

Review Articles

Childhood Vasculitis - An Update

MOHAMMAD IMNUL ISLAM¹, MANIK KUMAR TALUKDAR¹, SHAHANAAKHTER RAHMAN²

Introduction:

Vasculitis may be defined as the inflammation involving the blood vessel wall. Most types of vasculitis in children are rare, with the exception of Henoch-Schonlein purpura(HSP) and Kawasaki disease.¹ Vasculitis can involve vessels of any size and can affect any organ system. The clinical presentation varies according to the histological type, the size of the involved blood vessel segment and the distribution of the involved vessels.² This blood vessels inflammation may lead to tissue injury from vascular stenosis, occlusion, aneurysm, or rupture.³ New classification criteria for childhood vasculitis have recently been proposed and validation process is also completed.

Infectious triggers are still implicated in the aetiopathogenesis of Kawasaki disease and Henoch-Schonlein purpura. Several genetic polymorphism in vasculitides have now been described that may be relevant in terms of disease predisposition or development of disease complications⁴. The purpose of this review is to provide an update on the new developments in paediatric vasculitis, focusing on a new proposal for childhood vasculitis classification criteria.

Epidemiology:

In an English survey of family clinicians, the estimated overall annual incidence of new cases of vasculitis was 53.3 per 100,000 children under 17 years of age. The two most common vasculitides were Henoch-Schonlein purpura (HSP) and Kawasaki disease, with estimated annual incidences of 20.4 and 5.5 per 100,000 in children less than 17 years of age, respectively.⁵ The Pediatric Rheumatology Database Group reported that 3.3% of children followed at 26 pediatric rheumatology referral centers in the United States carried a diagnosis of vasculitis between 1992 and 1995. This result probably represents an underestimate, because children with HSP or

Kawasaki disease are often treated by paediatricians and not referred to specialty care center.⁶

New International Classification of Childhood Vasculitis:

An international consensus conference held in Vienna in June 2005 under the auspices of the European League against Rheumatism(EULAR) and Paediatric Rheumatology European Society (PReS) resulted in a new proposal for childhood vasculitis classification. As because, paediatric diseases were only considered in that proposal, giant cell arteritis was omitted. Another group of vasculitides, which includes vasculitic disorder that did not fit into any category or fit more than one, was defined.⁷ The proposed classification of childhood vasculitis is given below.

Table-I

New classification of childhood vasculitis⁷

-
- I. Predominantly large vessel vasculitis
 - Takayasu arteritis(TA)
 - II. Predominantly medium sized vessel vasculitis
 - Childhood polyarteritis nodosa(PAN)
 - Cutaneous polyarteritis
 - Kawasaki disease(KD)
 - III. Predominantly small vessels vasculitis
 - (A) GRANULOMATOUS
 - Wegener's granulomatosis (WG)
 - Churg-Strauss syndrome
 - (B) NON-GRANULOMATOUS
 - Microscopic polyangiitis
 - Henoch-Scho'nlein purpura
 - Isolated cutaneous leucocytoclastic vasculitis
 - Hypocomplementic urticarial vasculitis
 - IV Other vasculitides
 - Behcet disease
 - Vasculitis secondary to infection (including hepatitis B associated polyarteritis nodosa), malignancies, and drugs, including
 - hypersensitivity vasculitis
 - Vasculitis associated with connective tissue diseases
 - Isolated vasculitis of the central nervous system
 - Cogan syndrome
 - Unclassified
-

1. Assistant Professor, Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh

2. Professor, Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka-1000, Bangladesh

Correspondence: Dr. Mohammad Imnul Islam.

