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EDUCATIONAL REVIEW

Vasculitis: do we know more to classify better?

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Abstract The systemic vasculitides are a heterogeneous group of disorders characterized by the inflammation of blood vessels. The development and implementation of advanced diagnostic tests and genetic studies have resulted in substantial improvement in our understanding of vasculitis pathogenesis, resulting in the revision of the nomenclature and classification for vasculitis. Multicenter, collaborative studies are currently underway to develop improved diagnostic criteria. In this review, the major nomenclature and classification systems for vasculitides are summarized, with special emphasis on those emerging from the recent 2012 Chapel Hill Consensus Conference (CHCC).

Keywords Systemic vasculitis · Classification criteria · Nomenclature · ANCA-associated vasculitis · Chapel Hill Consensus Conference

Introduction

The vasculitides are a heterogeneous group of uncommon systemic disorders characterized by the inflammation of blood vessels leading to end organ injury [1]. The estimated incidence for overall childhood vasculitis is approximately 50 cases per 100,000 children per year [2]. While many vasculitides affect both children and adults, some are specific to a certain age group. Immunoglobulin A vasculitis (IgAV) [formerly Henoch–Schönlein purpura (HSP)] and Kawasaki disease (KD) are much more common in childhood, while giant cell arteritis (GCA) and cryoglobulinemic vasculitis almost never occur during childhood [3].

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Nomenclature system, classification criteria and diagnostic criteria

A nomenclature system includes names and definitions and provides a framework for developing classification and diagnostic criteria [4]. The products of the Chapel Hill Consensus Conference (CHCC) are nomenclature systems [5, 6].

Classification criteria are used for defining more homogeneous patient groups to facilitate research, but not for diagnosing or differentiating vasculitis from mimicking conditions [7]. The American College of Rheumatology (ACR) and Ankara Consensus Conference (Ankara) 2008 criteria are classification criteria [8–11].

Diagnostic criteria are applied to the individual patient by a physician so that a diagnosis can be made by ruling out other common conditions that may produce similar signs and symptoms [12]. There are no diagnostic criteria available for the primary systemic vasculitides.

History of vasculitis nomenclature and classification

In 1994, the International CHCC convened and proposed a nomenclature system for the most common forms of vasculitis which provided names and definitions [5].

With the substantial advances in our understanding of vasculitis pathogenesis, in 2012, a second International CHCC was held in order to add important categories of vasculitis not included in the CHCC 1994 nomenclature system [6]. The identification off anti-neutrophil cytoplasmic antibodies (ANCA) in 1982 was a great step forward in our understanding of pathogenesis in at least one group of diseases. In addition, much has been learned about clinical presentation and treatment during the last decade.

In 1990, the ACR proposed a series of classification criteria for systemic vasculitis in adults with the goal of providing a

standard method to identify homogeneous groups of patients for research purposes [8, 9]. Although children and adults have many signs and symptoms of vasculitis in common, they differ in the relative frequency of vasculitis subcategories and disease courses. While the ACR 1990 classification criteria were based on the more frequent features in adults, they failed to classify many children with vasculitis [13, 14]. Therefore, it is not completely justifiable to strictly apply the ACR 1990 classification criteria to the vasculitis seen in childhood [3]. With this background, in 2005, a preliminary classification criteria were proposed by a group of pediatric rheumatologists and nephrologists for some of the most common vasculitides in childhood, namely HSP (IgAV), KD, polyarteritis nodosa (PAN), granulomatous polyangiitis (GPA) [at that time Wegener granulomatosis (WG)] and Takayasu arteritis (TA) [15]. At the 2008 Ankara Consensus Conference, these criteria were validated, and the final form was endorsed by European League Against Rheumatism (EULAR), Paediatric Rheumatology European Society (PRES) and the Pediatric Rheumatology International Trials Organization (PRINTO) [10, 11].

Then, in 2010, EULAR established an expert panel which was given the task to perform a systematic literature review and identify deficiencies in the ACR 1990 classification criteria and CHCC 1994 nomenclature system. the members of the expert panel were provided with 17 points to be considered in the development of revised classification and diagnostic criteria [16]. Many of these points had already been incorporated in the Ankara 2008 criteria, such as the use of ANCA, magnetic resonance angiography (MRA) and computed tomography angiography (CTA) in the diagnosis [10]. This study also emphasized the need for the development of a classification tree, which was provided by CHCC 2012 [6].

