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Clinical overview of vasculitic syndromes in the pediatric age

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Abstract. – Vasculitic syndromes comprise a heterogeneous group of disorders sharing the hystopathologic features of inflammation and necrosis in blood vessels. Their clinical expression depends on site, type and size of the involved vessels and severity of the associated inflammatory symptoms. Classification of vasculitides based on the size of the affected vessels is the most widely used in children. Many different vasculitides with indistinguishable clinical presentation have very different prognosis and treatments. Among the primary systemic non-granulomatous vasculitides of medium-sized vessels in pediatrics we have to consider Kawasaki disease and among the small-sized ones Henoch-Schönlein purpura, which is the most frequent vasculitis of the pediatric age and is characterized by vascular deposition of IgA-dominant immune complexes. Accurate diagnosis is the mainstay for the definition of the best therapeutical proposal, though therapies available result largely empirical and based on trials with limited numbers of pediatric patients.

Key Words:

Vasculitic syndromes, Pediatrics.

Introduction

Vasculitis is a pathological process involving vascular walls and being characterized by the coexistence of inflammation and necrosis. A host of biological processes can cause vasculitides, but the hystopathological patterns that can be evidenced are few. Every vessel of every district can be involved and this explains the heterogeneous clinical expression which depends on site, type and caliber of the involved vessels, as well as on the severity of the inflammatory features. Primary systemic vasculitides often present with non-specific and sometimes subclinical symptoms that make early diagnosis a real challenge requiring a systematic diagnostic multi-disciplinary work-up. There are no generally accepted diagnostic criteria for vasculitides in pediatrics and the application of classification criteria as diagnostic criteria might result misleading. The demonstration of vasculitis on biopsy is still the gold-standard for the diagnosis, whilst prognosis is directly influenced by the diagnosis of the specific vasculitic syndrome[1]. The first post-mortem description of vasculitis dates back to 1866 when Kussmaul and Maier reported the macroscopic data of a necrotizing arteritis with thickening of arterial walls transformed in cordons with distinctive nodular protrusions. Davson recognized that patients presenting hypertension and visceral infarcts had muscular artery involvement in the context of a condition now framed as "nodous polyarteritis"[2]. In addition vasculitic involvement is a well-known feature of collagen diseases starting in the pediatric age such as systemic lupus erythematosus and Sjögren syndrome. A large number of hystorical attempts of classifying vasculitic syndromes can be identified, but differentiation of vasculitides upon a strictly clinical level is hazardous due to the overlapping of many clinical signs and their tendency to evolve in time[3]. The American College of Rheumatology has codified diagnostic criteria deriving from cases with classical vasculitic diseases: their use makes possible comparisons among patients and is useful for epidemiologic purposes. In 1994 an international Consensus Conference stated some denominations to make light upon the various already existing classifications and to decrease confusion about currently used nomenclature. Primary systemic vasculitis classification according to 1994 Chapel Hill criteria upon the size of vessels and hystopathologic features of inflammation is reported in the Table I and is the most widely accepted.

The same classification has been modified in order to focus upon features related to the pediatric age and is shown in the Table II[4,5].

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Table I. Classification of primary systemic vasculitides depending on the size of the involved vessel and their hystopathological features (Chapel Hill criteria, 1994).

Size of the inflamed vessels	Granulomatous inflammation	Non-granulomatous inflammation
Large	Horton gigantocellular arteritis Takayasu arteritis	
Medium		Nodous polyarteritis Kawasaki disease Central nervous system primary vasculitis
Small	Wegener granulomatosis Chürg-Strauss syndrome	Microscopic polyangiitis Henoch-Schönlein purpura Cutaneous leukocytoclastic angiitis Essential crioglobulinemic vasculitis

Another procedure of defining vasculitic syndromes is referred to the immuno-pathogenetic mechanism: the prevailing IgA-immune complex deposits in skin or kidney can distinguish Henoch-Schönlein purpura[6]. Antibodies directed towards neutrophil granulocyte granules (known as ANCA) were discovered by Davies and Hall in 1982 in a specific subset of vasculitic syndromes characterized by granulomatous inflammation: in this group we discriminate antibodies directed towards proteinase 3 or PR3 (c-ANCA) and antibodies directed towards myeloperoxidase or MPO (p-ANCA). At a cellular level there is evidence that ANCA can stimulate both respiratory burst with oxygen reactive product release and neutrophil granulocyte degranulation[7,8].

