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VASCULITIS IN CHILDREN

Shaima Muidh Asiri [1*], Naeem Salahuddin Mullaniazee [2], Ahmed Saeed Banheem [2], Humoud Mansour Alkhalaf [3], Hussain Saleh Aljawad [4], Malak Jehad Alali [5], Nawaf Mesaad Bahatheq [6], Amani Omar Al Sharif [7], Mohammed Khaled Alanazi [8], Abdullah Ahmed Hussain [9], Mohammed Talal Kheyami [10], Jumanah Talal Al-Malki [11]

[1] Department of Pediatric, East Jeddah General Hospital, Jeddah, Saudi Arabia, [2] Department of Pediatric, King Abdullah Medical Complex, Jeddah, Saudi Arabia, [3] College of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland, [4] College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, [5] College of Medicine, King Faisal University, Hofuf, Saudi Arabia, [6] College of Medicine, King Saud bin Abdul Aziz University for Health Sciences, Riyadh, Saudi Arabia, [7] Department of Pediatric, King Fahad Hospital, Jeddah, Saudi Arabia, [8] College of Medicine, Majmaah University, Al Majmaah, Saudi Arabia, [9] College of Medicine, Kind Abdulaziz University, Jeddah, Saudi Arabia, [10] Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, [11] College of Medicine, Taif University, Taif, Saudi Arabia

Abstract:

Vasculitis is a vascular disorder characterized by inflammation of the blood vessels' wall either as primary process or secondary to a systemic disorder. Though rare in paediatric age group, vasculitis may have a devastating and even fatal course. Vasculitides present with a wide range of clinical manifestation in childhood and they require a high index of suspicion for diagnosis. Vasculitis can be classified according to their clinical presentation, the size and location of the blood vessels affected, and histopathological patterns. Henoch- Schönlein purpura and Kawasaki disease are the two most common types of vasculitis occurring in children. Less common types include Takayasu arteritis, polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis, and others. Diagnosis of vasculitis is based on clinical, laboratory, and imaging features that should be collaborated to fulfil the established criteria for each form of the disease. Management depends on the stage of the disease (active disease, relapse, remission, or refractory disease) and should be tailored to each particular patient and each specific type of vasculitides. The aim of this article is to review the classification, clinical presentation, diagnosis, and management of different types of vasculitis in children.

Keywords: Children, classification, clinical manifestations, epidemiology, management, paediatric, vasculitis.

Corresponding author:

Dr. Shaima Muidh Asiri

Department of Pediatric, East Jeddah General Hospital,
Jeddah, Saudi Arabia
Phone (or Mobile) No.: +966556647919
Email: shimo-19@hotmail.com

QR code

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INTRODUCTION:

Vasculitis is a vascular disorder characterized by inflammation of the blood vessels' wall either as primary process or secondary to a systemic disorder1. Vasculitis can affect individuals at various age groups and may present with a wide variety of clinical manifestations according to the size, location, and type of blood vessel affected2,3. Vasculitis is rare in paediatric age group. However, the clinical presentation and progression of some forms of vasculitis in children may be devastating and even fatal4.

Vasculitis was reported to affect approximately 12 – 53.3 per 100,000 children below the age of 17 years5,6. Henoch- Schönlein purpura (also known as immunoglobulin A vasculitis) is by far the most common type of vasculitis reported in paediatric age group, with a mean annual incidence of 10.2 to 20.4 cases per 100,000 children. The second most common type is Kawasaki disease with an estimated annual incidence ranging between 1.6 to 5.5 cases per 100,000 children. Other types of vasculitis (such as Wegener's granulomatosis, polyarteritis nodosa, Takayasu arteritis, primary central nervous angiitis) are less common, and Churg-Straus disease is very rare5,6.

The aim of this article is to review the classification, clinical presentation, diagnosis, and management of different types of vasculitis in children.

