Update on vasculitis in childhood

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This review reports the advances on etiopathogenesis, clinical findings, outcome and treatment of the most common pediatric vasculitis. In particular, we focus on Henoch–Schönlein purpura renal involvement, its possible prevention and therapy. Owing to the worldwide awareness of new features of Kawasaki disease, this article discusses atypical and incomplete disease. The approach to patients with persistently active disease, the role of corticosteroids and new biological agents (antitumor necrosis factor) are discussed. The two main clinical forms of polyarteritis nodosa, systemic and cutaneous, are described, and the role of Group A *Streptococcus* infection in triggering the cutaneous form is highlighted. The use of magnetic resonance imaging in diagnosing, monitoring and guiding the treatment of Takayasu disease, and the improvement of long-term prognosis through reconstructive surgery and transluminal angioplasty for the vascular complications are also emphasized. Finally, we have highlighted the attempt of Ozen and an international group of experts to reach a consensus on classification criteria applied for the most common pediatric vasculitides.

Keywords:
Henoch–Schönlein purpura, Kawasaki disease, pediatric vasculitis, polyarteritis nodosa

future medicine

Vasculitis in children

In recent decades, a better understanding of disease pathogenesis has significantly improved the therapeutic approach, long-term prognosis and mortality in systemic pediatric vasculitides. Nevertheless, vasculitis in childhood remains a challenge for pediatric rheumatologists owing to the great variety of clinical presentation, overlapping of systemic and cutaneous features in the individual disorders, and lack of specific laboratory tests. Among pediatric rheumatic diseases, vasculitis is the most difficult to classify, and there is evidence that applying adult criteria to children is unsuitable in most cases. Recently, Ozen and colleagues, with an international group of experts with experience of childhood vasculitis, have attempted to reach a consensus on classification criteria for the most common pediatric vasculitides [1]. Ethnicity, gender and age can all be associated with the development of common primary vasculitis. Indeed, Kawasaki disease (KD) mainly affects young males of Asian origin; Henoch–Schöenlein purpura (HSP) mainly affects white Caucasian children and infrequently affects the black population [2]. Despite the fact that their pathogenic mechanisms are not yet fully recognized, the role of infections as triggering agents is well known.

Henoch–Schönlein purpura

HSP is a systemic small-vessel vasculitic syndrome characterized by nonthrombocytopenic purpuric rash, arthralgia, abdominal pain and nephritis. It is currently reported as one of the most common forms of systemic vasculitis in childhood, although it can occur at any age from infancy to adulthood. Children, especially boys, aged 3–15 years are predominantly affected while a few cases occur in infants and in adults. The incidence of HSP has been reported to be 10.2 per 100,000 in the Czech Republic, 12.9 per 100,000 children in Taiwan and 13.5 per 100,000 in Northern Ireland [2–4]. While in childhood the disease is self-limited in most cases, in adulthood the outcome is more severe, with a higher frequency of renal involvement requiring aggressive treatment [5–7]. Reports of familial occurrence are few. A correlation with upper respiratory tract infections is supported by its higher frequency in Winter and Spring. Among multiple organisms implicated in triggering the disease, Group A hemolytic *Streptococcus* is considered to be one of the possible causative agents. *Mycoplasma pneumoniae*, *Yersinia*, adenovirus, Epstein–Barr virus, hepatitis B virus and herpes zoster have also been associated with HSP, and several case reports have linked vaccinations against measles, varicella, rubella and Hepatitis A and B with the subsequent development of the disease. A relationship between *Bartonella henselae* and HSP was also reported in a recent Canadian study.

Pathogenesis

The hallmark of HSP is the widespread vascular deposition of immunoglobulin (Ig)A, supporting the assumption of an IgA-mediated immune reaction to different triggers in the disease pathogenesis. Further support for this hypothesis is the increased number of transforming

growth factor (TGF)-β-secreting T cells in the acute phase of the disease; in fact, TGF-β plays a pivotal role in IgA secretion.

The pathogenesis and risk factors for renal involvement in HSP are not currently fully clarified. The role of tumor necrosis factor (TNF)α in inducing functional and morphological changes in the glomeruli during the acute phase has been advocated in a recent study [8]. High expression of circulating vascular endothelial growth factor (VEGF) has also been previously reported on HSP, and recently, an association between functional haplotypes of VEGF and renal complications has been found [9]. In addition, a potential role of leptin in the pathogenesis of HSP has been advocated, but further studies are needed to confirm this hypothesis [10].

