Systemic Corticosteroids in Childhood Vasculitides

Gašper Markelj and Tadej Avčin

Introduction

Owing to the complexity and multisystemic nature of the disease, children with vasculitis often present to different pediatric subspecialists such as rheumatologists, cardiologists, nephrologists, and dermatologists. Different types of inflammatory infiltrate that may be predominantly neutrophilic, eosinophilic, or mononuclear affect the blood vessel wall. Classification of the most common childhood vasculitides was recently revised and is based on predominant vessel size and the presence of granulomatous vasculitis (Table 1) [1].

Clinical presentation of the most common childhood vasculitides usually develops abruptly, and diagnostic characteristics become apparent in a few days. In some less common vasculitides, various signs and symptoms may develop over weeks or months. Establishing the diagnosis of vasculitis requires a high index of suspicion and is often difficult and delayed. Clinical features such as fever, weight loss, fatigue of unknown origin, various skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers), neurological manifestations (headache, focal neurological signs), pain or inflammation of joints and muscles, serositis, hypertension, pulmonary infiltrates or hemorrhage together with laboratory features of increased inflammatory markers [erythrocyte sedimentation rate, C-reactive protein (CRP), leukocytosis], anemia, eosinophilia, hematuria, elevated factor VIII–related antigen (von Willebrand factor), presence of antineutrophil cytoplasmic antibodies (ANCA), circulating immune complexes, and cryoglobulins suggest a possible diagnosis. A definitive diagnosis often requires additional vessel imaging, such as magnetic resonance angiography or conventional angiography, and frequently biopsy of one or more sites.

G. Markelj • T. Avčin (✉)
Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Center Ljubljana, Ljubljana, Slovenia
e-mail: tadej.avcin@kclj.si

© Springer International Publishing Switzerland 2015

R. Cimaz (ed.), *Systemic Corticosteroids for Inflammatory Disorders in Pediatrics*, DOI 10.1007/978-3-319-16056-6_7

Table 1 EULAR/PReS classification of childhood vasculitis [1]

I. Predominantly large vessel vasculitis	Takayasu arteritis
II. Predominantly medium-sized vessel vasculitis	Kawasaki disease
	Childhood polyarteritis nodosa
	Cutaneous polyarteritis
III. Predominantly small vessel vasculitis	
A. Granulomatous	Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis
	Churg–Strauss syndrome
B. Nongranulomatous	Microscopic polyangiitis
	Henoch–Schönlein purpura
	Isolated cutaneous leukocytoclastic vasculitis
	Hypocomplementemic urticarial vasculitis
IV. Other vasculitides	Behçet's disease
	Vasculitis secondary to infection (including hepatitis B-associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis)
	Vasculitis associated with systemic connective tissue diseases
	Isolated vasculitis of the central nervous system
	Cogan syndrome
	Unclassified

Besides difficulties in establishing a diagnosis, assessment of vasculitic disease activity is often challenging and the outcome of some vasculitides may be serious or fatal [2–4]. Various forms of vasculitis account for 1–6 % of pediatric rheumatic diseases, but the true incidence and prevalence are unknown. The two most common childhood vasculitides, accounting for 60–80 % of all types of vasculitis, are Henoch–Schönlein purpura (HSP) and Kawasaki disease (KD). All other forms of vasculitis are uncommon – Takayasu arteritis (TA), polyarteritis nodosa (PAN) – or rare – granulomatosis with polyangiitis (GPA), central nervous system (CNS) vasculitis. There are, however, large geographical differences in relative disease frequency, with KD and TA being more prevalent in Japan and PAN more common in Turkey [2, 4, 5]. Several aspects of corticosteroid therapy in the most common childhood vasculitides are presented in this chapter.

Henoch–Schönlein Purpura

HSP is the most common childhood vasculitis. It is a systemic vasculitis with multiorgan involvement and presents with palpable purpura, arthritis or arthralgia, abdominal pain, with the possible addition of gastrointestinal hemorrhage and renal disease. The presence of purpura is a compulsory criterion for the diagnosis, other

signs or symptoms are present more variably. Other organs can also be involved including central nervous system vasculitis with seizures, coma, hemorrhage, Guillain–Barré syndrome, central and peripheral neuropathy, as well as involvement of the respiratory system with recurrent epistaxis, pulmonary hemorrhages, interstitial pneumonitis, parotitis, carditis, and stenosing urethritis. In boys the most frequent additional manifestation is scrotal pain and swelling [6–8].

The reported incidence of HSP varies between 10 and 30 cases per 100,000 children with an equal incidence in male and female patients. Most cases present in children younger than 10 years of age with mean age of presentation at 6 years. It occurs predominantly in the cold months of the year, often preceded by an upper respiratory tract infection. This suggests a potential infectious trigger and multiple case reports describe an association with various respiratory pathogens, most commonly with streptococcus, staphylococcus, and parainfluenza [2, 6–8].

The characteristic pathological feature of HSP vasculitis is a deposition of IgA antibodies – containing immune complexes in the vessel walls of the affected organs and kidney mesangium. Abnormal glycosylation of immunoglobulin A1 molecules predispose patients with HSP to form large immune complexes with impaired clearance. They are deposited in small vessel walls of the affected organs and in the kidney mesangium and trigger immune response with inflammatory reaction.

Clinical Manifestations

Cutaneous Involvement

Skin involvement is essential for the diagnosis to be made. The most common manifestations are palpable purpura and petechiae, but other forms of skin involvement like erythematous, macular, urticarial, and bullous rashes have been observed. Skin involvement is usually distributed symmetrically most prominently over the extensor surfaces of the lower limbs, buttocks, and forearms – on pressure-bearing surfaces (Figs. 1 and 2). Changes on the trunk and face are occasionally described in younger children with edema over the dorsa of the hands and feet as well as around the eyes and forehead. In 25–30 % of children with HSP, recurrence of purpura is observed.

