;44(5):618–22.
[14] Piram M, Maldini C, Biscardi S, De Suremain N, Orzechowski C, Georget E, et al. Incidence of IgA vasculitis in children estimated by four-source capture-recapture analysis: a population-based study. Rheumatology (Oxford) 2017;56(8):1358–66.
[15] Piram M, Mahr A. Epidemiology of immunoglobulin A vasculitis (Henoch-Schonlein): current state of knowledge. Curr Opin Rheumatol 2013;25(2):171–8.
[16] Kang Y, Park JS, Ha YJ, Kang MI, Park HJ, Lee SW, et al. Differences in clinical manifestations and outcomes between adult and child patients with Henoch-Schonlein purpura. J Kor Med Sci 2014;29(2):198–203.
[17] Goldstein AR, White RH, Akuse R, Chantler C. Long-term follow-up of childhood Henoch-Schonlein nephritis. Lancet 1992;339(8788):280–2.
[18] Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schonlein Purpura in adults: outcome and prognostic factors. J Am Soc Nephrol 2002;13(5):1271–8.
[19] Shrestha S, Sumingan N, Tan J, Alhous H, McWilliam L, Ballardie F. Henoch Schonlein purpura with nephritis in adults: adverse prognostic indicators in a UK population. QJM 2006;99(4):253–65.
[20] Uppal SS, Hussain MA, Al-Raqum HA, Nampoory MR, Al-Saeid K, Al-Assousi A, et al. Henoch-Schonlein's purpura in adults versus children/adolescents: a comparative study. Clin Exp Rheumatol 2006;24(2 Suppl. 41):S26–30.
[21] Eleftheriou D, Batu ED, Ozen S, Brogan PA. Vasculitis in children. Nephrol Dial Transplant 2015;30(Suppl. 1):i94–103.
[22] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international Chapel Hill consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65(1):1–11.
[23] Bohm M, Gonzalez Fernandez MI, Ozen S, Pistorio A, Dolezalova P, Brogan P, et al. Clinical features of childhood granulomatosis with polyangiitis (wegener's granulomatosis). Pediatr Rheumatol Online J 2014;12:18.
[24] Gibelin A, Maldini C, Mahr A. Epidemiology and etiology of wegener granulomatosis, microscopic polyangiitis, churg-strauss syndrome and goodpasture syndrome: vasculitides with frequent lung involvement. Semin Respir Crit Care Med 2011;32(3):264–73.
[25] Iudici M, Pagnoux C, Quartier P, Büchler M, Cevallos R, Cohen P, et al. Childhood- versus adult-onset ANCA-associated vasculitides: a nested, matched case-control study from the French Vasculitis Study Group Registry. Autoimmun Rev 2017;17(2):108–14.

[26] Zwerina J, Eger G, Englbrecht M, Manger B, Schett G. Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum 2009;39(2):108–15.
[27] Iudici M, Quartier P, Terrier B, Mouthon L, Guillevin L, Puéchal X, et al. Childhood-onset granulomatosis with polyangiitis and microscopic polyangiitis: systematic review and meta-analysis. Orphanet J Rare Dis 2016;11(1):141.
[28] Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA, et al. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 2007;120(7). p. 643 e9-14.
[29] Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, et al. Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. Arthritis Rheum 2013;65(9):2476–85.
[30] Erden A, Batu ED, Sönmez HE, Sarı A, Armagan B, Arıcı ZS, et al. Comparing polyarteritis nodosa in children and adults: a single center study. Int J Rheum Dis 2017;20(8):1016–22.
[31] McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for Health professionals from the American Heart association. Circulation 2017;135(17):e927–99.
[32] Sarica R, Azizlerli G, Köse A, Dişçi R, Ovül C, Kural Z, et al. Juvenile Behcet's disease among 1784 Turkish Behcet's patients. Int J Dermatol 1996;35(2):109–11.
[33] Ozen S. The spectrum of vasculitis in children. Best Pract Res Clin Rheumatol 2002;16(3):411–25.
[34] Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease: from east to west. Clin Rheumatol 2010;29(8):823–33.
[35] Kotter I, Vonthein R, Müller CA, Günaydin I, Zierhut M, Stübiger N, et al. Behcet's disease in patients of German and Turkish origin living in Germany: a comparative analysis. J Rheumatol 2004;31(1):133–9.
[36] Mohammad A, Mandl T, Sturfelt G, Segelmark M. Incidence, prevalence and clinical characteristics of Behcet's disease in southern Sweden. Rheumatology (Oxford) 2013;52(2):304–10.