Antiendothelial cell antibodies (AECA) have been found to play an important role in many vascular disorders, including HSP [11]. In a recent study, IgA AECA have been shown to be significantly increased in the acute phase of HSP, and to enhance the secretion of interleukin (IL)-8 via mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK; MEK/ERK) signaling pathway [12]. α_1-antitrypsin deficiency has been linked to an increased incidence of vasculitic syndromes, including HSP, in association with antiendothelial cell antibodies [13].

Clinical manifestations

Lacking specific laboratory tests, the diagnosis is based upon clinical manifestations, but may be delayed when joint involvement precedes skin alterations or when acute surgical abdomen is the presenting manifestation. Abdominal ultrasound may help the diagnosis, revealing an intussusception, the major gastrointestinal complication in HSP, although gangrene or overt perforation may also ensue. Moreover, a routine stool evaluation should be performed in any child with true or suspected HSP to detect occult blood, even in the absence of symptoms. In childhood, glomerulonephritis affects up to a third of patients and only rarely represents a severe life-threatening complication. Microscopic hematuria, isolated or associated with mild proteinuria, is common and does not require a renal biopsy; urinalysis is suggested up to at least 6 months from onset. A close monitoring of renal function and a renal biopsy are mandatory in children with nephrotic or nephritic syndrome, hypertension and reduced creatinine clearance [14]. Predictive factors for nephritis, relapse and severe proteinuria in a large cohort of HSP children resulted in older age at onset, persistent purpura and severe gut vasculitis [15].

HSP nephritis is comparable to IgA nephropathy (Berger's disease), since the two conditions are similar with regard to clinical course, outcome and therapy. Indeed, graft survival in HSP and IgA nephropathy demonstrates similar 5-year graft and patient survivals [16,17].

Therapy

The choice of therapy is still a dilemma because the disease is self-limited in most children; the role of corticosteroids is still debated since they lead to rapid symptomatic improvement of extrarenal symptoms, but do not influence the final prognosis and can occasionally mask severe gastrointestinal complications [18]. Despite the fact that routine use of prednisone in HSP is not supported by sound evidence-based data, the drug is often given to patients with severe abdominal pain [19,20].

No therapy is suggested for cases with mild urinary abnormalities, while high-dose steroids and immunosuppressive drugs are recommended for severe renal involvement. Controlling renal damage and reducing the risk of renal failure are the major concerns; azathioprine added to steroids and methylprednisolone pulses followed by oral steroids and oral cyclophosphamide have all been shown to be effective, even though the clinical evidence is not strong. The best prevention of renal damage is not yet proven, and hopefully further studies will clarify the risk factors that lead to severe renal disease.

Kawasaki disease

KD, the most common systemic vasculitis in infants and young children after HSP, is reported as the leading cause of acquired heart disease in children in North America, Europe and Japan. Moreover, it is regarded as a potential risk factor for premature atherosclerosis, adult ischemic heart disease and sudden death in early adulthood.

Epidemiology

Although KD has been reported all over the world, it is most frequent among Asian populations, especially Japanese. In Japan, the annual incidence is reported as 90–134 per 100,000, which is significantly higher than in Europe (3.6–6.9 per 100,000) and in the USA (6–9 per 100,000 children under 5 years old). In Hawaii, where most people are of Asian ancestry, the incidence is higher than in USA, but lower than

Japan, supporting the assumption that both genetic predisposition and environmental factors are critical [21,22].

A family history of KD may be a risk factor for increased severity and recurrence of the disease. Actually, siblings of patients with KD have a significantly greater chance of acquiring the illness than children in the general population.

Pathogenesis

Despite numerous studies, the cause of KD remains uncertain. Identification of the infectious etiology of KD has proved to be very difficult, despite many efforts by investigators worldwide. The peak incidence in early childhood and the virtual absence in adulthood suggest that a microbe causing an asymptomatic infection in most individuals could be a possible trigger, with acquired immunity by adulthood. The rarity of illness in infants in the first months of life advocates passive protection by maternal antibodies. Among common infantile febrile diseases, adenoviral infection characterized by prolonged fever, conjunctivitis, lymphoadenopathy and mucous membrane changes, high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) strongly resembles KD [23]. Recently, a novel human corona virus has been associated with KD [24], but these results have not been replicated [25]. *Mycoplasma pneumoniae* infection, characterized by fever, rash, conjunctivitis and lymphoadenopathy, has also been associated with KD.