Small-Sized Vessel Vasculitides

Diseases inserted in this group might involve arterioles, capillaries and venules. Table III illustrates all non-infectious forms of small-sized vessel vasculitides.

Table II. Classification of primary systemic vasculitides according Chapel Hill criteria modified for the pediatric age.

Large-sized vessels	Takayasu arteritis
Medium-sized vessels	Kawasaki disease
Medium and small-sized vessels	Juvenile nodous polyarteritis Wegener granulomatosis
Small-sized vessels	Henoch-Schönlein purpura
All vessels	Central nervous system primary vasculitis Behçet's disease

Henoch-Schönlein purpura, also known as "rheumatic purpura", is surely the most frequent vasculitic syndrome in the pediatric age and is characterized by purpura which is "palpable" under the fingertips and intestinal "angina" with abdominal pain or post-ischemic melena. It has the incidence peak in 5-year-aged children and has been related to respiratory way infections caused by *Streptococcus pyogenes*, vaccinations or drug administration. Skin involvement with nodular purpura involving symmetrically glutei and lower limbs, in subsequent waves, is typical because observed in 100% patients. The other main symptoms of Henoch-Schönlein purpura are abdominal pain in association with occult blood in

Table III. Classification of the non-infectious vasculitides involving small-sized vessels.

Vasculitides associated with ANCA-positivity
- Microscopic polyangiitis
- Wegener granulomatosis
- Chürg-Strauss syndrome

Immune complex vasculitides
- Henoch-Schönlein purpura
- Essential cryoglobulinemic vasculitis
- Vasculitis associated with systemic lupus erythematosus
- Vasculitis associated with Sjögren syndrome
- Vasculitis associated with rheumatoid arthritis
- Orticarioid hypocomplementemic vasculitis
- Behçet's disease
- Goodpasture syndrome
- Serum sickness
- Drug-induced vasculitis

Paraneoplastic vasculitides
- Vasculitis associated with malignant lymphoproliferative neoplasms
- Vasculitis associated with myelodysplastic syndromes
- Vasculitis induced by carcinoma

Vasculitides associated with inflammatory bowel disease

feces, enterorrhagia or intussusception risk, arthritis or arthralgias, painful angioedema of hands, feet or scrotum and glomerulonephritis of variable severity (caused by IgA-deposits, similarly to Berger nephropathy) upon which the general prognosis of the disease is depending. Skin biopsy can reveal neutrophil granulocytes in the small-sized vessels with IgA-dominant immune complexes. About half patients can display renal involvement signs, but kidney damage progression towards chronic renal insufficiency can be demonstrated only in 10-20% cases[9]. Diagnosis of this vasculitis is clinical and can be reinforced upon the checking of a normal number of platelets, normal or increased number of leukocytes, increased level of serum IgA (in 50% cases), increased complement fractions as C_3 and C_4, increased inflammatory markers and normal clotting times. American College of Rheumatology diagnostic criteria for Henoch-Schönlein purpura reported in Table IV appear rather vague and do not consent its identification without the reasonable doubt of underestimating other nosographic entities: it would be better to draw out of these criteria the age or to consider the possibility of articular and renal involvement among the diagnostic clues.

Recovery of classical Henoch-Schönlein purpura tends to be spontaneous after an alternating course which sometimes can result prolonged for many months: prognosis in the long term is inclusively good if renal involvement can be excluded by periodic urinalysis. Though guidelines for Henoch-Schönlein purpura treatment are actually lacking the consensus about non-steroidal anti-inflammatory drugs is unanimous when the disease is limited to joint involvement or when hand and foot angioedema are observed; furthermore brief periods of steroids can mitigate gastrointestinal angina. Moderate-high dose steroids (1-2 mg/kg/day) associated with cyclophosphamide (90 mg/m^2/day) or azathioprine (2 mg/kg/day) can be used when renal involvement is demonstrated[10].

Table IV. Diagnostic criteria for Henoch-Schönlein purpura from American College of Rheumatology (1990).