The proposed classification criteria for paediatric vasculitides were mainly based on a literature review and a consensus based process and were not formally validated. The project was divided into two phases. In the first phase the Delphi technique was used to gather opinions from a wide range of paediatric rheumatologists and nephrologists.⁸ They completed a four page email survey in which they were asked to choose the best working general classification for vasculitis observed in children between the criteria suggested by the CHCC (Chapel Hill Classification criteria)⁷, a modification of this for children, a modification of the Fink classification criteria⁹ and also from Lie classification criteria.¹⁰

The criteria that were reviewed by this process included those of the ACR for Henoch-Schonlein purpura (HSP)¹¹, Takayasu arteritis (TA)¹², Wegener's granulomatosis (WG)¹³ and Polyarteritis nodosa (PAN)¹⁴ as well as the Japan KD research committee¹⁵ and American Heart Association (AHA) criteria for Kawasaki disease (KD)¹⁶ and the childhood PAN criteria of Brogan et al.¹⁷

The second phase involved a consensus conference using NGT (Nominal group technique). Ten international experts, all are paediatricians, from nine different countries met for the consensus conference. Final consensus was based on previous survey data, the literature, clinical and scientific expertise via a round robin guided discussion with agreement of at least 80% of the participants was defined as consensus. Final criteria were developed to classify a child as HSP, KD, childhood PAN, WG, or TA, with changes introduced based on paediatric experience. Mandatory criteria were suggested for all diseases except WG.⁷

Validation of the EULAR/ PReS criteria for the classification of childhood vasculitides:

With support from the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trial Organization (PRINTO) and Paediatric Rheumatology

European Society (PReS), PRINTO/PReS established a formal statistical validation process with a large scale data collection that culminated in the final 2008 Ankara Consensus Conference.¹⁸ After obtaining consent from parents/child and ethics committee approval, 97

PRINTO/PReS institutions in 36 countries enrolled children with selected vasculitides, into a three step study. In step 1 web based data collection was completed after fulfilling the inclusion criteria. The rarest form of vasculitis

(cryoglobulinaemic vasculitis, Churg-Strauss syndrome) were excluded because of their low prevalence while Kawasaki disease was excluded because it was under evaluation by another paediatric group. In step 2 a blinded classification using Delphi technique was done by a panel of paediatric rheumatologist/nephrologists. In step -3, an NGT (Nominal group technique) consensus conference was held in Ankara in 2008 to discuss the statistical performance of clinical / laboratory findings and of different classification criteria for HSP, c-PAN, c-TA, c-WG.¹⁹

Classification criteria for (individual) Childhood Vasculitides

In relation to the classification criteria for separate categories of childhood vasculitis disease, five major disorders were selected for specific attention. These were Henoch-Schonlein purpura, Kawasaki disease, Takayasu arteritis, Wegener's granulomatosis and Polyarteritis nodosa. In addition to polyarteritis nodosa, two distinct additional categories were considered, namely cutaneous polyarteritis and microscopic polyangitis⁷.

Henoch-Schonlein purpura

The major change in the criteria was to make palpable purpura a mandatory criterion, as it has been shown to improve the specificity of the criteria significantly when compared in an international study of patients with PAN.²⁰ The consensus panel chose histopathology showing typically leucocytoclastic vasculitis predominant with IgA deposit or proliferative Glomerulonephritis with predominant IgA deposit for all doubtful cases such as for purpura with atypical characteristics or distribution. Addition of arthritis and renal involvement to the group of criteria was also suggested. The final HSP definition had greater sensitivity than the 2005 EULAR endorsed criteria. The sensitivity and specificity of the final HSP (EULAR/PRINTO/PReS) classification definition was 100% and 87% respectively.¹⁹

Table-II

*Classification criteria for Henoch-Schonlein purpura*¹⁹

(Mandatory criterion)- Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance and at least one of four following criteria:

Diffuse abdominal pain

- Histopathology –leucocytoclastic vasculitis predominant with Ig A deposit or proliferative Glomerulonephritis with predominant with Ig A deposit
- Arthritis or arthralgia
- Renal involvement (any haematuria and/or proteinuria)

Kawasaki Disease (KD):

The Japanese classification for KD requires the presence of five of the following six criteria: characteristic fever, bilateral conjunctivitis, changes of lips and oral cavity, polymorphous exanthema, changes of peripheral extremities, and cervical

lymphadenopathy.¹⁵ The American classification differs in that fever plus four of the remaining five criteria are required.¹⁶ This American classification format was adopted as the basis of the present classification criteria. Because of the importance of coronary artery disease, as pointed out in the fifth revised edition of the Japan Kawasaki disease research committee guidelines¹⁵ and the American Heart Association (AHA) diagnostic guidelines,¹⁶ children with typical echocardiographic changes could be classified as having KD without fulfilling four of the remaining criteria.