Systemic inflammation in many organs, including the myocardium, CNS, liver, lungs, kidneys and lymph nodes, in addition to artery involvement has been well documented in KD. Following a complex immune response, significant overproduction of different cytokines and activation of endothelial cells have been identified.

KD has some similarities to toxin-mediated diseases, both from a clinical and an immunological point of view. The role of one or more superantigens capable of stimulating large numbers of T cells produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the etiology of KD, but no general consensus has been achieved. After the first report by Abe and colleagues describing selective expansion of $V\beta2^+$ and $V\beta8^+$ T cells in patients with acute KD, but not in the convalescent phase [26], a plethora of other similar studies have been published, both with positive and negative evidence for a superantigen-driven process [27].

The role of an infectious trigger that induces the disease in a genetically susceptible host is strongly suggested by the epidemiology of the disease in Japanese and North-American epidemics resembling the spread of viral or bacterial infections. The role of one or more superantigens, capable of stimulating large numbers of T cells, produced by certain strains of *Staphylococcus* or *Streptococcus* has been discussed in the etiology of KD, with no general consensus. Leung and colleagues studied the prevalence of superantigen-secreting bacteria in children with KD, but did not find a significant difference between patients and controls with other febrile illnesses [28]. However, future studies should further examine the potential role of Vβ2-stimulatory superantigens in KD.

The pattern of vessel inflammation in KD is characterized by edema and infiltration of neutrophil, $CD8^+$ T cells and macrophages. Shulman and colleagues investigated the role of IgA immune response in KD, suggesting that a viral agent entering the respiratory tract causes an oligoclonal IgA response [29]. Indeed, IgA-secreting plasma cells were found in the inflammatory infiltrate of tissues and vascular walls of KD patients. In addition, it was suggested that vascular endothelial cell growth factor may play a role in vessel wall edema, leading to subendothelial accumulation of monocytes and macrophages; the inflammatory infiltrate would then migrate to the media, causing its destruction and the development of aneurysms [30].

Clinical manifestations

In this review, we will not detail the well-known clinical manifestations and diagnostic criteria; however, an emerging challenge for physicians is represented by atypical and incomplete KD cases, as recently defined [21]. In atypical forms, along with typical high fever lasting more than 5 days and not responsive to antibiotics, the presenting symptoms are acute surgical symptoms (e.g., appendicitis, cholestasis and acute pancreatitis) [31] or neurological manifestations (e.g., seizures and facial palsy), while the remaining typical clinical manifestations may develop over time. The term 'incomplete' should be reserved for patients who lack the classical diagnostic criteria, but who present fever, at least two of the clinical criteria and coronary alterations by echocardiography [21]. The increasing number of patients who do not develop the typical manifestations raises concerns about the sensitivity of diagnosis based upon published clinical criteria [21,32]. Medical history, physical examination and laboratory tests, including elevated

white blood cell count, ESR, CRP and low hemoglobin, sodium and albumin levels, could help to rule-out illnesses mimicking KD. Hyponatremia (<135 mEq/l) is detected in approximately 44% of patients in the first week of illness, and may represent a risk factor for coronary artery aneurysms (CAA), which occur in children exhibiting severe inflammation and increased vascular permeability. Among other risk factors for developing coronary damage, low albumin levels (<3.5 g/dl) are frequently observed on the second week of disease KD. Whilst hyponatremia may be related to water retention, low albumin levels may be due to both microvascular permeability and reduced protein production in the liver [33].

Few data are available on infants aged less than 6 months, who often display an atypical or incomplete course with persistence of inflammation leading to rapid and severe coronary damage. To date, due to the lack of awareness of occurrence of KD in newborns, the diagnosis is sometimes missed [34]. A recent study performed in Japan demonstrated that older age was also an independent risk factor for coronary sequelae [35]. A survey involving general pediatricians and pediatric infectious disease specialists reported that KD is rarely suspected at the extremes of pediatric age and that such patients are at risk for CAA due to delayed diagnosis and treatment [36]. In adults, KD is seldom observed and usually has an atypical onset.