At least 2 among these 4:
"Palpable" purpura (Skin hemorrhagic and mildly raised lesions, which are not secondary to platelet count reduction)
Onset age inferior than 20 years
Acute abdominal pain (Pain is diffuse and gets worse after meals and sometimes is associated with hematic diarrhoea due to intestinal ischemia)
Granulocytes in the vessel wall at the skin biopsy (Skin biopsy is reserved to doubtful cases, though the confirmation of granulocytes in the vessel walls constitutes a strong diagnostic criterion)

In 50% of adulthood vasculitic syndromes ANCA-positivity can mark specifically Wegener granulomatosis, Chürg-Strauss syndrome and microscopic polyangiitis. Their clinical presentation is variable: many patients develop a vasculitic syndrome in the context of non-specific features characterized by malaise, weight loss, nocturnal sweating and fever; some more specific symptoms reflect an organic involvement determined by the necrotizing vasculitic process.

In *Wegener granulomatosis* there is a strong clinical predilection for airways and kidney: this is a necrotizing granulomatous small vessel vasculitis involving upper airways or lungs and kidneys, occurring at any age. The etiology of Wegener granulomatosis, like other primary systemic vasculitides, remains unknown: existing evidence suggests an autoimmune process characterized by neutrophils and endothelial cells as active participants and involvement of c-ANCA directed against PR3. However other concomitant factors like infections, environmental and genetic factors appear to be necessary in influencing disease susceptibility. Whereas the first publications on Wegener granulomatosis in childhood were based on case reports, some studies in recent years allow to compare clinical findings, disease course, morbidity and mortality rates for childhood and adult onset patients: Wegener granulomatosis in childhood is more frequently complicated by subglottic stenosis and nasal deformity while treatment-related morbidity and malignancies are less common compared to adults. Nose involvement is characterized by mucosal ulcerations and recurring epistaxis in consequence of a granulomatous inflammation that might determine nasal septum perforation and nasal cartilage destruction. Renal involvement can be shown by microhematuria and is described in 20% cases. Table V singles out the diagnostic features of Wegener granulomatosis defined by the American College of Rheumatology, in which c-ANCA positivity, though highly specific, has not been contemplated.

The introduction of a combined treatment with cyclophosphamide and glucocorticoids have re-

Table V. Diagnostic criteria for Wegener granulomatosis from American College of Rheumatology (1990).

At least 2 among these 4:
Mouth and nose inflammation with ulcerative features
Infitrates or nodules at the chest X-ray film
Urinalysis abnormalities (microhematuria (> 5 red blood cells per high power field) or urinary red cell casts in the sediment)
Granulomatous inflammation with fibrinoid necrosis at the biopsy (nasal mucosa, lung, kidney, skin)

sulted in a dramatic improvement of patient outcome; however commonly occurring disease relapses and risk of chronic organ damage at all ages make the long-term follow-up and the establishment of new therapeutic regimens necessary. Relapses of Wegener granulomatosis are the primary clinical problem occurring within the first 18 months of therapy and in as many as 50% patients by 5 years of follow-up. A simplified scheme for the treatment of Wegener granulomatosis using the couple cytotoxic agent-steroid is shown in the Table VI.

In the forms limited to upper airways (in which c-ANCA can result negative) only cotrimoxazole (trimethoprim at the dose of 8 mg/kg/day and sulphametoxazol at the dose of 40 mg/kg/day, both to divide in two daily doses) can be administered due to its anti-vasculitic effect[11,12].

Chürg-Strauss syndrome has been increasingly recognized during the past few decades, but remains an uncommon disease of unknown etiology that has to be differentiated from Wegener granulomatosis. The disorder had been traditionally classified as a variant of nodous polyarteritis until its updated description by Churg and Strauss in 1951. Although it shares various clinical laboratory and pathologic features with other vasculitic syndromes a distinct clinical combination makes it a separate entity. The presence of asthma, along with other allergic symptoms, peripheral or tissue eosinophilia and systemic vasculitic signs should prompt the clinician to consider this diagnosis, seek potential confirmation with a tissue biopsy and begin therapy to minimize complications or prevent permanent organ damage. In addition to asthma and peripheral eosinophilia (superior than 10%) in the period preceding the disease onset, Chürg-Strauss syndrome can frequently involve gastrointestinal tube, cardio-vascular apparatus and also peripheral sensory-motor nerves with mononeuritis due to epineural vessel inflammation. Table VII lists the diagnostic criteria for Churg-Strauss syndrome.