Table-III

*Classification Criteria for Kawasaki Disease*⁷

Fever persisting for at least five days (mandatory criterion) plus four of the following five features:

- Changes in peripheral extremities or perineal area Polymorphous exanthema
- Bilateral conjunctival injection
- Changes of lips and oral cavity: injection of oral and pharyngeal mucosa
- Cervical lymphadenopathy

In the presence of coronary artery involvement (detected on echocardiography) and fever, fewer than four of the remaining five criteria are sufficient.

Childhood Polyarteritis Nodosa (c-PAN):

For the diagnosis of c-PAN, histopathological and angiographic findings are crucial and for this reason this combined criterion was mandatory in the 2005 EULAR/PRES criteria.⁷ The major change to the original c-PAN criteria was the removal of the criteria for the signs and symptoms for vasculitis in specific organ systems and testicular pain or tenderness. This change led to an increase of the sensitivity and to a simplification of the final criteria. The sensitivity and specificity of the final EULAR/PRINTO/PRES c-PAN classification definition was 89.6% and 99.6% respectively, with compared with 86.3% and 99.6% of the preliminary EULAR c-PAN proposal.¹⁹

Table-IV

Classification Criteria for Childhood Polyarteritis Nodosa

A systemic inflammatory disease characterised by histopathology – evidence of necrotising vasculitis in small and mid-size arteries

OR

Angiographic abnormalities: aneurysms, stenosis or occlusions (mandatory criteria), plus one of the five following criteria :

- Skin involvement (livedo reticularis, tender subcutaneous nodules, superficial and deep skin infarction, distal phalanx or other peripheral tissue - necrosis /gangrene)
- Myalgia or muscle tenderness
- Systemic hypertension (>95th centile for height)
- Peripheral neuropathy
- Renal involvement (proteinuria, haematuria, impaired renal function < 50% normal)

Childhood Wegener’s Granulomatosis (c-WG):

The ACR criteria requires the presence of two of the following four features for classification as WG: nasal-oral inflammation, abnormal chest x ray, abnormal urinalysis, and granulomatous inflammation on biopsy.¹³ For childhood WG (c-WG) the main differences from the ACR criteria were the addition of chest CT scan results, the inclusion of ANCA positivity and more specific items for upper and lower respiratory involvement. Very minor changes were made to the original 2005 EULAR/PRES c-WG that includes any detected ANCA (immunofluorescence/MPO/PR3) as a positive finding. The sensitivity and specificity of the

final 2009 EULAR/PRINTO/PRES classification definition were 93.3% and 99.2% respectively, compared with 88% and 100% for the preliminary EULAR c-WG proposal.¹⁹

Table-V

*Classification Criteria for Wegener's Granulomatosis*¹⁹

Three of the following six features should be present:

- Histopathology: Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area
- Upper airway involvement
- Laryngo-tracheo-bronchial stenosis
- Pulmonary involvement (nodules, cavities or fixed infiltrates in chest x-ray or CT)
- ANCA positivity'
- Renal involvement *

*Haematuria and/or significant proteinuria.

If a kidney biopsy is done it characteristically shows necrotising pauci-immune glomerulonephritis.

Childhood Takayasu arteritis (c-TA):

For childhood-TA (c-TA), angiographic findings are crucial in the diagnosis and thus this criterion had already been defined as mandatory in the 2005 EULAR/PRES c-TA criteria.⁷ This study also considered more recent imaging modalities, such as CT or MRI, which were not considered at the time the ACR criteria were published. Other differences from the ACR were the combination of pulse deficit and claudication, which were both very frequent (75%) and highly specific, the addition of hypertension (more frequent than in the other c-vasculitides) and the removal of the age limit criterion.²¹

Table-VI

Classification criteria for Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or MR) of the aorta or its main branches showing aneurism/dilatation (mandatory criterion), plus at least one of the following five features:

- Pulse deficit or claudication
- Four limb blood pressure discrepancy
- Bruits
- Hypertension
- Acute phase reactant (ESR > 20 mm in 1st hr or CRP value above normal)

Treatment of Vasculitis:

Over the past few years there had been significant advances in the understanding of pathogenesis and treatment of vasculitides. These advances will hopefully lead to more specific and targeted treatments, with consequent improvements in clinical outcomes. In common with other systemic disease, the aims of therapy are:

(i) induction of remission; (ii) maintenance of remission; and (iii) prevention of relapse.²²

Henoch-Schonlein Purpura:

Treatment is supportive with maintenance of good hydration, nutrition, and electrolyte balance and with control of pain with simple analgesics such as acetaminophen or non steroidal anti-inflammatory drugs (NSAIDs) and, if necessary, control of hypertension. Short-term glucocorticoid therapy is effective in relieving the pain of severe orchitis, severe gastrointestinal disease or hemorrhage. The severity of disease may prompt the use of intravenous methylprednisolone.²³ More potent immunosuppressive agents, such as cyclophosphamide or azathioprine, are reserved for children with biopsy-proven crescentic glomerulonephritis or other life-threatening complications such as cerebral or pulmonary hemorrhage.⁶

Kawasaki Disease:

The American Academy of Pediatrics and the American Heart Association recommend that children who fulfill the criteria of KD are hospitalized and treated with aspirin and intravenous immunoglobulin (IVIG).²³ Aspirin was the first medication used for treatment of KD because of its anti-inflammatory and antithrombotic effects. IVIG offers a remarkable combination of efficacy and safety for the treatment of KD and its use within the first 10 days of illness reduces the incidence of coronary artery aneurysms by more than 70%.²⁴ At present, most clinicians who specialize in the care of KD use pulsed doses of intravenous methylprednisolone (IVMP) in children whose inflammation persists despite at least two doses of IVIG.²⁵

Childhood Polyarteritis Nodosa(c-PAN):

Induction of remission of systemic PAN is with high doses of corticosteroids and cyclophosphamide (given usually as intravenous monthly doses for 6 months) in combination with antiplatelet doses of aspirin.²⁶ Azathioprine, methotrexate, IVIG, and more recently

biologic agents such as TNF-inhibitors have been used in a number of patients.¹⁷

Childhood Wegener’s granulomatosis(c-WG):

Treatment for c-WG with corticosteroid, cyclophosphamide, plasma exchange (particularly for pulmonary capillaritis and/or rapidly progressive glomerulonephritis) routinely employed to induce remission, followed by low dose corticosteroid and azathioprine to maintain remission.²⁶ Anti-platelet doses of aspirin are empirically employed on the basis of the increased risk of thrombosis associated with disease process.²⁷ Co-trimoxazole is commonly added for the treatment of c-WG, serving both as prophylaxis against opportunistic infection and as a possible disease modifying agent.²⁸

Childhood Takayasu Arteritis (c-TA):

Corticosteroids are still the mainstay of treatment for c-TA. In addition, Methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide have been used in children.²⁹ Anti-TNF therapy might be beneficial in c-TA.³⁰

Conclusion:

Vasculitis is rare in children. Apart from HSP, these cases are usually not seen by most practicing paediatricians. The final EULAR/PRINTO/PRES criteria had an overall better performance for all the diseases, with substantially better specificity for defining the disease. The consensus that was reached on the new international classification of childhood vasculitis hopefully will provide paediatricians with a valuable tool for standardizing clinical definitions in the study of vasculitides affecting children. Now a days, treatments of vasculitis continue to improve, with the use of different immunosuppressive medications and newer biological agents. It is expected that newer treatments will improve the outcome of childhood vasculitides.

References:

- 1 Tracy V. Ting, Philip J Hashkes. Update on childhood vasculitides. *Curr Opin Rheumatol* 2004; 16: 560-5.
- 2 Nadia J C, Susanne M B. Vasculitis and Thrombophlebitis . *E medicine* [updated 2010 Oct 16; cited 2010 Oct 25]. Available from <http://emedicine.medscape.com/article1008239>.
- 3 Brogan PA, Dillon MJ. Vasculitis from the paediatric perspective. *Curr Rheumatol Rep* 2000; 2: 411-16.