Prognosis

The long-term prognosis of KD has significantly improved in recent years because of a better knowledge of the disease and to the early treatment with intravenous immunoglobulin (IVIG), although CAA still develop in up to 5% of patients [21]. The major concern remains the development of giant aneurysms (GA; diameter of coronary lumen ≥8 mm), which rarely regress and often become stenotic, leading to myocardial ischemia even in early adulthood. Besides, GA are a potential risk for rupture in the acute phase or later thrombosis owing to stasis of blood flow, raising the problem of anticoagulation therapy in children and especially infants [37,38].

Coronary lesions are known to develop progressive intimal hyperplasia, even many years after KD. An immunohistochemical study was performed by Suzuki and colleagues on a KD child without CAA who suffered sudden infant death. A slightly thick intima, disruption of the lamina interna and signs of persistent inflammation were found, suggesting that even coronary arteries that appear normal on ultrasound may be damaged [39].

Therapy

IVIG (2 g/kg) with aspirin (50–80 mg/kg) given within 10 days from fever onset is the correct current therapy in KD; however, 10–20% of children fail to respond to this treatment. No specific guidelines are available for the management of refractory patients, specifically those in whom parameters of inflammation do not subside and fever persists or recurs. Most will respond to a second IVIG infusion, but up to a third remain febrile.

There are different therapeutic approaches to refractory KD. Either a third dose of IVIG (2 g/kg) or corticosteroids may be given, although patients failing to respond to a second IVIG infusion appear to be refractory to a third dose [21,40,41]. Owing to previous studies reporting a high rate of coronary alterations in patients treated with corticosteroids, there has been some reluctance to use this therapy either as first-line treatment or as additional therapy in children who do not respond to IVIG. Since no association between corticosteroids and the increased incidence of CAA has been observed in recent reports, the use of corticosteroids as rescue therapy, either oral or pulsed (methylprednisolone 30 mg/kg, one to three courses), in children refractory to IVIG has been suggested to be an alternative, safe treatment [42–44].

Other therapies that have been tried in cases of aggressive disease recalcitrant to IVIG and corticosteroids, mainly published as single case reports or small series, include cyclophosphamide, cyclosporine, ulinastatin and plasma exchange [45,46].

Infliximab (Remicade®), a monoclonal antibody against TNFα, has also been successfully administered to children refractory to IVIG and corticosteroids; and with severe coronary involvement, but results of different reports have been conflicting [47].

Although diagnostic criteria suggest that KD cannot be diagnosed before day 5 from fever onset, the presence of all typical symptoms may argue for earlier diagnosis and raises the question of when to start IVIG therapy; it is still controversial whether IVIG has greater efficacy in preventing cardiac sequelae when given before or after day 4 off onset [48].

The prevention of thrombosis and stenosis following myointimal proliferation is the main concern. To date, low-dose aspirin (3–5 mg/kg/day)

has proved to be effective in children with small to medium-sized aneurysms, and there are anecdotal reports of the use of other antiplatelet agents (e.g., clopidrogel) [21]. Although long-term oral anticoagulation with warfarin is recommended in children with GA secondary to KD, its efficacy and safety are not currently well defined. Recently, Levy and colleagues studied a cohort of KD children to determine whether oral anticoagulation might prevent myocardial ischemia at 12-month follow-up [37]. The authors concluded that warfarin does not protect against ischemia, nor does it influence the regression of aneurysms. Considering the risk of bleeding and the difficulty in monitoring international normalized ratio (INR) in children given long-term warfarin therapy, further studies are required before including oral anticoagulation in the guidelines for GA treatment.

Finally, live viral vaccines are an additional concern for children with KD, since IVIG therapy blocks an active immune response. An interval of at least 6–9 months after IVIG is recommended before the administration of such vaccines.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a rare vasculitic disease that can present with a variety of signs and symptoms. Histologically, it is characterized by fibrinoid necrosis of the small- and medium-sized arteries. The classification of this disorder is still debated; in adults, classical PAN and microscopic polyangiitis are recognized. The American College of Rheumatology (ACR) suggested criteria for classification in 1990, with specificity and sensitivity around 80% in adults, but these criteria have not been validated in children.