Arthritis

Three quarters of children with HSP have arthritis or arthralgia. The most commonly affected joints are the large joints of the lower extremities. There is marked periarticular swelling and tenderness, usually without erythema, warmth, and effusion. The joint disease is transient and resolves within a few days to 1 week without chronic damage.

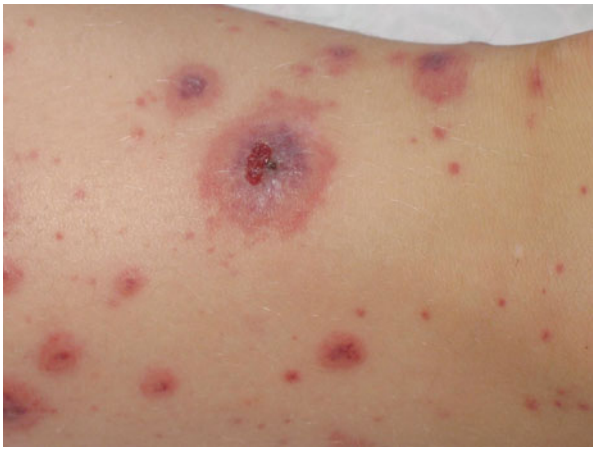

Fig. 1 Hemorrhagic necrotic skin lesions in a patient with Henoch–Schönlein purpura

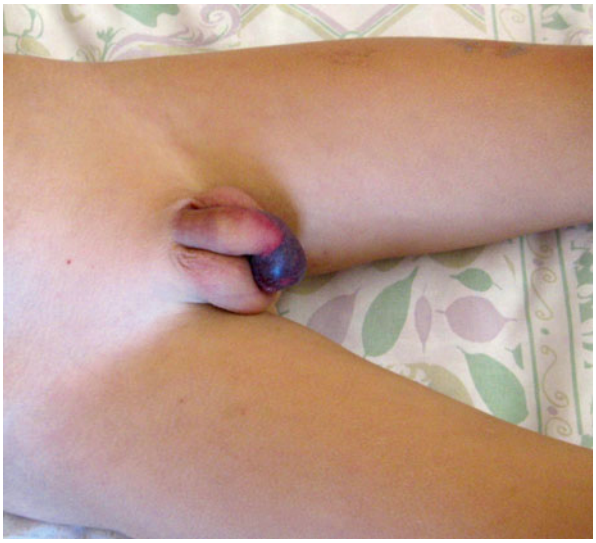

Fig. 2 Penile involvement in a patient with Henoch–Schönlein purpura

Gastrointestinal Manifestations

Edemas and submucosal and intramural hemorrhage due to vasculitis of the bowel wall cause diffuse abdominal pain in approximately two thirds of children with HSP. The proximal small bowel is most commonly affected. Symptoms usually appear within 1 week after onset of the rash, but in up to one third of cases they may precede other manifestations. The most common severe gastrointestinal complication is intussusception, which occurs in 3–4 % of patients. It presents with severe, often colicky abdominal pain and vomiting. Other severe, although less common

gastrointestinal complications, include gangrene of the bowel, bowel perforation, massive hemorrhage, acute pancreatitis, enteritis, and hepatobiliary involvement.

Renal Disease

Renal involvement with glomerulonephritis is reported in approximately one third of children with HSP. It usually presents with isolated microscopic hematuria; there might be a variable degree of proteinuria with normal renal function. In less than 10 % of cases it may be a serious, potentially life-threatening complication with acute nephritic syndrome with hypertension and renal failure. It seldom precedes the onset of rash and usually develops within 4 weeks after disease onset. The extent of the disease can be determined in the initial 3 months, and in a few children nephritis can occur much later in the course, sometimes after numerous cutaneous recurrences.

Treatment

The use of glucocorticosteroids (GCs) in HSP has been a source of controversy and debate [9–13]. In the majority of cases, management of HSP includes supportive care with maintenance of good hydration, nutrition, electrolyte balance, and control of pain and hypertension. Although GCs have a dramatic influence on decreasing the severity of joint and cutaneous involvement of the disease they are usually not indicated for management of these manifestations. The evidence of using early GC treatment to shorten duration of abdominal pain and to decrease the risk of intussusception and surgical intervention is based only on case reports and small studies and is not strong enough to recommend it to all patients with HSP and abdominal involvement, since the majority of patients improve spontaneously [14]. GCs are generally used for patients with HSP and severe abdominal pain and hemorrhage, with prompt symptomatic improvement. Ronkainen et al. reported reduced abdominal and joint pain with prednisone of 1 mg/kg/day for 2 weeks, with weaning over the subsequent 2 weeks [15]. However, studies have not demonstrated a clear advantage of prednisolone over supportive therapy.

Short-term GC therapy is effective in the management of pain in severe orchitis. In pulmonary hemorrhage, which is a rare but potentially fatal complication of HSP, aggressive immunosuppressive treatment with a combination of intravenous methylprednisolone pulses and other immunosuppressive agents is used.

A recent Cochrane Review and other long-term studies showed there is no evidence from randomized controlled studies that the use of GCs can prevent kidney disease in children with HSP or change the long-term prognosis of renal involvement [16]. Urine and blood pressure abnormalities 8 years after HSP are associated with nephritis at its onset. However, prednisone can be effective in treating renal symptoms: 61 % of renal symptoms resolve in patients treated with prednisone, compared with 34 % of patients treated with placebo [17]. Mild renal involvement

with microscopic hematuria or mild proteinuria does not require immunosuppressive treatment, but these patients need close follow-up. GCs are still the main therapy for rapidly progressive glomerulonephritis or nephrotic syndrome, which is usually accompanied by crescents on kidney biopsy. Although the quality of evidence is low, pulse intravenous methylprednisolone followed by a 3–6-month course of oral steroids with the addition of cyclophosphamide or cyclosporine A is used. Additional treatment in small studies included intravenous immunoglobulins, plasmapheresis, and anti-clotting therapy [5, 9–13, 15, 18, 19].