CLASSIFICATION AND CLINICAL PRESENTATION OF VASCULITIS IN CHILDREN:

Vasculitis can occur as a primary disease or secondary to an underlying systemic illness. Primary vasculitides have many classification systems. They can be classified according to the size of the blood vessel involved (most common presentation), the clinical presentations, the etiology, or the histopathological patterns of vascular wall involvement. Secondary vasculitis may occur due to an underlying wide range of diseases such as infections (e.g. hepatitis B and C, varicella, human immunodeficiency virus (HIV), connective tissue diseases (e.g. sarcoidosis, systemic lupus erythematosus, inflammatory bowel disease, or dermatomyositis), or drugs (e.g. antithyroid medications and leflunomide)1.

The most common currently used classification of vasculitis is the Chapel Hill Consensus Conference (CHCC) that was established in 1994 and updated in 20137. According to the 2013 revised CHCC classification, vasculitis is categorized into small vessel, medium vessel, large vessel vasculitis, variable-vessel vasculitis, and single-organ vasculitis. The small-vessel vasculitis is further classified into immune complex vasculitis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The detailed 2013 revised CHCC classification of vasculitis is depicted in table 1.

Because the CHCC classification was mainly concerned with and focusing about vasculitis in adults, a new classification was developed by the European League against Rheumatism (EULAR) and the Pediatric Rheumatology European Society (PRES) for classification of vasculitis in children below the age of 18 years8. This classification is demonstrated in table 2. The EULAR/PRES takes into consideration more types of vasculitis that are specifically common among pediatric age group.

Henoch-Schönlein purpura (immunoglobulin A (IgA) vasculitis)

Henoch-Schönlein purpura (also referred to IgA vasculitis) is the most common vasculitis in children. It is characterized by an immune-mediated inflammation of the small-sized blood vessels and deposition of immunoglobin A (IgA) antibodies. Clinically, the disease manifests with palpable purpura or cutaneous petechiae that cluster in crops, associated with arthritis, arthralgia, renal dysfunction (e.g. proteinuria, hematuria, or red blood cells casts), diffuse abdominal pain, proliferative glomerulonephritis, or leukocytoclastic vasculitis. Biopsy is the definite diagnostic modality for Henoch-Schönlein purpura. The histopathological finding of IgA deposition is confirmatory to the diagnosis9.

Kawasaki disease

Kawasaki disease is the second most common type of vasculitis in children. It implies acute inflammation of the medium sized blood vessels in various locations. Clinically, it presents with acute fever for at least five days associated with bilateral conjunctival injection, cervical lymphadenopathy, injected oral mucosa, polymorphous exanthema, palms and feet erythema, and perineal edema and erythema. The cervical lymphadenopathy should be documented by the presence of at least one enlarged lymph node larger than 1.5 centimeters in maximum diameter. The involvement of oral mucosa appears in the form of strawberry tongue, erythematous pharynx, and fissured injected lips. Cutaneous affection occurs in the form of hand and feet edema

and erythema during the acute phase and desquamation during the convalescent phase. Kawasaki disease is usually self-limited, and it predominantly affects infants and young children10.

Takayasu arteritis

Takayasu arteritis is the only type of large-vessel vasculitis that occur in childhood. It is characterized by insidious progressive granulomatous inflammatory changes affecting large-sized vessels particularly the pulmonary arteries, the aorta and its branches. The ongoing insidious inflammation results, on the long term, into stenosis, stricture formation, occlusion, development of secondary aneurysms, and subsequent thrombosis and thromboembolism. Clinically, major vessel stenosis or occlusion manifests as unequal radial pulses, reduced pulse force and volume, hypertension, unequal blood pressure on both arms (the cut-off value is 10 mmHg differences between both limbs), and auscultatory bruit over the affected large vessels. On laboratory investigation, raised acute phase reactants is demonstrated. Diagnosis can be confirmed by angiographic studies (e.g. computed tomography angiography (CTA), magnetic resonance angiography (MRA), or conventional angiography) demonstrating stenosis of one or more of these vessels11.