Typical of Chürg-Strauss syndrome is positivity for p-ANCA (directed against MPO). Its treatment has been mainly extrapolated from other vasculitides and literature addressing drug therapy for this specific syndrome is limited. Steroids are the mainstay of treatment for every phase of Churg-Strauss syndrome when rapid results are desired. Disease activity can be controlled with drugs directed towards tumour necrosis factor such as infliximab or etanercept, whilst plasmapheresis and intravenous immunoglobulins (2 g/kg) simultaneously administered in association with prednisone (1 mg/kg/day for 1 month) and cyclophosphamide (2 mg/kg/day for 6 months) might determine a stable remission. Mycophenolate mofetil, a pro-drug interfering with lymphocyte "de novo" purine synthesis (administered at the dose of 2 grams in a day) combined with prednisone has revealed to be useful in the treatment of cutaneous and neurological forms of Churg-Strauss syndrome[13-15].

Microscopic polyangiitis is very similar to Wegener granulomatosis, but inflammation is not of granulomatous type. In the pediatric age microscopic polyangiitis associated with c-ANCA positivity, specific to PR3, can manifest with systemic small vessel involvement and histological demonstration of pauci-immune necrotizing glomerulonephritis: kidneys are of-

Table VI. Most commonly used regimen to treat systemic Wegener granulomatosis.

	Cytotoxic agent	Corticosteroid
Induction therapy	*Cyclophosphamide* (2 mg/kg/day)	*Prednisolone* (1 mg/kg/day to taper weekly up to 10 mg/day mg/day in a 6-month-period)
Maintenance therapy	*Azathioprine* (2 mg/kg/day)	*Prednisolone* (5-10 mg/day)

Table VII. Diagnostic criteria for Churg-Strauss syndrome from American College of Rheumatology (1990).

At least 4 among these 7:
Asthma (Or history of wheezing or diffuse expiratory whistling sounds)
Eosinophilia > 10% on the peripheral differential white blood cell count
History of any allergy (With the exception of drug allergy)
Mononeuropathy/polyneuropathy
Lung non-fixed infiltrates (migratory or transient) at the chest X-ray film
Paranasal sinus abnormalities
Biopsy (Including arteries, arterioles or venules) showing accumulations of eosinophil granulocytes in the extravascular areas

ten involved, but naso-pharyngeal and ocular diseases appear to be much rarer. The main clinical manifestations are in a decreasing frequency influenza-like symptoms, hematuria or proteinuria, acute renal failure, pulmonary-renal syndrome, purpura and ischemic cerebral insults. Early treatment with steroids and cytotoxic agents enables a favorable prognosis of c-ANCA-associated microscopic polyangiitis in children[16]. *Essential cryoglobulinemic vasculitis* can be associated with hepatitis C virus infection, reduction of serum C_4 level, rheumatoid factor positivity and cryoglobulin deposits in the walls of small-sized vessels. There is a well-established link between cryoglobulinemia and hepatitis C virus: the same virus is believed to be the cause of cryoprotein formation and tissue deposition in skin and kidney. Moreover successful treatment of hepatitis C virus infection has resulted in the resolution of cryoglobulinemia and vasculitis. Alpha-interferon is effective in cases of hepatitis C virus infection, whilst in other cases this disease responds to non-steroidal anti-inflammatory drugs, steroids or cyclophosphamide.

Cutaneous leukocytoclastic angiitis is a vasculitic syndrome limited to thin-walled post-capillar venules in derma which is lacking of systemic signs and appears very similar to Arthus phenomenon, manifesting 7 to 21 days after the administration of drugs such as penicillins, thiazide diuretics, quinolones, propylthiouracil, allopurinol, phenytoin, hydralazine or monoclonal antibodies. The commonest presentation, irrespective of the age, is palpable purpura and the sites most commonly affected are the extremities. In 10% cases this angiitis can recur with intervals of months or years, but usually recovers with the administration of antihistaminics or non-steroidal anti-inflammatory drugs.