Prognosis

In two thirds of children, disease is self-limiting with excellent spontaneous resolution of symptoms and signs. HSP recurs spontaneously or with repeated respiratory tract infections in one third of children usually in the first 6 weeks. Recurrent episodes are usually shorter and milder than the preceding one.

In the short term, morbidity and mortality are associated with gastrointestinal tract lesions or central nervous system vasculitis. The long-term morbidity of HSP is related to the degree of HSP nephritis. Overall, less than 5 % of children with HSP progress to end-stage renal failure. Poor prognostic factors are development of a major indication of renal disease within the first 6 months of disease onset, occurrence of numerous exacerbations, renal failure at onset, hypertension, or increased number of glomeruli with crescents on renal biopsy [2, 4, 6–9].

Kawasaki Disease

KD is the second most common vasculitis in childhood. It is an acute self-limiting vasculitis of unknown origin with clinical signs of prolonged fever, polymorphous rash, nonexudative conjunctivitis, mucosal changes, cervical lymphadenopathy, and erythema or desquamation of the extremities. Untreated KD can have severe complications and significant morbidity or even mortality. It can progress in 25 % of cases to cause coronary artery abnormalities, such as dilatation and ectasia; 2–3 % of untreated patients die as a result of coronary vasculitis. KD is a leading cause of acquired cardiovascular disease in children and is potentially an important cause of long-term cardiac disease in adult life. Since adequate and timely therapy can largely prevent these complications, early and accurate diagnosis is of great importance.

The disease has a higher incidence in Asian populations with a male predominance; there is marked seasonality with heightened incidence in winter and early spring in temperate climates. The majority (85 %) of children with KD are younger than 5 years.

The exact mechanisms of the disease are still unresolved nearly 50 years after it was described by Kawasaki in 1967. KD may result from an exposure of a genetically

predisposed individual to a possible infectious environmental trigger. Up to 33 % of patients with KD have at least one concurrent infection at the time of diagnosis, but no correlation between a specific agent and the severity of the disease course has been identified [20, 21].

Clinical Manifestations

The diagnosis of KD is based on clinical criteria (Table 2) established by the Japanese Ministry of Health and adopted by the American Heart Association. If less than four of the principal features are present but two-dimensional echocardiography detects coronary artery abnormalities, patients are diagnosed with incomplete KD. Frequently, features of KD develop sequentially rather than simultaneously, which might result in misdiagnosis and treatment delay. In addition to the principal clinical findings, several other symptoms can be present, such as extreme irritability, arthritis, rhinorrhea, weakness, hydrops of the gallbladder, and mild anterior uveitis.

The clinical diagnosis can further be hindered in a subset of patients, mostly younger than 12 months of age or older than 5 years, with less than four of the principal features but with laboratory results or echocardiographic evidence that suggest the diagnosis of KD. These patients present with incomplete KD.

The variability in patient presentation should encourage clinicians to consider KD in any case of prolonged and unexplained fever.

Additional supplementary laboratory criteria can aid in establishing the correct diagnosis: decreased levels of albumin (<3 g/dl); increased C-reactive protein; increased erythrocyte sedimentation rate >40 mm/h; elevated alanine aminotransferase; leukocytosis >15,000/mm; normochromic, normocytic anemia for age; and sterile pyuria >10 white blood cells/mm^3.

Table 2 Diagnostic criteria for Kawasaki disease [22]

Fever (>39 °C) for at least 5 days	
AND at least four of the following five diagnostic features	
Polymorphous exanthema	
Bilateral bulbar conjunctival injection without exudate	
Changes in lips and oral cavity	Erythema, fissured cracked lips, strawberry tongue, or diffuse injection of oral and pharyngeal mucosae
Cervical lymphadenopathy	(>1.5 cm diameter), usually unilateral
Changes in extremities	Acute: erythema of palms and soles; edema of hands and feet
	Subacute: periungual peeling of fingers and toes (in the second and third week)
WITH exclusion of other diseases with similar clinical features	

The differential diagnosis of KD includes (1) various infections such as Epstein–Barr virus, adenovirus, echovirus, measles, toxic shock syndrome, scarlet fever, Rocky Mountain spotted fever, leptospirosis; (2) autoimmune diseases such as systemic-onset juvenile idiopathic arthritis or polyarteritis nodosa; and (3) juvenile mercury poisoning and adverse drug reactions including Stevens–Johnson disease.

The clinical course of the disease consists of four phases. In the acute phase, which lasts 1–2 weeks if untreated, children have a high spiking fever and principal symptomatic features. At this time, they may present with cardiac manifestation including valvulitis, pericarditis, and myocarditis. In the following subacute phase, children are at greatest risk of sudden death due to myocardial infarction. The subacute phase lasts approximately 2 weeks and is characterized by resolution of the fever. The third phase is the convalescent phase after cessation of symptoms and continues until acute-phase inflammatory markers return to normal serum levels. In the fourth, chronic phase, patients with coronary artery involvement require follow-up management (Figs. 3 and 4).

To reduce the risk of coronary artery involvement in later phases of the disease, diagnosis should be made in the acute stage so as to administer timely treatment and reduce inflammation [2, 4, 20, 21].