Polyarteritis nodosa (macroscopic polyarteritis)

Polyarteritis nodosa (also known as classic polyarteritis nodosa or microscopic polyarteritis) is the second most common medium-sized vessel disease occurring in children after Kawasaki disease. It is characterized by systemic wide-spread necrotizing inflammation affecting medium as well as small-sized blood vessels12. Clinically, it starts with a prodrome of fever, generalized fatigue, and malaise, and presents later on with multi-system involvement affecting skin, kidneys, peripheral nerves, musculoskeletal, and vascular system. Cutaneous manifestations include cutaneous infarctions, livedo reticularis, or tender subcutaneous nodules. Renal affection manifests as reduction of glomerular filtration rate, haematuria, proteinuria, or even red blood cells casts in urine. Sensory, motor, or sensory motor peripheral neuropathy may occur, and mononeuritis multiplex is a common neurological deficit in polyarteritis nodosa in children. Hypertension is also common due to stenosis of affected blood vessels13. Confirmation of diagnosis is made by either a biopsy that demonstrated necrotizing medium and/or small vessel vasculitis or angiographic imaging showing stenosis, occlusion, or aneurysmal formation12. Polyarteritis nodosa have two distinct forms during childhood: infantile polyarteritis nodosa and cutaneous polyarteritis nodosa. The infantile form is a grave form of the disease that predominantly occur in infants or children below the age of two years, and it presents with severe cardiovascular and neurological deficits14. The cutaneous form, on the other hand, is less severe and restricted to cutaneous and musculoskeletal systems15.

Churg-Strauss syndrome (Eosinophilic granulomatosis with polyangiitis)

Churg-Strauss syndrome is a granulomatous small-sized vasculitis that rarely presents in childhood. It is characterized by the presence of bronchial asthma, eosinophilia on peripheral blood films, and positive antineutrophilic cytoplasmic antibodies (ANCA) directed against both myeloperoxidase and proteinase 3. Churg-Strauss disease is also referred to as allergic granulomatosis and angiitis or eosinophilic granulomatosis with polyangiitis16.

Wegener's granulomatosis (granulomatosis with polyangiitis)

Wegener's granulomatosis is another rare form of childhood vasculitis characterized by granulomatous inflammation of small- and medium-sized blood vessels, and has a special predilection lungs and kidneys' vessels. As Churg-Strauss disease, Wegner's granulomatosis is associated with the presence of antineutrophil cytoplasmic antibodies (ANCA), but it is directed specifically against proteinase 3 only17. Clinically, it presents with manifestations of respiratory and renal manifestations such as recurrent haemoptysis, haematuria, proteinuria, or red blood casts in urine. Diagnosis requires chest radiography (e.g. Chest X-ray or computer tomography (CT)) demonstrating cavitary lesions, nodules, or inflammatory infiltrates, endoscopic interventions showing stenosis of the larynx, trachea, and/or bronchi, and laboratory studies revealing positive cANCA. A biopsy showing granulomatous infiltration or necrotizing pauci-immune glomerulonephritis is diagnostic18.

Microscopic polyangiitis

Microscopic polyangiitis is a small-vessel non-granulomatous vasculitis characterized by the presence of antineutrophil cytoplasmic antibodies (ANCA), but it is directed specifically against myeloperoxidase. It is similar to polyarteritis nodosa (or macroscopic polyangiitis) but has a more aggressive and more specific involvement of the renal vasculature. It usually present with rapidly progressive focal segmental glomerulonephritis with

or without pulmonary manifestations (e.g. hemoptysis).

Primary central nervous system angiitis

Primary angiitis of the central nervous system (also referred to as isolated central nervous system vasculitis) is a rare type of vasculitis that affects the central nervous system only. It presents clinically with recurrent focal neurological deficits such as hemiparesis, sensory dysfunction, cranial nerves palsy, seizures, or disturbed consciousness. To date, no reliable diagnostic criteria were established for diagnosis of primary angiitis of the central nervous system. Diagnosis is usually made by clinical suspicion, exclusion of other diagnoses, and magnetic resonance cerebral angiography demonstrating small and medium-sized vessel stenosis or occlusion19.

Behçet's syndrome

Behçet's syndrome is a wide-spread multisystemic inflammatory disease affecting the small and medium-sized blood vessels particularly in the central nervous system, eyes, cutaneous, mucosal, joints, and gastrointestinal systems. It manifests as recurrent oral ulcers, recurrent genital ulcers, arthritis, pustular skin eruptions, erythema nodosum, and neurological deficits. Diagnosis of Behçet's syndrome is made on a clinical basis, even though, positive pathergy test and a biopsy from active oral or genital lesion may help confirmation of the diagnosis20.