- 4 Despina E ,Michel J D, Paul A B. Advances in Childhood vasculitis. *Curr Opin Rheumatol* 2009; 21: 411-18.
- 5 Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002; 360:97.
- 6 Fatma D, Robert P S. Vasculitis in children. *Pediatr Clin NAm* 2005; 52: 547-75.
- 7 S Ozen, N Ruperto, M J Dillon, A Bagga, K Barron et al. EULAR/PReS endorsed consensus criteria* for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; 65:936-41.
- 8 S Ozen, M J Dillon. A new international classification of childhood vasculitis. *Pediatr Nephrol* 2006; 21:1219-22.
- 9 Jennette JC, Falk RJ, Anrassy K, Bacon PA, Churg J. Nomenclature of systemic vasculitides. Proposal of an International Consensus Conference. *Arthritis Rheum* 1994; 37: 187-92.
10. Dillon MJ. Primary vasculitis in children. In: Maddison PJ, Isenberg DA, Woo P, Glass DN, editors. *Oxford textbook of rheumatology*, 2nd edition. Oxford university press, Oxford 1998.
11. Mills JA, Michel BA, Bloch DA, Lie JT, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. *Arthritis Rheum* 1990; 33: 1114-21.
12. Arend WP, Michel BA, Bloch DA, Lie JT, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum* 1990; 33: 1129-34
13. Leavitt RY, Michel BA, Bloch DA, Lie JT, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of Wegener’s granulomatosis. *Arthritis Rheum* 1990; 33: 1101-07.
14. Lightfoot RW, Michel BA, Bloch DA, Lie JT, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of Polyarteritis nodosa. *Arthritis Rheum* 1990; 33: 1088-93.

15. The Japan Kawasaki Disease Research Committee .Diagnostic guidelines for Kawasaki Disease, 5th revised edition, Tokyo 2002.
16. Jane WN, Michel AG, Iiyod YT, Jane CB, Larry MB et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease:A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004; 114:1708-33.
17. Ozen S, Anton J, Arisory N, Bakkaloglu A, Besbas N . Juvenile polyarteritis: results of a multicenter survey of 110 children. *J Pediatr* 2004;145:517-22.
18. N Ruperto, S Ozen, A Pistorio, A Martini, P Brogan et al. EULAR/PRINTO/PReS criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part1 : Overall methodology and clinical characterization. *Ann Rheum Dis* 2010;69:790-7.
19. N Ruperto, S Ozen, A Pistorio, A Martini, P Brogan et al. EULAR/PRINTO/PReS criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part1 : Final classification criteria. *Ann Rheum Dis* 2010;69: 798-06.
20. Ozen S, Besbos N, Saatci U, Bakkaloglu A. Diagnostic criteria for polyarteris nodosa in childhood. *J paediatr* 1992; 120: 206-9.
21. Belostatsky VM, Shah V, Dillon MJ. Clinical features in 17 paediatric patients with Wegener granulomatosis. *Pediatr Nephrol* 2002; 17: 754-61.
22. Watts RA, Scott DGI, Pusey CD, Lockwood CD. Vasculitis-aims of therapy. An overview. *Rheumatology* 2000; 39: 229-37.
23. Sundel R P, Petty R E. Kawasaki Disease. In Cassidy JT, Petty R E, Laxer RM, Lindsey CB, editors. *Textbook of Peadiatric Rheumatology*. 5th edition. Philadelphia : Elsevier Saunders; 2005.
24. Sundel RP. Update on the treatment of Kawasaki disease in childhood. *Curr Rheumatol Rep* 2002; 4: 474.
25. Burns JC, Capparelli EV, Brown JA, Newberger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998;17: 1144.
26. Dillon MJ. Vasculitis treatment: new therapeutic approaches. *Eur J Pediatr* 2006; 165:351-7.
27. Stassen PM, Derks RP, Kallenberg CG, Stageman CA. Venous thromboembolism in ANCA associated vasculitis: incidence and risk factors. *Rheumatology* 2008;47: 530-4.
28. Stageman CA, Tervaert JW, de jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole for the prevention of relapses of Wegener's granulomatosis. Dutch Co-trimoxazole Wegener study group. *N Eng J Med* 1996;335:16-20.
29. Liang P, Hoffman GS. Advances in the medical and surgical treatment of Takayasu arteritis. *Curr Opin Rheumatol* 2005;17:16-24.
30. Hoffman GS, Merkel PA , Brasington RD , Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50: 2296-04.