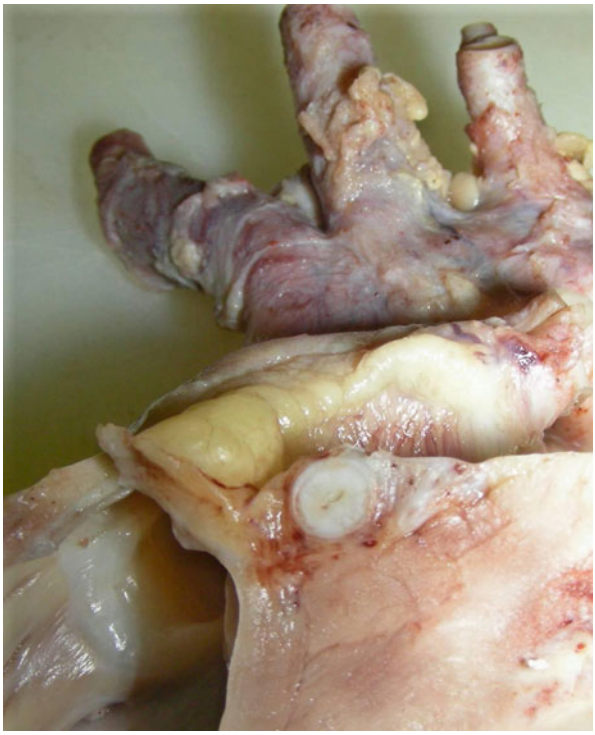

Fig. 3 Coronary artery vasculitis in a child with treatment-resistant Kawasaki disease and ischemic cardiomyopathy

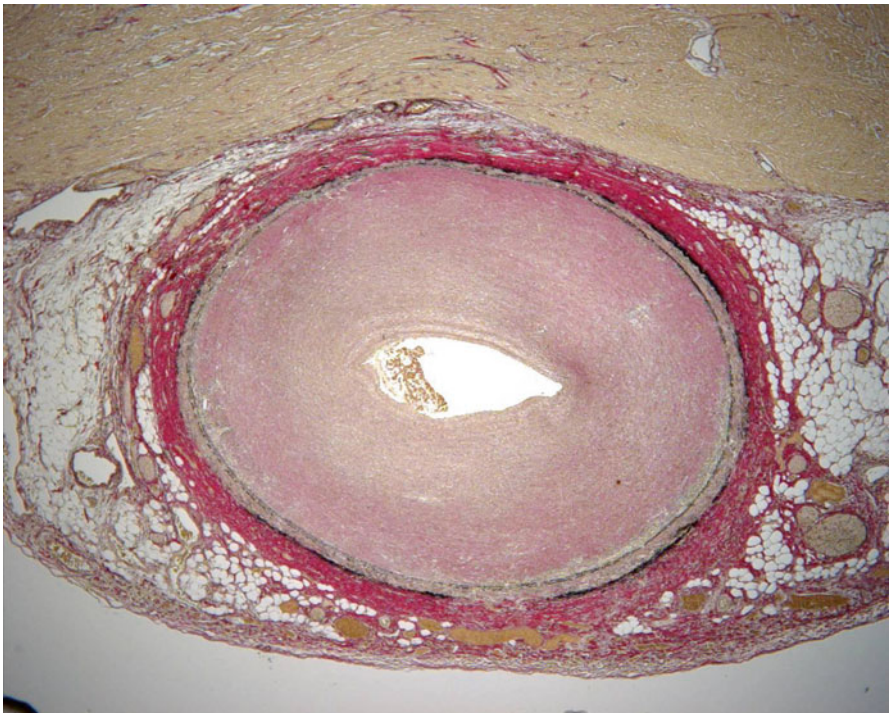

Fig. 4 Histological changes in coronary artery vasculitis in treatment-resistent Kawasaki disease

Treatment

The aim of acute-phase management in KD is to reduce inflammation, particularly inflammation in the coronary arteries and myocardium. Early treatment, before day 10 of the disease, with a single dose of intravenous immunoglobulin (IVIG) over 12 h at a dosage of 2 g/kg has been shown to greatly reduce the risk of coronary artery lesions. In addition to IVIG, high "anti-inflammatory" doses of acetylsalicylic acid (ASA) of 80–100 mg/kg/day in divided doses in the United States and of 30–50 mg/kg/day in divided doses in the United Kingdom and Japan are used in the acute phase. The dose of ASA is lowered to an "antiplatelet" dose (3–5 mg/kg/day) following defervescence. ASA is continued until inflammatory markers have returned to normal and there is no evidence of coronary artery lesions. However, a Cochrane Review concluded there is insufficient evidence in support of using ASA in the acute phase for coronary artery prevention [23].

Between 11 and 23 % of patients with KD treated with IVIG remain with a recurrent fever at least 36 h after the first IVIG infusion. IVIG-resistant patients are at higher risk of developing coronary artery aneurysms. There are several additional options to further decrease the ongoing inflammation, with a second dose of IVIG

of 2 g/kg, intravenous GC pulse therapy, anti-tumor necrosis factor-α antibodies, and cytotoxic agents [24–27].

Early retrospective studies have shown that GCs were associated with an increased risk of coronary artery aneurysms. These results have almost certainly reflected selection bias as the sickest patients received steroids. Subsequent clinical trials that evaluated the use of GC in addition to IVIG have yielded seemingly confusing results [28, 29].

However, a recent meta-analysis provided convincing evidence that steroids combined with IVIG as initial treatment reduce the overall risk of coronary artery aneurysms in severe KD. The meta-analysis included nine clinical studies involving 1,011 patients (536 patients received IVIG and GC, 475 only IVIG). Six studies were prospective randomized controlled studies, one was a retrospective report, and two were nonrandomized controlled studies. They found that significantly fewer patients receiving IVIG and GC developed coronary artery aneurysms than those receiving IVIG alone. They also found no significant differences in frequency of severe adverse events between the steroid and nonsteroid treatment group. However, different studies used heterogeneous GC dosing regimens and it is difficult to translate the results into clinical practice [30].

Since 80 % of patients with KD respond to ASA and IVIG, and coronary artery aneurysms are most commonly seen in patients who fail to respond to IVIG, markers that would predict IVIG resistance are needed. If we could identify IVIG nonresponders, corticosteroids might be considered as an additional treatment to IVIG in this group of patients. There are several scoring systems available but none is sensitive or specific enough to be used in different populations. For example, the Kobayashi score, used by Japanese investigators in the RAISE study, had a low sensitivity for prediction of IVIG nonresponders in other studies [31, 32].