There are currently no diagnostic criteria for the primary systemic vasculitides. However, in practice, both the definitions provided by CHCC and the classification criteria are used for diagnostic purposes. A multinational observational study, the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study, was designed to develop and validate diagnostic criteria and to improve and validate classification criteria for systemic vasculitides [17].

Chapel Hill Consensus Conference 2012

Chapel Hill Consensus Conference 2012 updated the definitions of vasculitis utilizing the improved understanding of the etiopathogenesis and clinical features of vasculitis subtypes [6] (Table 1). Consequently, when appropriate knowledge of the entity was available, most of the eponyms were replaced with more descriptive names. This was particularly effective in the small-vessel vasculitides (see below).

Table 1 Classification of vasculitis[a]

I. Large-vessel vasculitis (LVV)
-Takayasu arteritis (TAK)
-Giant cell arteritis (GCA)
II. Medium-vessel vasculitis (MVV)
-Polyarteritis nodosa (PAN)
-Kawasaki disease (KD)
III. Small-vessel vasculitis (SVV)
A. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)
-Microscopic polyangiitis (MPA)
-Granulomatosis with polyangiitis (Wegener granulomatosis) [GPA (WG)]
-Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) [EGPA (CSS)]
B. Immune complex SVV
-Anti-glomerular basement membrane (anti-GBM) disease
-Cryoglobulinemic vasculitis (CV)
-IgA vasculitis (Henoch–Schönlein) [IgAV (HSP)]
-Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
IV. Variable vessel vasculitis
-Behçet's disease (BD)
-Cogan's syndrome (CS)
V. Single-organ vasculitis
-Cutaneous leukocytoclastic angiitis
-Cutaneous arteritis
-Primary central nervous system vasculitis
-Isolated aortitis
-Others
VI. Vasculitis associated with systemic disease
-Lupus vasculitis
-Rheumatoid vasculitis
-Sarcoid vasculitis
-Others
VII. Vasculitis associated with probable etiology
-Hepatitis C virus-associated cryoglobulinemic vasculitis
-Hepatitis B virus-associated vasculitis
-Syphilis-associated aortitis
-Drug-associated immune complex vasculitis
-Drug-associated ANCA-associated vasculitis
-Cancer-associated vasculitis
-Others

Classification in this table is adapted from Jennette et al. [6]

Small-vessel vasculitis

The recent progress in our understanding of the pathogenesis of small-vessel vasculitis (SVV) has enabled experts to categorize it into two main groups depending on the etiologic process: ANCA-associated vasculitis (AAV) and immune complex SVV [6].

The CHCC 2012 categorization emphasized the significance of ANCA in the pathogenesis of three SVV diseases. Soon after the discovery of ANCA in 1982 [18], numerous in vitro experiments and clinical observations documented that ANCA can activate neutrophils and monocytes to mediate vascular inflammation. In 2002, the first animal model of myeloperoxidase-ANCA (MPO-ANCA)-associated vasculitis was developed by Xiao et al [19]. In 2010, Primo et al described a putative animal model of AAV caused by proteinase 3-ANCA (PR3-ANCA) [20]. Work led mainly by C. Savage's group has also shed much light on the role of ANCA [21]. Studies suggest a theoretical sequence of pathogenic events: loss of tolerance, production of pathogenic levels of ANCA, ANCA binding to the antigens at the surface of neutrophils and activation of neutrophils, acute necrotizing injury with fibrinoid necrosis and leukocytoclasis by ANCA-associated neutrophils, an innate inflammatory response recruiting monocytes and T lymphocytes elicited by this acute injury [21, 22]. B cells and the alternative complement pathway are also involved in the pathogenesis of SVV [21]. A number of studies have also emphasized the difficulties in differentiating microscopic polyangiitis (MPA), GPA (WG), and PAN; and the importance of ANCA in this context [23, 24].

In CHCC 2012, AAV was defined as necrotizing vasculitis with few or no immune deposits, predominantly affecting small vessels associated with MPO- or PR3-ANCA [6]. A prefix should be added to indicate ANCA reactivity as all AAV patients do not have ANCA. AAV is subdivided into MPA, GPA (WG), and eosinophilic granulomatosis with polyangiitis (EGPA) [formerly Churg–Strauss syndrome (CSS)]. Since the granulomatous and eosinophilic features of the latter two vasculitides had become evident, the eponyms WG and CSS were replaced with GPA and EGPA, respectively. GPA (WG) is necrotizing vasculitis predominantly affecting small- to medium-sized vessels, and necrotizing granulomatous inflammation usually involves the upper and lower respiratory tracts [6]. EGPA (CSS) was defined as a necrotizing vasculitis of small- to medium-sized vessels which often involves the respiratory tract together with eosinophil-rich and necrotizing granulomatous inflammation [6].