[37] Olivieri I, Leccese P, Padula A, Nigro A, Palazzi C, Gilio M, et al. High prevalence of Behcet's disease in southern Italy. Clin Exp Rheumatol 2013;31(3 Suppl. 77):28–31.
[38] Mahr A, Belarbi I, Wechsler B, Jeanneret D, Dhote R, Fain O, et al. Population-based prevalence study of Behcet's disease: differences by ethnic origin and low variation by age at immigration. Arthritis Rheum 2008;58(12):3951–9.
[39] Karincaoglu Y, Borlu M, Toker SC, Akman A, Onder M, Gunasti S, et al. Demographic and clinical properties of juvenile-onset Behcet's disease: a controlled multicenter study. J Am Acad Dermatol 2008;58(4):579–84.
[40] Kim DK, Chang SN, Bang D, Lee ES, Lee S. Clinical analysis of 40 cases of childhood-onset Behcet's disease. Pediatr Dermatol 1994;11(2):95–101.
[41] Kone-Paut I, Darce-Bello M, Shahram F, Gattorno M, Cimaz R, Ozen S, et al. Registries in rheumatological and musculo-skeletal conditions. Paediatric Behcet's disease: an international cohort study of 110 patients. One-year follow-up data. Rheumatology (Oxford) 2011;50(1):184–8.
[42] Kone-Paut I, Yurdakul S, Bahabri SA, Shafae N, Ozen S, Ozdogan H, et al. Clinical features of Behcet's disease in children: an international collaborative study of 86 cases. J Pediatr 1998;132(4):721–5.
[43] Krause I, Uziel Y, Guedj D, Mukamel M, Harel L, Molad Y, et al. Childhood Behcet's disease: clinical features and comparison with adult-onset disease. Rheumatology (Oxford) 1999;38(5):457–62.
[44] Pivetti-Pezzi P, Accorinti M, Abdülaziz MA, La Cava M, Torella M, Riso D, et al. Behcets disease in children. Jpn J Ophthalmol 1995;39(3):309–14.
[45] Nanthapisal S, Klein NJ, Ambrose N, Eleftheriou D, Brogan PA. Paediatric Behcet's disease: a UK tertiary centre experience. Clin Rheumatol 2016;35(10):2509–16.
[46] Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33(8):1068–73.
[47] Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990;33(8):1065–7.
[48] Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis 2010;69(5):798–806.
[49] Ruperto N, Ozen S, Pistorio A, Dolezalova P, Brogan P, Cabral DA, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part I: overall methodology and clinical characterisation. Ann Rheum Dis 2010;69(5):790–7.
[50] Hocevar A, Rotar Z, Jurčić V, Pižem J, Čučnik S, Vizjak A, et al. IgA vasculitis in adults: the performance of the EULAR/PRINTO/PRES classification criteria in adults. Arthritis Res Ther 2016;18:58.
[51] Kone-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, et al. Consensus classification criteria for paediatric Behcet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis 2016;75(6):958–64.
[52] Batu ED, Sönmez HE, Sözeri B, Butbul Aviel Y, Bilginer Y, Özen S. The performance of different classification criteria in paediatric Behcet's disease. Clin Exp Rheumatol 2017;108(6):119–23.
[53] Dolezalova P, Price-Kuehne FE, Özen S, Benseler SM, Cabral DA, Anton J, et al. Disease activity assessment in childhood vasculitis: development and preliminary validation of the Paediatric Vasculitis Activity Score (PVAS). Ann Rheum Dis 2013;72(10):1628–33.
[54] Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40(2):371–80.
[55] Jauhola O, Ronkainen J, Koskimies O, Ala-Houhala M, Arikoski P, Hölttä T, et al. Renal manifestations of Henoch-Schonlein purpura in a 6-month prospective study of 223 children. Arch Dis Child 2010;95(11):877–82.
[56] Kaku Y, Nohara K, Honda S. Renal involvement in Henoch-Schonlein purpura: a multivariate analysis of prognostic factors. Kidney Int 1998;53(6):1755–9.
[57] Belostotsky VM, Shah V, Dillon MJ. Clinical features in 17 paediatric patients with Wegener granulomatosis. Pediatr Nephrol 2002;17(9):754–61.

[58] Ozen S, Anton J, Arisoy N, Bakkaloglu A, Besbas N, Brogan P, et al. Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr 2004;145(4):517–22.
[59] Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011;90(1):19–27.