Eleftheriou et al. proposed that corticosteroids should be considered for: (1) IVIG-resistant patients with persistent inflammation and on-going fever of more than 48 h after receiving a first dose of IVIG of 2 mg/kg; (2) patients with features of more severe disease such as age younger than1 year, markers of severe inflammation, including persistently elevated CRP, liver dysfunction, hypoalbuminemia and anemia, features of hemophagocytic lymphohistiocytosis, and/or shock; and (3) patients with evolving coronary or peripheral aneurysms with on-going inflammation at presentation. It was suggested that intravenous preparations of prednisolone equivalent to 2 mg/kg should be used for 5–7 days, or until CRP normalizes. This should be followed by oral prednisolone weaning over 2–3 weeks. However, given the absence of strong evidence, some flexibility of steroid regimens for individual patients is suggested [31].

Polyarteritis Nodosa

The third most common childhood vasculitis in the Western hemisphere is polyarteritis nodosa (PAN). It is a necrotizing vasculitis of medium-sized muscular arteries and it accounts for approximately 3 % of childhood vasculitides. The EULAR/PReS classification criteria for PAN require evidence of inflammation of medium or small arteries either by histopathology or angiography and one of the following five

criteria: involvement of skin, myalgia, hypertension, peripheral neuropathy, or renal involvement [22]. The etiology remains unclear; its association with hepatitis B, which is frequent in adult patients, is extremely rare in children.

The onset of the disease usually begins before 10 years of age. It starts with non-specific systemic symptoms with malaise, fever, weight loss, skin rash, myalgia, abdominal pain, and arthropathy. Laboratory markers of inflammation are usually elevated. PAN can affect a vessel and its supply anywhere in the body, although the lungs are typically spared. Owing to involvement of the medium-sized vessels, there can be ischemic symptoms of the affected organs such as ischemic heart pain, ischemic testicular involvement, focal neurological signs with hemiplegia, visual loss, and mononeuritis multiplex. Renal involvement can present as hematuria, proteinuria, and hypertension. Inflammation of the small arteries of the skin can present with variable skin lesions from livedo reticularis, purpura, or necrosis and possibly digital gangrene (Figs. 5 and 6). Characteristic features are painful subcutaneous nodules along the affected vessels [2, 33, 34].