Behçet's disease belongs to the chapter of chronic systemic vasculitic syndromes involving vasa vasorum, described as networks of microvessels in the wall of arteries and veins of various organ systems: the disease specifically affects muco-cutaneous and ocular sites of young adults, more commonly of male sex. Inflammation of Behçet's disease has an extremely variable localization and even in the context of the same involved vessel there are different degrees of involvement which can determine a complete occlusion. This vasculitis, firstly codified by the greek ophthalmologist Adamantiades and the turkish dermatologist Behçet, is characterized by relapsing course with a prevalence varying geographically in consequence of a higher diffusion in countries along the ancient Silk Road including Italy, Greece, Turkey, Israel, Saudi Arabia, Iran, China, Korea and Japan. The classic finding in Behçet patients is the presence of recurrent muco-cutaneous ulcers: oral aphthous ulcerations are usually the initial symptom, but the triad "oral aphtae, recurrent genital ulcers, chronic uveitis" is known since Hyppocrates' era (V century B.C.) to be typical. Ocular disease can reveal itself with the involvement of anterior and/or posterior segments of the eye: the main manifestations include iridocyclitis, hypopyon, mild to moderate vitreitis, retinal vasculitis, optic disc hyperemia and macular edema. Other potential clinical signs of Behçet's disease include skin lesions, vascular, neurological and articular disease: suggestive is the recurrence of clinical signs even for a long time before a definite diagnosis can be made. Behçet's disease etiology remains still unknown, though an immuno-genetic basis is widely accepted due to the association with the HLA-B51 haplotype in many populations, which could confer a more invalidating prognosis. There is no pathognomonic laboratory test in Behçet's disease and diagnosis is based on systemic clinical findings: diagnostic criteria have been extrapolated from a 1990-study referred to 914 patients recruited from 12 centers of 7 countries (these criteria are listed in the Table VIII).

Table VIII. Diagnostic criteria for Behçet's disease.

Recurrent oral ulcers (major/minor aphtae and herpetiform ulcerations recurring at least 3 times in 1 year) plus 2 among:
Recurrent genital ulcers
Ocular lesions (Anterior or posterior uveitis, retinal vasculitis)
Skin lesions (Erythema nodosum, pseudofolliculitis, acne-like lesions in the post-adolescental age with no history of corticosteroid treatment)
Pathergy test positivity (Performed by puncturing the forearm skin with sterile needles: the early reaction must be read by the physician, appears within 24 hours, maximizes in 48 hours and is a 1-2 mm elevated lesion surrounded by a reddish area)

Among minor diagnostic features also subcutaneous thrombophlebitis, deep vein thrombosis, artery occlusion and/or aneurysm formation, epididimitis, central nervous system involvement, arthralgias or arthritides and various gastrointestinal signs can be encountered at every age. Childhood can be the onset age with typical signs such as chronic uveitis in 30% cases and much less frequently oral aphtae. Musculo-skeletal and central nervous system involvement (with chronic meningo-encephalitis, pseudotumor cerebri, spastic tetraparesis and brain strokes) have been also reported as starting clinical signs of Behçet's disease in children. Some transient forms of neonatal Behçet's disease characterized by muco-cutaneous ulcers with necrotizing aspect can be observed in sons of Behçet mothers. Therapeutic programs might appear complex because numerous specialists have to provide for the overall cure of these patients: the choice of a specific drug is dependent on the clinical picture displayed by the individual patient. In the uncomplicated forms initial therapy is represented by steroids, but the general mainstay of treatment remains immunosuppression with agents such as cyclosporin (at the dosage of 5 mg/kg/day), cyclophosphamide and chlorambucil. Prognosis of anterior uveitis is usually good, while patients with posterior lesions tend to have some degree of visual loss, even with adequate treatment[17].

Medium-Sized Vessel Vasculitides

The main visceral arteries and their branches are involved in the diseases here described.

Nodous polyarteritis is a multi-systemic necrotizing vasculitis of medium- and small-sized muscular arteries: typical is renal (in 85% cases) and visceral involvement. Lesions tend to be localized in artery bifurcations and characterized by fibrinoid necrosis of vessel walls with occlusion, thrombosis and infarction. Sometimes cicatricial fibrosis can determine aneurismal dilation until a diameter of 10 mm. Skin is involved in 50% cases with purpura, nodules, ulcerations and gangrene. In 15% cases ANCA positivity can be demonstrated, whilst 30% cases are associated with Australia antigen (HBsAg)-positivity. There are marked differences in the clinical presentation of children with nodous polyarteritis: their survival is generally better than in adults and relapses happen less frequently. In an observational study conducted above 110 children with a mean age of 9 ± 3 years with juvenile forms of nodous polyarteritis which has joined 21 reumatologic centers all over the world these following conclusions have emerged: in 30% cases there is skin or musculo-skeletal involvement, in 4.6% a classical form associated with HBsAg-positivity and predominating renal involvement, in 8.1% ANCA-positivity with elective lung or kidney involvement and in 57.2% a multi-systemic disease. Biopsy of the involved districts reveals medium-little sized artery vasculitis with necrotizing features, while angiography can otherwise reveal artery aneurysms. In the Table IX clinical criteria for nodous polyarteritis diagnosis are listed.