[60] Lin MT, Sun LC, Wu ET, Wang JK, Lue HC, Wu MH. Acute and late coronary outcomes in 1073 patients with Kawasaki disease with and without intravenous gamma-immunoglobulin therapy. Arch Dis Child 2015;100(6):542–7.
[61] Wulffraat NM, Vastert B. Time to share. Pediatr Rheumatol Online J 2013;11(1):5.
[62] Chartapisak W, Opastiraku S, Willis NS, Craig JC, Hodson EM. Prevention and treatment of renal disease in Henoch-Schonlein purpura: a systematic review. Arch Dis Child 2009;94(2):132–7.
[63] Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. J Pediatr 2006;149(2):237–40.
[64] Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation 2006;113(22):2606–12.
[65] Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. Eur J Pediatr 2007;166(2):131–7.
[66] Berdej-Szczot E, Małecka-Tendera E, Gawlik T, Firek-Pędras M, Szydłowski L, Gawlik A. Risk factors of immunoglobulin resistance and coronary complications in children with Kawasaki disease. Kardiol Pol 2017;75(3):261–6.
[67] Davies S, Sutton N, Blackstock S, Gormley S, Hoggart CJ, Levin M, et al. Predicting IVIG resistance in UK Kawasaki disease. Arch Dis Child 2015;100(4):366–8.
[68] Tremoulet AH, Jain S, Kim S, Newburger J, Arditi M, Franco A, et al. Rationale and study design for a phase I/IIa trial of anakinra in children with Kawasaki disease and early coronary artery abnormalities (the ANAKID trial). Contemp Clin Trials 2016;48:70–5.
[69] Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68(3):310–7.
[70] Mukhtyar C1, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68(3):318–23.
[71] Batu ED, Sönmez HE, Hazırolan T, Özaltın F, Bilginer Y, Özen S, et al. Tocilizumab treatment in childhood Takayasu arteritis: case series of four patients and systematic review of the literature. Semin Arthritis Rheum 2017;46(4):529–35.
[72] Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med 2014;370(10):921–31.
[73] Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 2014;370(10):911–20.
[74] Caorsi R, et al. Monogenic polyarteritis: the lesson of ADA2 deficiency. Pediatr Rheumatol Online J 2016;14(1):51.
[75] Caorsi R, Penco F, Schena F, Gattorno M. A case series of adenosine deaminase 2-deficient patients emphasizing treatment and genotype-phenotype correlations. J Rheumatol 2015;42(8):1532–4.
[76] Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med 2014;371(6):507–18.
[77] Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018;128(7):3041–52.
[78] Zhou Q, Wang H, Schwartz DM, Stoffels M, Park YH, Zhang Y, et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. Nat Genet 2016;48(1):67–73.
[79] Ohnishi H, Kawamoto N, Seishima M, Ohara O, Fukao T. A Japanese family case with juvenile onset Behcet's disease caused by TNFAIP3 mutation. Allergol Int 2017;66(1):146–8.
[80] Aeschlimann FA, Batu ED, Canna SW, Go E, Gül A, Hoffmann P, et al. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease. Ann Rheum Dis 2018;77(5):728–35.
[81] Filiz S, Kocacik Uygun DF, Verhard EM, van Dissel JT, Uygun V, Bassorgun C, et al. Cutaneous leukocytoclastic vasculitis due to Salmonella enteritidis in a child with interleukin-12 receptor beta-1 deficiency. Pediatr Dermatol 2014;31(2):236–40.
[82] Conyers RK, Cole TS. Successful second bone marrow transplantation in a Wiskott-Aldrich syndrome patient with systemic vasculitis. J Allergy Clin Immunol 2016;137(5):1615–6.
[83] Vece TJ, Watkin LB, Nicholas S, Canter D, Braun MC, Guillerman RP, et al. Copa syndrome: a novel autosomal dominant immune dysregulatory disease. J Clin Immunol 2016;36(4):377–87.
[84] Taşkıran EZ1, Sönmez HE2, Ayvaz DÇ3, Koşukcu C4, Batu ED2, Esenboğa S, et al. Hypomorphic RAG1 defect in a child presented with pulmonary hemorrhage and digital necrosis. Clin Immunol 2017;187:92–942.
[85] Morishita K1, Guzman J, Chira P, Muscal E, Zeft A, Klein-Gitelman M, et al. Do adult disease severity subclassifications predict use of cyclophosphamide in children with ANCA-associated vasculitis? An analysis of ARChiVe study treatment decisions. J Rheumatol 2012;39(10):2012–20.
[86] Brogan P, Eleftheriou D. Vasculitis update: pathogenesis and biomarkers. Pediatr Nephrol 2018;33(2):187–98.