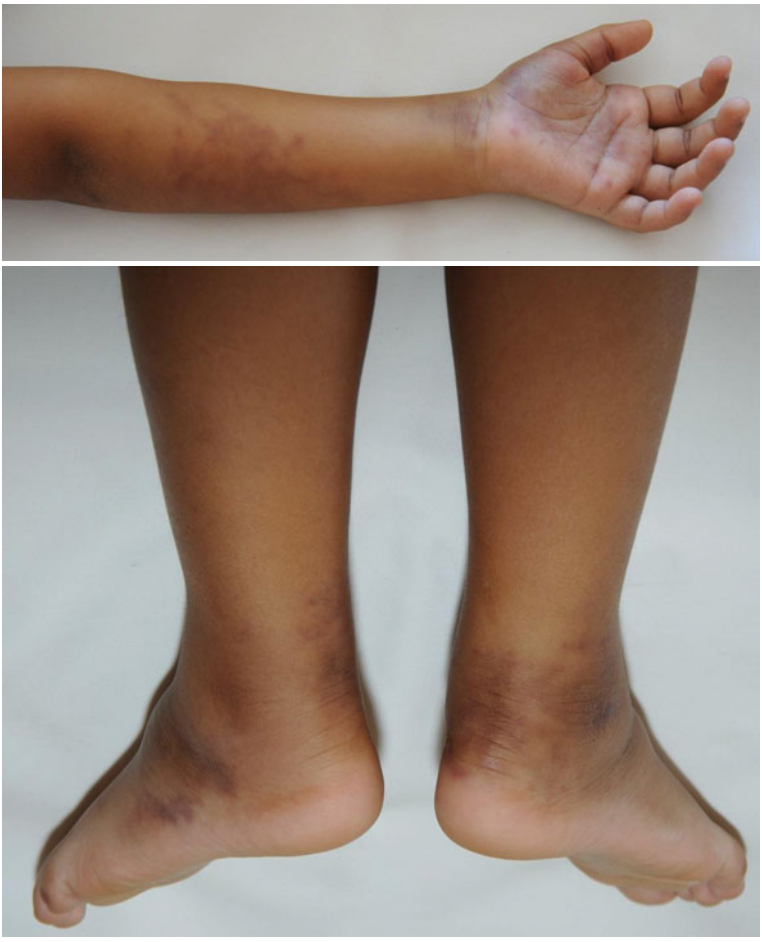

Fig. 5 Skin rash in a patient with polyarteritis nodosa

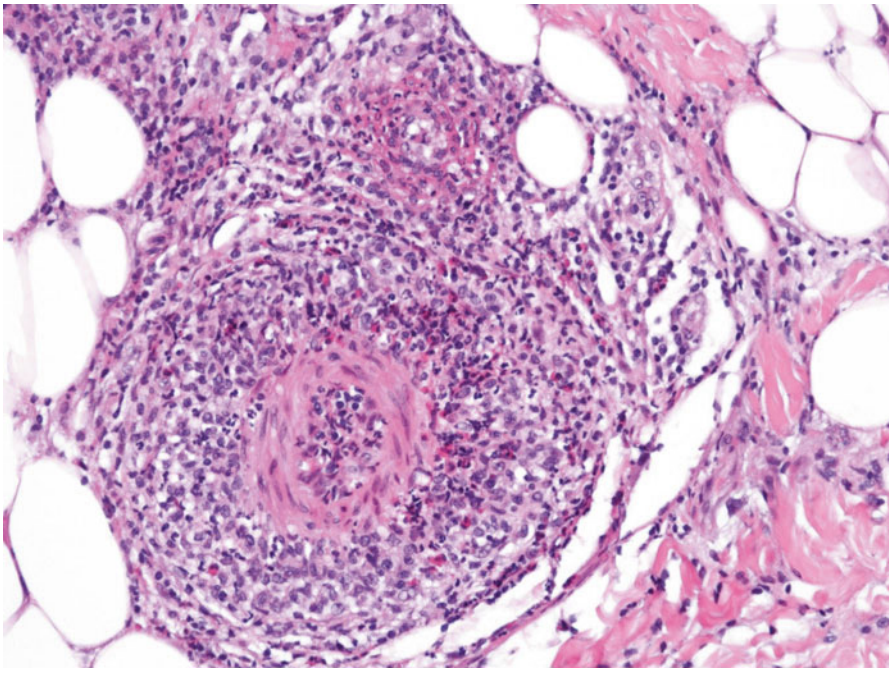

Fig. 6 Necrotizing arteritis in a child with polyarteritis nodosa

Cutaneous PAN is limited to the skin and musculoskeletal system and is often associated with antecedent streptococcal infection. It characteristically presents with fever, painful subcutaneous nodules, purpura, livedo reticularis, myalgias, arthralgias, and arthritis. Skin lesions are mostly present on the lower limbs.

Treatment

Treatment of childhood PAN is primarily based on clinical experience and adult studies. There have not been any randomized clinical trials to compare different induction and maintenance therapies for childhood systemic PAN. The cornerstone of induction therapy is GC with an additional cytotoxic agent. Induction therapy can be given as pulse intravenous methylprednisolone (30 mg/kg/day; maximal dose 1 g) for 3 consecutive days, followed by oral prednisolone with tapering, or orally with prednisolone (1–2 mg/kg/day) for 4 weeks with weaning over the next 6–8 weeks. Additional therapy with cyclophosphamide either oral (2 mg/kg/day) for 2–3 months or monthly intravenous pulses (500–1,000 mg/m^2) for 6 months may be warranted for induction therapy. In life-threatening situations, IVIG or plasmapheresis can be beneficial. For maintenance therapy after remission is achieved, daily or alternate-day prednisolone in doses of 0.3–0.7 mg/kg with oral azathioprine

(2 mg/kg/day) is used for up to 18 months. Alternatives to azathioprine include methotrexate or mycophenolate mofetil. Successful treatments with infliximab or rituximab have also been reported.

For treatment of cutaneous PAN the mainstay of therapy are NSAIDs or GCs in moderate doses. In cases of persistent or relapsing disease, steroid-sparing agents such as methotrexate, colchicine, and IVIG have been used. Owing to its connection with streptococcal infection, continuous penicillin prophylaxis might be beneficial [2, 4, 33, 34].

Takayasu Arteritis

TA is a granulomatous vasculitis of the aorta with its major branches, most commonly the subclavian, carotid, and renal arteries. Childhood TA is a disease of adolescence with a mean age of diagnosis at 13 years and is more common in female patients and in Asian populations. Consensus criteria of EULAR/PReS require as mandatory for classification of childhood TA typical angiographic abnormalities of the aorta or its main branches and pulmonary arteries plus one of five additional criteria: (1) pulse deficit or claudication, (2) blood pressure discrepancy in any limb, (3) an audible bruit, (4) hypertension, or (5) elevated acute-phase reactants [22].

Disease presents with nonspecific systemic features such as headaches, fevers, fatigue, back pain, myalgia and arthralgia, abdominal pain, and claudication of the extremities. Nearly 90 % of patients have hypertension at diagnosis. During the disease course, additional specific symptoms, determined by the distribution of vessel involvement, usually develop. With involvement of the aortic arch or its major branches signs of so-called supradiaphragmatic–aortic arch disease evolve: CNS symptoms with headache, ischemic strokes, cerebral aneurysms and seizures, claudication in the upper extremities, absent peripheral pulses, and cardiac manifestations such as cardiomyopathy, congestive heart disease, and valvular disease.

Infradiaphragmatic–midaortic syndrome often presents with hypertension, lower extremity claudication, abdominal bruits, and abdominal pain, which can be severe and intermittent with bloody diarrhea. With renal artery involvement, hypertension leads to encephalopathy [2, 4, 35, 36].

Treatment

Treatment of TA includes immunosuppression with corticosteroids, methotrexate, cyclophosphamide, or biological anti-inflammatory therapy for active vessel wall inflammation. Symptomatic treatment includes anticoagulation and antihypertensive therapy. Complications including various types of aortoarterial stenosis/occlusion or dilatation sometimes require surgical or endovascular management, such as percutaneous transluminal angioplasty [2, 4, 35]. In a recent single-center study of

21 patients with TA, 85.7 % of patients required prednisone therapy and 65.7 % of patients were treated with methotrexate. Ten of 21 patients required additional therapy to control the disease: infliximab, additional intravenous steroids, cyclophosphamide, anakinra, and etanercept. Eight (38.1 %) patients required surgical intervention [36].

ANCA-Associated Vasculitides

A group of vasculitides with predominantly pathological involvement of small and medium-sized blood vessels and association with antineutrophil cytoplasmic antibodies (ANCAs) are called the ANCA-associated vasculitides (AAV). They have overlapping clinical features with involvement of the lungs and kidneys. AAV are associated with a high frequency of disease- and treatment-related morbidities. Untreated AAV have near 100 % mortality with a mean survival of 5 months [2, 4]. In up to 60 % of patients, relapses occur. The three classic vasculitides are granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg–Strauss syndrome) [2, 4].