Table IX. Diagnostic criteria for nodous polyarteritis from American College of Rheumatology (1990).

At least 3 among these 10:
Weight loss superior than 4 kg
Livedo reticularis (Mottled reticular pattern over the skin)
Testicular pain or tenderness
Myalgia, muscular weakness or leg tenderness
Mononeuropathy/polyneuropathy
Diastolic blood pressure superior than 90 mmHg
Elevated azotemia (> 40 mg/dl) or creatininemia (> 1.5 mg/dl) (Not due to dehydration or urinary way obstruction)
Australia antigen (HBsAg) positivity in serum
Arteriographic abnormalities (Aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibro-muscular dysplasia, or other non-inflammatory causes)
Biopsy of small or medium-sized artery containing polymorphonucleate granulocytes

Drugs prevalently used in the pediatric age are corticosteroids and cyclophosphamide, but also leflunomide and mycophenolate mofetil[18].

Kawasaki disease is an acute multi-systemic vasculitic syndrome of infancy involving small and medium-sized muscular arteries with unknown pathogenesis: its greatest incidence is under 2 years of age and its frequency is 10 times higher in Japan than in other countries. We distinguish an acute phase (1st-2nd week), a subacute phase (3rd-4th week) and a phase of convalescence (4th-8th week). In addition to fever persisting for 5 days during the acute phase at least 4 clinical signs among bilateral non-purulent conjunctivitis, oropharyngitis, cervical lymph node enlargement, polymorphous skin eruption and changes in the extremities must be recognized. Conventional blood tests may be helpful, but none are diagnostic and most have low specificity: typical is an acute inflammatory response with increased erythrocyte sedimentation rate, neutrophil leucocytosis, normocytic anemia, eosinophilia, hypoalbuminemia, hypokalemia, raised levels of fibrinogen and liver transaminases. A raised platelet count (until 1,000,000/mm^3) is common in the phase of convalescence, when fever abates and skin digital desquamation or arthralgias might occur. Rarely the child can even be thrombocytopenic. Coronary lesions can develop until 6-8 weeks after the onset of fever, but the risk of acute myocardial ischemia is higher in the first 2 months. To establish the diagnosis of Kawasaki disease other disorders with similar presentation have to be excluded as staphylococcal infections (scalded skin syndrome, toxic shock syndrome), streptococcal diseases (scarlet fever, toxic shock-like syndrome), measles and other viral exanthems (rubella or infections caused by Enterovirus, Epstein-Barr virus, Cytomegalovirus, human Herpesvirus 6, Parvovirus B19), Mycoplasma, Stevens-Johnson syndrome, drug-induced adverse reactions or juvenile idiopathic arthritis. Diagnosis of Kawasaki disease remains merely clinical and diagnostic criteria are schematized in the Table X.

Heart involvement defines prognosis for Kawasaki disease. Atypical or incomplete cases are described above all in infants under the age of 1 year and these ones present the higher risk of developing cardiac sequelae[19]. Treatment of Kawasaki disease has to be started in the first 10 days since the onset and requires intravenous immunoglobulins (2 g/kg body weight in single infusion lasting 10-12 hours) and aspirin (acethylsalicilic acid, 80-100 mg/kg/day in 4 doses until the normalization of the inflammation markers, then at the anti-aggregant dosage of 3-5 mg/kg/day in single daily administration for 6-8 weeks if no permanent coronary artery abnormalities can be detected). High-dose intravenous immunoglobulins are highly effective in reducing the development and severity of coronary artery aneurysms, while benefit deriving from aspirin is confined to its analgesic and antipyretic properties. Untreated disease leads to coronary lesions in 20-40% of patients, whereas appropriate therapy with immunoglobulins and aspirin reduces the incidence of coronary lesions to less than 5%: even when treated with intravenous immunoglobulin regimens within the first 10 days of illness 5% of ill children at the least develop transient coronary artery dilation and 1% giant aneurysms[20].

Table X. Diagnostic criteria for classical Kawasaki disease.