In childhood, there are two main categories of PAN described:

- Cutaneous form, which is more benign and frequently associated with streptococcal infections;
- Systemic form, which can affect all vessels and that can be life threatening, especially in cases of renal and cerebral involvement.

The diagnosis of PAN is clinical, with the support of histological or angiographic evidence of a diseased vessel. Therefpre, a biopsy is often necessary for diagnosis, even if magnetic resonance imaging (MRI); or magnetic resonance angiography (MRA) are useful in detecting aneurysms. Unfortunately, there are no good biological diagnostic or prognostic markers for this disorder, even if antibodies against cytoplasm of neutrophils (ANCA), often with a perinuclear pattern, are now a useful hint. The myeloperoxidase is the usual antigen of the peripheral (p)-ANCA positivity. Laboratory testing demontrates evidence of inflammation, with elevation of acute phase reactants. When renal vasculitis is present, renal function and urinalysis will be required.

PAN is almost always characterized by an insidious onset and by constitutional signs or symptoms, such as unexplained fever and weight loss. Cutaneous lesions, such as palpable purpura, dermal necrosis and livedo reticularis, are often present. Skin nodules can be found on the lower limbs, in the pretibial area and around the malleoli. In the case of multisystem involvement, abdominal pain, myalgia/arthralgia, mononeuropathy or polyneuropathy will be present.

In classical PAN, aneurysms may develop in kidney, gut and CNS, and the disease outcome is closely correlated to the organ system involvement. Signs and symptoms depend on the vessels involved, the main feature often being organ infarction (e.g., gut and kidney). Hypertension due to renal involvement is frequent. Corticosteroids are the main treatment; in children with severe disease, in particular those with renal involvement, cyclophosphamide orally or intravenously administered in addition to steroids is recommended. Prognosis is severe, with mortality as high as 20% in some series.

Cutaneous polyarteritis is a rare condition characterized by crops of painful subcutaneous nodules (prevalent on the soles and the medium aspect of feet), livedo reticularis and myalgia/arthralgia, in the absence of constitutional symptoms. Group A *Streptococcus* infection has been reported as a trigger event in some series, even though this association is still controversial. In these cases, a long-term prophylaxis with penicillin may be effective in preventing relapses. Patients usually respond to short courses of steroids, although the disease course is prolonged or characterized by frequent recurrences in several cases. Controlled studies are required to define the best treatment and the risk of systemic involvement.

A recent large multicenter study has characterized pediatric patients who had been diagnosed with PAN through necrotizing vasculitis of the small- and mid-size arteries or with characteristic findings on angiograms [32]. A total of 21 pediatric centers worldwide participated, with 110 patients. The mean age of patients was 9 years (range: 1–16 years), and there was no sex

predominance. Cases were classified as: 30% cutaneous PAN; 4.6% classic PAN associated with hepatitis B surface antigen (HBsAg); 8.1% microscopic polyarteritis associated with ANCA and 57.2% systemic PAN. All patients with HBsAg-associated classic PAN were diagnosed with renal angiograms, and antiviral treatment was administered in most cases. Patients classified with systemic PAN had multiple system involvement, almost all had constitutional symptoms, and all had elevated acute-phase reactants. Corticosteroids and cyclophosphamide were the first choices of immunosuppressive treatment. After a median follow-up period of 6 years, the overall mortality was 1.1%. The study concluded that there is an overall better survival and a lower relapse rates in children than in adults.

Finally, another advance in this field is related to classification criteria: Box 1 illustrates the recently proposed consensus criteria for classification of PAN in childhood.

Takayasu arteritis

Takayasu arteritis (TA) is a segmental inflammatory arteritis leading to stenosis and aneurysms of large muscular arteries, mainly the aorta and its major branches. It is very rare in childhood, although it follows Kawasaki disease and HSP in frequency. Females are affected more than males. The presenting symptoms of the patients are fever, night sweats, anorexia, weight loss and musculoskeletal symptoms. Symptoms related to hypertension and pulse deficits are common. The ACR classification criteria based on adult experience have been revised along with the other pediatric vasculitides (Box 2). The diagnosis is confirmed by characteristic findings of diseased aorta and its major branches seen on angiography. However, the differential diagnosis is sometimes difficult, particularly when differentiating with fibromuscular dysplasia, which is often associated with severe hypertension.