Childhood-onset granulomatosis with polyangiitis primarily affects the upper and lower respiratory tract and kidneys. According to the EULAR/PReS guidelines, three out of six criteria are needed for classification of childhood-onset granulomatosis with polyangiitis: histopathological evidence of granulomatous inflammation; upper airway involvement, laryngo-tracheo-bronchial involvement; radiologic evidence of pulmonary involvement; ANCA positivity or renal involvement with proteinuria; hematuria, red blood cell cast; necrotizing pauci-immune glomerulonephritis. At diagnosis more than 90 % of patients have constitutional symptoms with fever, malaise, and weight loss, and 80 % have pulmonary manifestations that may include pulmonary hemorrhage, nodules, infiltrates, pleurisy, oxygen dependency, or respiratory failure. Involvement of the upper respiratory system with recurrent epistaxis, sinusitis, mastoiditis, nasal or oral ulcerations, nasal septum perforation, and subglottic stenosis are present in 80 % of the patients at diagnosis. Three quarters of patients have renal involvement. About 90 % of patients are ANCA-positive, with a great majority positive for cytoplasmic-ANCA (c-ANCA) or PR3-positive ANCA [37–39]. In a recent Japanese report of 23 patients with GPA, the proportion of MPO-ANCA-positive patients was higher, nearly one third, than in Western populations.

A necrotizing vasculitis that affects capillaries, venules, or arterioles most commonly in kidneys or lungs is called microscopic polyangiitis. In nearly all the patients described, constitutional symptoms of fever, weight loss, malaise, and arthralgias were present. Besides renal disease, which may include hypertension, hematuria, proteinuria, or even renal failure in one third of the patients, ischemic cerebral insults or necrotizing vasculitic lesions of the skin are present in 30 % of the patients. Three quarters of patients have perinuclear ANCA [2, 3, 38, 40].

Eosinophilic granulomatosis with polyangiitis (EGPA) affects small and medium-sized vessels primarily in severely asthmatic or allergic patients. There are no specific criteria for EGPA in children. The American College of Rheumatology classification criteria requires four of the following for diagnosis: (1) history of asthma, (2) history of allergies, (3) peripheral eosinophilia of 10 %, (4) mono- or polyneuropathy, (5) migratory pulmonary infiltrates, (6) paranasal sinus pain or radiographic opacities, or (7) biopsy demonstrating extravascular eosinophils. The most common features in children at diagnosis are asthma, pulmonary infiltrates, sinusitis, involvement of the skin with vasculitis rash, cardiac disease, gastrointestinal symptoms, polyneuropathy, and in rare cases kidney disease. Only 25 % of children with EGPA are ANCA-positive [2, 4, 41].

Treatment

Principles of treatment are similar for all AAV with induction and maintenance therapy. Treatment options have been mainly adapted from adult studies or case series. Treatment with a combination of GC and oral cyclophosphamide (CYC) has long been the standard of care for induction therapy and achieves remission in more than 90 % of patients. Before acceptance of this treatment protocol, the majority of severe cases in children were fatal. For GPA, the induction phase lasts for 3–6 months and includes prednisolone administered orally (1–2 mg/kg/day; max. 60 mg/day) in divided doses for 2–4 weeks followed by tapering. In extremely ill patients, 1–3 days of intravenous pulse methylprednisolone of 30 mg/kg/day is used. In addition to GCs, cyclophosphamide administered orally (2 mg/kg/day) or intravenous pulses of 0.5–1.0 g/m^2 monthly are used. Owing to significant treatment-related toxicities such as immunosuppression with serious infections, hemorrhagic cystitis, infertility, or development of malignancies and the high risk of relapse, different alternatives to CYC are being sought. Alternative immunosuppressants for less severe or steroid-dependent disease include methotrexate, azathioprine, mycophenolate mofetil, anti-tumor necrosis factor-α, and rituximab. Plasmapheresis can also provide additional benefits for most patients with severe disease.

For maintenance therapy, methotrexate, mycophenolate mofetil, or azathioprine for 18–24 months is used. Options for refractory disease include biological therapy: infliximab or rituximab and IVIg [2, 4, 40, 41].

Central Nervous System Vasculitis

Inflammatory disease of blood vessels in the brain in children not associated with vasculitis in other organs is called CNS vasculitis of childhood. It may be primary or secondary, associated with infection, rheumatic or systemic inflammatory disease, malignancies, metabolic disease, or medications and radiation therapy.

If the disease is diagnosed early, the inflammation and neurologic damage may be reversible. Based on the angiography findings, primary vasculitis is classified as: (1) large to medium-sized vessels primary central nervous system vasculitis (cPACNS) with abnormal angiography and (2) small vessel–cPACNS with normal angiography [42–45].

Patients with angiography-positive cPACNS typically present with focal neurologic symptoms and can have normal systemic inflammatory markers and cerebrospinal fluid analysis. Conventional angiography or magnetic resonance angiography demonstrates large or medium-sized vessel stenosis, occlusion, or bending. Focal areas of acute ischemia in a vascular distribution are found on magnetic resonance imaging. If new lesions appear within 3 months after diagnosis, cPACNS is further classified as progressive in contrast to nonprogressive disease. Patients with progressive disease more frequently have headaches, cognitive dysfunction, and behavioral changes.

Patients with diffuse or focal neurologic symptoms and angiography-negative cPACNS may have fever, malaise, and other systemic features at presentation. Usually the cerebrospinal fluid is pathological with increased opening pressure, pleocytosis, and elevated proteins; systemic inflammatory markers may be normal. Gray matter and white matter are involved unilaterally or bilaterally and changes are usually multifocal. To confirm the diagnosis, brain biopsy is needed and reveals lymphocytic nongranulomatous vasculitis [42–45].

Treatment

For nonprogressive cPACNS, treatment is controversial. It may include anticoagulation and corticosteroids, which can help to prevent recurrence and improve neurologic recovery.

Progressive cPACNS and angiography-negative cPACNS are treated aggressively with induction therapy for 6 months that includes cyclophosphamide (500–750 mg/m^2/month) and corticosteroids (2 mg/kg/day initially with tapering) followed by maintenance therapy with mycophenolate mofetil or azathioprine for 18 months [42–45].