MPA was not classified as a separate entity prior to CHCC 2012. It is defined as a necrotizing small-vessel vasculitis with few or no immune deposits [6]. In other words, MPA is the pauci-immune SVV in the absence of evidence for GPA (WG) or EGPA (CSS) [25]. Current clinical methods have revealed that at least 80–90 % of MPA (mostly MPO-ANCA) and GPA (WG) (mostly PR3-ANCA) patients and approximately 40 % of EGPA (CSS) patients have ANCA [26]. These three AAV, especially GPA (WG) and MPA, are included in the same clinical studies. However, a recent genome-wide association study (GWAS) has provided evidence that GPA (WG) and MPA are indeed different diseases, while the strongest genetic associations were with the antigenic specificity of ANCA, not with the clinical syndrome [27]. GPA (WG) is associated with different HLA genes compared with MPA, and single-nucleotide polymorphisms associated with the genes encoding α1-antitrypsin and proteinase 3 [27].

Immune complex vasculitis is characterized by moderate to marked vessel-wall deposits of immunoglobulin and/or complement components, predominantly those affecting small vessels [6]. Anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgAV (HSP) and hypocomplementemic urticarial vasculitis (formerly anti-C1q vasculitis) are gathered under the umbrella term of immune complex vasculitis [6].

IgAV (HSP) affects small vessels with IgA1-dominant immune deposits [6]. IgA is a major class of immunoglobulin important in mucosal immunity [28], and the glycosylation of IgA1 is important in facilitating the clearance of IgA1 molecules [28]. An abnormal glycosylation of the IgA1 hinge region leads to accumulation of IgA1-dominant macromolecular complexes which activate the alternative complement pathway and result in the recruitment of inflammatory cells [29]. In CHCC 2012, the descriptive term "IgA vasculitis" replaced the eponym Henoch–Schönlein [6]. It is as yet unknown why IgAV (HSP) and IgA nephropathy behave very differently as their pathogenesis and pathology are not different: IgA nephropathy is characterized by mainly a slow and chronic course, while IgAV (HSP) has an acute and self-limiting course.

Medium-vessel vasculitis

Medium-vessel vasculitis (MVV) predominantly targets medium-sized arteries which are defined as the main visceral arteries and their branches; however, any size artery may be affected [6]. The two major variants in MVV are PAN and KD. A notable difference in the CHCC 2012 update was the addition of a negative ANCA to the definition of PAN, which is a valuable feature in distinguishing PAN from MPA [6, 30]. CHCC 2012 defined PAN as a necrotizing vasculitis of medium- or small-sized arteries without glomerulonephritis or vasculitis in arterioles, venules or capillaries which is not associated with ANCA [6]. Thus, the clinical features observed in PAN are expected to be the reflection of the inflammation of the medium- or small-sized arteries. Kidney involvement will be due to the vasculitis of medium-sized arteries located before the glomerular capillaries, such as the lobar and arcuate arteries. The main renal features will therefore be hypertension, mild hematuria and proteinuria. However, it is interesting to note that in patients with familial Mediterranean fever, a number of ANCA(−) patients have been defined with both glomerulonephritis and proven vasculitis of medium-sized vessels, suggesting an overlap of these groups [31].

KD is a MVV which often involves coronary arteries and is associated with the mucocutaneous lymph node syndrome [6]. KD may also involve medium-sized arteries—but only rarely.

Large-vessel vasculitis

Large-vessel vasculitis (LVV) mainly affects the aorta and its branches and includes the major categories of TA and GCA [6]. TA is mainly a disease of young adults, whereas the onset of GCA is usually in patients older than 50 years of age. GCA involves the temporal artery and is often associated with polymyalgia rheumatica [6]; it does not occur in children. The age of the patient at onset of LVV appears to be the major discriminating factor between TA and GCA in CHCC 2012.