Cogan's syndrome

Cogan's syndrome is another rare form of vasculitis that primarily affects the eyes and the inner ears. It presents with insidious progressive diminution of vision associated with interstitial painful keratitis, insidious progressive tinnitus, vertigo, and sensorineural hearing loss. Systemic manifestations may also occur such as malaise, muscle cramps, headache, abdominal pains, and diarrhea21.

DIAGNOSIS OF VASCULITIS IN CHILDREN:

As aforementioned, vasculitis can present with a wide variety of clinical manifestations involving several systems. Therefore, the diagnosis of these cases presents a challenge to many physicians. Diagnosis of vasculitis depends, to a large degree, on the clinical manifestations of the disease and the existence of clinical and laboratory criteria that fulfils the diagnosis of a suspected disease22. If vasculitis is suspected, secondary causes should be excluded first. The patient's drug history should be revised to exclude the intake of medications that may result in vasculitis such as antithyroid medications, tumour necrosis factor inhibitors, leflunomide, and minocycline. An infectious aetiology is then to be searched such as group A streptococcal bacterial infection, hepatis B and C, human immunodeficiency virus (HIV), varicella, herpes zoster, Epstein-Barr virus, parvovirus B19, syphilis, tuberculosis, typhus, and others. Malignancies (e.g. leukaemia and lymphoma) and connective tissue diseases (e.g. systemic lupus erythematosus, dermatomyositis, inflammatory bowel disease, rheumatoid arthritis, and Goodpasture's disease) should also be excluded22–24.

After exclusion of secondary causes of vasculitis, a thorough history taking and full physical examination should be carried out to limit the differential diagnosis of the disease to specific types of vasculitis depending on their diagnostic criteria. The following investigations should then be made to support or negate the suspected differential diagnoses:

Laboratory studies

Though no specific lab test is diagnostic for any type of vasculitis, many tests may support the diagnosis of vasculitis. For instance, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive proteins (CRP), anaemia, and elevated white blood cells are indicators of inflammation25,26. Thrombocytopenia may exist in children with Henoch-Schönlein purpura, and eosinophilia occurs in patients with Churg-Strauss syndrome). Urine analysis may reveal haematuria or red blood cells casts as an indicator for renal involvement. More specific tests include plasma von Willebrand factor (CWF) and gamma-globulins which are elevated during endothelial injury and antineutrophilic cytoplasmic antibodies (ANCA) which are elevated in Churg-Strauss disease, Wegner's granulomatosis, and microscopic polyangiitis27. Laboratory tests are also essential to exclude secondary vasculitis such as elevated antinuclear antibodies (ANA) in systemic lupus erythematosus, low complement level in cryoglobulinemia, and raised anti-glomerular basement membrane protein (GBM) proteins in pulmonary renal syndrome22.

Imaging studies

Imaging of different systems may be also essential for making the diagnosis of vasculitis in children. Pulmonary involvement can be demonstrated as pulmonary nodules, cavitary lesions, or persistent

infiltrates on plain chest X-rays or computed tomography (CT). Bronchoalveolar lavage, bronchoscopy, and pulmonary function tests may also be required16–18,22. Echocardiography can demonstrate structural and functional cardiac abnormalities secondary to vasculitis. Angiographic studies (such as CTA, MRA, or conventional angiography) are usually required, and sometimes mandatory, to diagnose vascular involvement such as stenosis, occlusion, or aneurysmal formation11,12,20,22. CT or MRI brain, nasal sinuses, orbits, and/or ears may also be needed for assessment of involvement of these organs19,21,25.

Tissue biopsy

Biopsy is usually the gold standard or definitive diagnostic modality for the vast majority of vasculitides. The biopsy may be taken from any affected organ such as skin (in Henoch-Schönlein purpura), lymph nodes (in Kawasaki disease), lung (in Wegner's granulomatosis), kidneys (in microscopic polyangiitis), or even brain (in primary angiitis of the central nervous system)9–12.