References

1. Ozen S et al (2006) EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. Ann Rheum Dis 65(7):936–941
2. Weiss PF (2012) Pediatric vasculitis. Pediatr Clin North Am 59(2):407–423
3. Batu ED, Ozen S (2012) Pediatric vasculitis. Curr Rheumatol Rep 14(2):121–129
4. Cassidy JT et al (2011) Textbook of pediatric rheumatology, 6th edn. Saunders Elsevier, Philadelphia

5. Gardner-Medwin JM et al (2002) Incidence of Henoch-Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. Lancet 360:1197–1202
6. Saulsbury FT (1999) Henoch-Schönlein purpura in children: report of 100 patients and review of the literature. Medicine (Baltimore) 78(6):395–409
7. Trnka P (2013) Henoch–Schönlein purpura in children. J Paediatr Child Health 49:995–1003
8. Trapani S et al (2005) Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. Semin Arthritis Rheum 35(3):143–153
9. Kawasaki Y (2011) The pathogenesis and treatment of pediatric Henoch–Schönlein purpura nephritis. Clin Exp Nephrol 15:648–657
10. Huber AM et al (2004) A randomized, placebo-controlled trial of prednisone in early Henoch Schönlein purpura. BMC Med 2:7
11. Weiss PF et al (2007) Effects of corticosteroid on Henoch-Schönlein purpura: a systematic review. Pediatrics 120:1079–1087
12. Weiss PF et al (2009) Variation in inpatient therapy and diagnostic evaluation of children with Henoch Schönlein purpura. J Pediatr 155(6):812.e1–818.e1
13. Weiss PF et al (2010) Corticosteroids may improve clinical outcomes during hospitalization for Henoch-Schönlein purpura. Pediatrics 126(4):674–681
14. Szer IS (1999) Gastrointestinal and renal involvement in vasculitis: management strategies in Henoch-Schönlein purpura. Cleve Clin J Med 66:312–317
15. Ronkainen J et al (2006) Early prednisone therapy in Henoch-Schonlein purpura: a randomized, double-blind, placebo-controlled trial. J Pediatr 149:241–247
16. Chartapisak W et al (2009) Interventions for preventing and treating kidney disease in Henoch-Schönlein Purpura (HSP). Cochrane Database Syst Rev (3):CD005128
17. Jauhola O et al (2012) Outcome of Henoch-Schönlein purpura 8 years after treatment with a placebo or prednisone at disease onset. Pediatr Nephrol 27(6):933–939
18. Davin JC (2011) Henoch-Schonlein purpura nephritis: pathophysiology, treatment and future strategy. Clin J Am Soc Nephrol 6:679–689
19. Eleftheriou D et al (2009) Biologic therapy in primary systemic vasculitis of the young. Rheumatology 48:978–986
20. Jamieson N, Singh-Grewal D (2013) Kawasaki disease: a clinician's update. Int J Pediatr 2013:645391
21. Yim D et al (2013) An update on Kawasaki disease II: clinical features, diagnosis, treatment and outcomes. J Paediatr Child Health 49(8):614–623
22. Ozen S et al (2010) EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis 69(5):798–806
23. Baumer JH et al (2006) Salicylate for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev (4):CD004175
24. Brogan RJ et al (2009) Infliximab for the treatment of intravenous mmunoglobulin resistant Kawasaki disease complicated by coronary artery aneurysms: a case report. Pediatr Rheumatol Online J 7:3
25. Burns JC et al (2005) Infliximab treatment for refractory Kawasaki syndrome. J Pediatr 146:662–667
26. Oishi T et al (2008) Infliximab treatment for refractory Kawasaki disease with coronary artery aneurysm. Circ J 72:850
27. Weiss JE et al (2004) Infliximab as a novel therapy forrefractory Kawasaki disease. J Rheumatol 31:808–810
28. Inoue Y, Okada Y, Shinohara M et al (2006) A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: clinical course and coronary martery outcome. J Pediatr 149:336–341
29. Newburger JW et al (2007) Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. N Engl J Med 356:663–675

30. Chen S et al (2013) Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart 99(2):76–82
31. Eleftheriou D et al (2014) Management of Kawasaki disease. Arch Dis Child 99(1):74–83
32. Kobayashi T et al (2013) Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 379(9826):1613–1620
33. Kawakami T (2012) A review of pediatric vasculitis with a focus on juvenile polyarteritis nodosa. Am J Clin Dermatol 13(6):389–398
34. Ozen S et al (2004) Juvenile polyarteritis: results of a multicenter survey of 110 children. J Pediatr 145:517–522
35. Cakar N et al (2008) Takayasu arteritis in children. J Rheumatol 35:913–919
36. Szugye HS et al (2014) Takayasu Arteritis in the pediatric population: a contemporary United States-Based Single Center Cohort. Pediatr Rheumatol 12:21
37. Akikusa JD et al (2007) Clinical features and outcome of pediatric Wegener's granulomatosis. Arthritis Rheum 57:837–844
38. Bohm M et al (2014) Clinical features of childhood granulomatosis with polyangiitis (wegener's granulomatosis). Pediatr Rheumatol Online J 12:18. doi:10.1186/1546-0096-12-18
39. Cabral DA et al (2009) Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. Arthritis Rheum 60:3413–3424
40. Sun L et al (2014) Clinical and pathological features of microscopic polyangiitis in 20 children. J Rheumatol 41(8):1712–1719
41. Zwerina J et al (2009) Churg-Strauss syndrome in childhood: a systematic literature review and clinical comparison with adult patients. Semin Arthritis Rheum 39:108–115
42. Benseler SM et al (2006) Primary central nervous system vasculitis in children. Arthritis Rheum 54:1291–1297
43. Calabrese LH et al (1992) Primary angiitis of the central nervous system: diagnostic criteria and clinical approach. Cleve Clin J Med 59:293–306
44. Gowdie P et al (2012) Primary and secondary central nervous system vasculitis. J Child Neurol 27(11):1448–1459
45. Iannetti L et al (2012) Recent understanding on diagnosis and management of central nervous system vasculitis. Child Clin Dev Immunol Vol. doi:10.1155/2012/698327