Fever which persists for 5 (or more) days plus at least 4 of the following 5 clinical signs:
Bilateral non-purulent conjunctivitis
Polymorphous skin rash
Changes in the lips and mouth (Reddened, dry or cracked lips, strawberry-tongue, oral or pharyngeal erythema)
Changes in the extremities (Erythema of palms or soles, indurative edema of hands or feet, skin desquamation of hands, feet and perineum)
Acute cervical lymph node enlargement (With a diameter superior than 1 cm)

Central nervous system primary vasculitis is a heterogeneous disease manifesting as a distinct entity or as part of other systemic diseases such as systemic lupus erythematosus and nodous polyarteritis. It is a rare disorder in children and can be associated with cerebrospinal fluid neutrophil pleiocytosis. Central nervous system angiography, even if not characterized by largely accepted sensitivity or specificity, is usually performed in these children, whilst encephalic biopsy can be required in few selected cases for a definite diagnosis[21].

Large-Sized Vessel Vasculitides

This group includes inflammatory diseases concerning the aorta and its major branches. *Takayasu arteritis* or "pulseless disease" is a

rare non-specific inflammatory process of unknown etiology with an unpredictable course that may lead to vessel stenosis or occlusion, mostly reported in females and more frequently observed in Eastern countries. The disease begins at an age comprised between 15 and 30 years, being associated with non-specific signs such as malaise, fever, nocturnal sweating, weight loss, arthralgias as well as acute inflammatory parameter increase and anemia. Aortic arch vessels might present obliterative phenomena and generate the absence of pulses at the upper limbs or non-measurable blood pressure, transient strokes related to carotid or vertebro-basilar arterial systems, dysarthria, visual abnormalities, acquired coarctation, nephro-vascular hypertension, heart failure or pulmonary hypertension. Aorta angiography is extremely useful in the diagnostic interpretation of these patients as shown in the Table XI.

Table XI. Diagnostic criteria for Takayasu arteritis from American College of Rheumatology (1990).

At least 3 among these 6:
Onset age inferior than 40 years
"Claudicatio" of the limbs (Development and worsening of fatigue and discomfort in muscles of extremities during exercise, especially the upper extremities)
Decreased brachial artery pulse
Systolic blood pressure difference superior than 10 mmHg between arms
Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
Arteriogram abnormalities (Narrowing or occlusion of the entire aorta, its primary branches or large arteries in the proximal upper or lower extremities not due to arteriosclerosis, fibro-muscular dysplasia or other non-inflammatory causes)

No drug can fully prevent complications caused by Takayasu arteritis. In the acute phase steroids show rapid efficacy, but have to be tapered until the control of symptoms; in the steroid-resistant forms cyclophosphamide (at the dosage of 2 mg/kg/day) or methotrexate, mycophenolate mofetil, azathioprine, high-dose intravenous immunoglobulins and tumour necrosis factor-alpha inhibitors can be introduced. Sometimes the surgical correction of vascular occlusions becomes unavoidable with revascularization surgery, endoarterectomy and angioplastic procedures[22].

Horton temporal arteritis, also known as "gigantocellular arteritis", is a panarteritis involving the mid-size and large arteries originating from the aortic arch, in particular the temporal surface artery. The disease can be observed in the elderly, particularly females, and can be manifest with variable symptoms such as cephalea, fever, visual disorders even leading to blindness, jaw claudication or widespread myalgias. Temporal arteritis is closely related to "polymyalgia rheumatica", which consists of morning stiffness occurring in the neck region or in the shoulder, lasting more than 1 month, exacerbated by movement and spreading to elbows, that is rarely observed in pediatrics. Treatment of this form of arteritis is based on the use of moderate-high doses of steroids over a long period of time[23,24].

In conclusion, it can be assumed that diagnosis of vasculitic syndromes can derive from the integration of clinical and laboratoristic data, both positive and negative, among which we have to consider renal function, IgA, ANCA, anti-nuclear antibodies, rheumatoid factor, complement fractions (C_3, C_4), cryoglobulins, serology for hepatitis B and hepatitis C, occult blood search in the feces, evalutation for eventual hematuria or proteinuria, paranasal sinus and thorax radiography or computed tomography, nervous conduction study and – lastly – biopsy of one of the involved district such as skin, muscle, nerves, lung and kidney[25]. With the greater understanding of the pathogenetic mechanisms involved in the vasculitic process it will hopefully become possible to develop much more focused therapies for these everchanging and life-threatening disorders with the aim of decreasing long-term morbidity and mortality as well as drug-induced adverse effects.

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