More recently, MRI has been used to establish the diagnosis of TA in children, to monitor disease activity and guide treatment. Early in the disease of TA, smooth muscle-thickened vessel walls (which may not be the only manifestation of vascular inflammation) may be not detected by conventional angiography. However, MRI can visualize the thickened vessel wall directly and, in addition, it can show other signs of active inflammation, such as mural edema with T2-weighted imaging and increased wall vascularity, with enhanced imaging. Owing to the rarity of the disease, there are no controlled studies of medical treatment of children with TA. Corticosteroids are used in acute disease and cyclophosphamide is an effective alternative; methotrexate has also been used both in adults and children with good results [33]. Subsequent reconstructive surgery and transluminal angioplasty may be employed for the vascular complications. TA is a disease with severe prognosis, 5-year mortality rates being reported in children as high as 35–40%.

Future perspective

We speculate that the newly proposed classification of pediatric vasculitides will be used in clinical studies, from both an epidemiological and a

Box 1. EULAR/PRES-endorsed consensus criteria for classification of childhood polyarteritis nodosa.

A child is classified as having childhood polyarteritis nodosa (PAN) if they have a systemic illness in the presence of one of the following as a mandatory criterion:

- Biopsy showing small- and mid-size artery necrotizing vasculitis

and/or

- Angiographic abnormalities* (aneurysms or occlusions)

And in the presence of at least two out of the following seven criteria:

- Skin involvement (livedo reticularis, tender subcutaneous nodules and other vasculitic lesions)
- Myalgia or muscle tenderness
- Systemic hypertension, relative to childhood normative data
- Mononeuropathy or polyneuropathy
- Abnormal urine analysis and/or impaired renal function
- Testicular pain or tenderness
- Signs or symptoms suggesting vasculitis of any other major organ system (gastrointestinal, cardiac, pulmonary or CNS)

**Should include angiography if magnetic resonance angiography is negative.*
EULAR: European League Against Rheumatism; PRES: Pediatric Rheumatology European Society.
Taken from [1].

Box 2. EULAR/PRES-endorsed consensus criteria for classification of Takayasu arteritis.

At least one of the following four should be present in the presence of angiographic abnormalities (conventional, computed tomography or magnetic resonance) of aorta or its main branches (a mandatory criterion):

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

Limitations of current classification criteria for childhood vasculitis:

- Applying adult criteria to children is unsuitable in most cases.
- The great variety of clinical presentation, overlapping of systemic and cutaneous features and lack of specific laboratory tests make the diagnosis of pediatric vasculitis a difficult one.
- Ozen and colleagues have attempted to reach a consensus on classification criteria for the most common pediatric vasculitides.

Definition of risk factors for renal involvement and prevention of Henoch–Schönlein purpura glomerulonephritis:

- The pathogenesis and the risk factors for renal involvement in Henoch–Schönlein purpura (HSP) are not currently fully clarified. Tumor necrosis factor (TNF)α appears to play a role in inducing functional and morphological changes in the glomeruli during the acute phase.
- Best prevention of renal damage is still under debate: steroids do not prevent renal involvement.
- High-dose steroids and immunosuppressive drugs are recommended for severe renal involvement.

Atypical and incomplete Kawasaki disease:

- The term 'atypical' should be reserved for patients with fever, acute surgical symptoms or neurological manifestations as presenting signs, while the remaining typical clinical manifestations may or may not develop over time.
- The term 'incomplete' should be reserved for patients who lack the classical diagnostic criteria, but who present fever, at least two of the clinical criteria and coronary alterations by echocardiography.
- Medical history, physical examination and laboratory tests, including elevated white blood cell count, erythrocyte sedimentation rate, C-reactive protein and low hemoglobin, sodium and albumin levels could help to rule-out illnesses mimicking Kawasaki disease (KD).

Refractory Kawasaki disease:

- Treatment of refractory KD is still a dilemma. Oral or pulsed corticosteroid rescue therapy in children refractory to intravenous immunoglobulin is an alternative and safe treatment.
- Infliximab (Remicade®), a monoclonal antibody against TNFα, has been given to children with coronary aneurysms, refractory to intravenous immunoglobulin and corticosteroids. Results are conflicting.