MANAGEMENT:

Management of vasculitis in children requires appropriate diagnosis and assessment of the disease activity. Vasculitis usually presents with a relapsing and remitting course of disease activity. Treatment of the disease during the active state is different from that to be administered during disease remission26,28. Disease is considered active either during the first presentation, the development of a new relapse, or diseases with refractory courses. Activity is usually determined by a combination of clinical, laboratory, and imaging assessment. Clinical activity implies the evolution of new manifestations, laboratory activity is detected by the elevation of certain lab markers such as ESR or CRP, and radiological activity is considered when new lesions occur in the affected organs29–31.

During disease activity, induction therapy is usually initiated to suppress the active inflammatory phase of the disease and to induce long-term remission32,33. Once remission occurs, maintenance treatment is given to protect the patient against future relapses. The most common medications used for treatment of vasculitis in children include glucocorticoids (both oral and parenteral), non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressive medications (such as cyclophosphamide, rituximab, methotrexate, azathioprine, tocilizumab and others), and antihistamines25,32,34–36. The treatment plan should be tailored to each patient and particular type of vasculitides. Also, the benefits and risks of treatment should be weighed because many of the immunosuppressive medications used for treatment of vasculitis have serious adverse evets. For instance, patients with Kawasaki disease and Henoch-Schönlein purpura may not be offered aggressive therapy because the diseases are known to be self-limited9,10. In contrast, chronic forms of vasculitis such as microscopic polyangiitis, Wegner's granulomatosis, and Churg's Strauss syndrome should be treated promptly and aggressively for induction of remission and prevention of relapses12,16,17,19. Vasculitis with simple cutaneous manifestations such as cutaneous polyarteritis nodosa may only require supportive measures to treat the skin manifestations15.

CONCLUSION:

Vasculitis is rare in children and they constitute a challenge in diagnosis. Vasculitides present with a wide range of clinical manifestation in childhood and they require a high index of suspicion for diagnosis. Vasculitis can be classified according to their clinical presentation, the size and location of the blood vessels affected, and histopathological patterns. The most common two types of vasculitides occurring in children are Henoch-Schönlein purpura and Kawasaki disease. Less common types include Takayasu arteritis, polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, microscopic polyangiitis, and others. Diagnosis of vasculitis is based on clinical, laboratory, and imaging features that should be collaborated to fulfil the established criteria for each form of the disease. Management depends on the stage of the disease (active disease, relapse, remission, or refractory disease) and should be tailored to each particular patient and each specific type of vasculitides.

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TABLES

Table 1: The revised 2013 CHC classification of vasculitis[7].

Vasculitis type	Examples
Large vessel vasculitis	▪ Giant cell (temporal) arteritis ▪ Takayasu arteritis
Medium vessel vasculitis	▪ Polyarteritis nodosa ▪ Kawasaki disease
Small vessel vasculitis	
- **ANCA- associated**	▪ Microscopic polyangiitis ▪ Granulomatosis with polyangiitis (Wegener's granulomatosis) ▪ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- **Immune-complex**	▪ Anti-glomerular basement membrane disease ▪ Cryoglobulinemic vasculitis ▪ IgA vasculitis (Henoch-Schönlein purpura) ▪ Hypocomplementemic urticarial vasculitis
Variable-vessel vasculitis	
Behçet's syndrome	
Cogan's syndrome	
Single-organ vasculitis	
Vasculitis associated with a systemic disease	
Vasculitis associated with probable aetiology	

Table 2: the EULAR/PRES classification of childhood vasculitis[8].

Type of vasculitis	Examples
Predominately large vessel	▪ Takayasu arteritis
Predominately medium-sized vessel	▪ Childhood polyarteritis nodosa ▪ Cutaneous polyarteritis nodosa ▪ Kawasaki disease
Predominately small vessel	
- Granulomatous	▪ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) ▪ Granulomatosis with polyangiitis (Wegener's)
- Non-granulomatous	▪ Microscopic polyangiitis ▪ IgA vasculitis (Henoch-Schönlein purpura) ▪ Isolated cutaneous leukocytoclastic vasculitis ▪ Hypocomplementemic urticarial vasculitis
Other vasculitides	▪ Behçet's syndrome ▪ Secondary vasculitides due to infection, malignancy, or drugs, including hypersensitivity vasculitis ▪ Isolated vasculitis of the central nervous system ▪ Cogan's syndrome ▪ Unclassified