Polyarteritis nodosa:

- The classification of this disorder is still debated, and the American College of Rheumatology criteria have not been validated in children.
- Two main categories of polyarteritis nodosa are recognized in childhood:
  - Cutaneous form, more benign and frequently associated to streptococcal infections;
  - Systemic form, which can affect all vessels and can be life threatening, especially in case of renal and cerebral involvement.

Takayasu disease:

- The diagnosis is confirmed by characteristic findings of diseased aorta and its major branches observed on angiography.
- Magnetic resonance imaging is a useful noninvasive tool to establish the diagnosis of Takayasu arteritis in children, monitor disease activity and guide treatment.

EULAR: European League Against Rheumatism; PRES: Pediatric Rheumatology European Society.
Taken from [1].

therapeutic point of view. Finding more homogeneous disease categories could have a positive impact on the design of treatment trials: therefore, giving a better future knowledge of the optimal treatment strategies.

The pathogenesis of Kawasaki disease is still largely unknown, and hopefully in the next few years, modern technology and advances in basic immunology will enable better understanding of the underlying mechanisms.

Executive summary

- Vasculitis in childhood still remains a challenge for pediatric rheumatologists, and new classification criteria are required to enable early diagnosis and to improve the therapeutic approach.
- Although their pathogenic mechanisms are not currently fully recognized, the role of infections as triggering agents is well known.
- Henoch-Shönlein purpura (HSP) is the most common systemic vasculitis in children, and has a good prognosis in most cases. Although HSP has a strong correlation with upper respiratory tract infections, no specific trigger has been identified.
- The pathogenesis and the risk factors for renal involvement in HSP are not yet fully clarified. Predictive factors for nephritis, relapse and severe proteinuria appear to be older age at onset, persistent purpura and severe gut vasculitis.
- Corticosteroids lead to rapid symptomatic improvement of extrarenal symptoms, but do not influence the final prognosis, and can occasionally mask severe gastrointestinal complications.
- No therapy is suggested for cases with mild urinary abnormalities, for severe renal involvement high-dose steroids and immunosuppressive drugs are recommended.
- Atypical and incomplete Kawasaki disease (KD) is an emerging challenge for physicians attending to children, especially infants, presenting with high fever and rash. The increasing number of patients who do not develop the typical manifestations raises concerns about the sensitivity of diagnosis based upon the published clinical criteria.
- Medical history, physical examination and laboratory tests, including elevated white blood cell count, erthrocyte sedimentation rate, C-reactive protein and low hemoglobin, sodium and albumin levels, could help to rule-out illnesses that mimic KD
- Infants aged less than 6 months often display an atypical or incomplete course with persistence of inflammation leading to rapid and severe coronary damage. In newborns, the diagnosis is sometimes missed due to the lack of awareness.
- The long-term prognosis of KD has significantly improved in recent years, although coronary artery aneurysms still develop in up to 5% of patients.
- Giant aneurysms rarely regress and often become stenotic, leading to myocardial ischemia, even in early adulthood. They are a potential risk for rupture in the acute phase or later thrombosis due to stasis of blood flow, raising the problem of anticoagulation therapy in children and especially infants
- A total of 10–20% of KD children fail to respond to intravenous immunoglobulin (IVIG) and high-dose aspririn; no specific guidelines are available for the management of refractory patients in whom parameters of inflammation do not subside and fever persists or recurs. Most KD children will respond to a second IVIG infusion, although up to a third remain febrile.
- Either a third dose of IVIG (2 g/kg) or corticosteroids may be given, although patients failing to respond to a second IVIG infusion appear to be refractory to a third dose.
- The use of corticosteroids as a rescue therapy, either oral or pulsed (methylprednisolone 30 mg/kg, one to three courses), in children refractory to IVIG has been suggested as an alternative and safe treatment.
- Infliximab (Remicade®), a monoclonal antibody against tumor necrosis factor-α, proved to be effective and safe in children who were refractory to IVIG and corticosteroids and with severe coronary involvement; however, results are conflicting.
- Polyarteritis nodosa and Takayasu, although rare, must be suspected in children with fever, malaise, weight loss and elevated acute-phase reactants

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