Other categories of vasculitis

The CHCC 2012 categorizations also incorporated new categories of vasculitis, such as variable vessel vasculitis (VVV), single-organ vasculitis, vasculitis associated with systemic disease and vasculitis associated with probable etiology [6]. VVV can affect vessels of any size and type, and this category includes Behçet disease (BD) and Cogan's syndrome. Among these, BD is quite common in the countries along the Silk Road; for example, in Turkey it is more common than ANCA-associated vasculitides. It should be emphasized that BD has prominent mucocutaneous features, similar to KD.

According to the ACR criteria, hepatitis B reactant is one of the classification criteria for PAN [32]. However, in CHCC 2012, hepatitis B virus-associated vasculitis belongs to the subcategory of "vasculitis associated with probable etiology" [6]. This distinction emphasizes the difference in pathogenesis, since it is now known that infection-related PAN (or PAN-like disease) is an immune complex disease, whereas classic PAN is not. This distinction also relates to treatment differences, where antiviral treatment is a part of the treatment in hepatitis B virus-related disease.

An autosomal recessive genetic disorder called "deficiency of adenosine deaminase 2 (ADA2)" (DADA2) has recently been described along with causative mutations in the *CERCR1* gene [33, 34]. This disorder is characterized by systemic inflammation along with vascular features, including early-onset strokes, recurrent fevers and vasculitis. The pathology is often a necrotizing arteritis, reminiscent of PAN [33–35]. The patient who has vasculitis secondary to ADA2 deficiency should also be classified in the subcategory of "vasculitis associated with probable etiology", since this represents a vasculopathy secondary to a genetic mutation [6].

Ankara 2008 criteria

The differences between the ACR criteria [32, 36–38] and the Ankara 2008 criteria [10] are summarized in Table 2.

IgAV (Henoch–Schönlein purpura)

During the revision process at the 2008 Ankara Consensus Conference, palpable purpura became a mandatory criterion, and any biopsy demonstrating "predominant" IgA deposits was accepted to be consistent with IgAV (HSP) [10]. This revision was mainly possible due to recent observations that IgA immune-complexes define the pathogenesis of the disease [10, 15]. Purpura was designated as the necessary criterion since it was present in all children with IgAV (HSP) in the web-based pediatric vasculitis registry of PRINTO [10]. Joint involvement, which is more common in children with IgAV (HSP) than in adults [39], and renal involvement, which determines the long-term prognosis [40], were both considered as new criteria. The age criterion was deleted since it was considered to be redundant.

Polyarteritis nodosa

The biopsy definition of ACR was considered to be very non-specific, and thus the characteristic histopathological feature of PAN, which is the necrotizing arteritis, replaced the former. Designation of the typical histopathology or angiographic abnormalities became a mandatory criterion, and after the removal of the criteria for the signs and symptoms of vasculitis in specific organ systems, PAN classification criteria took its final form. Hepatitis B serology positivity, which was one of the ACR criteria for PAN, is unusual in childhood PAN, probably due to the vaccination protocols [41]. Thus, this criterion was deleted during revision.

Renal involvement was defined as hematuria, proteinuria or impaired renal function. The skin involvement was also provided in detail as livedo reticularis or skin nodules or skin infarcts. This was especially specified since livedo vasculitis of the previous criteria set was present in only a small proportion of patients. Again the database for PAN indeed revealed a variation of organ involvement in childhood cases. However, most of these involvements failed to reach a significant specificity and were not involved as separate items to the criteria.

Granulomatous polyangiitis (WG)

The ACR classification criteria were developed prior to ANCA being defined [37]. It is now known that approximately 90 % of GPA (WG) patients are ANCA-positive (mostly PR3-ANCA) [42]. Thus, any sign of ANCA positivity was added to the group of criteria for GPA (WG) classification. The presence of subglottic, tracheal or endobronchial stenosis was also considered to be a new criterion, since it is especially common in pediatric GPA (WG) patients [43, 44]. Furthermore, the evolving technology in imaging using Computed tomography (CT) scan results was acknowledged in the definition of pulmonary involvement.

Table 2 ACR criteria [32, 36–38] versus Ankara 2008 criteria [10] regarding vasculitis classification

Vasculitis	Classification criteria [reference number]	
	ACR criteria [32, 36–38]	Ankara 2008 criteria [10]
IgA vasculitis/HSP	≥2 of the following: -≤20 years of age at disease onset -Palpable purpura -Acute abdominal pain -Biopsy showing granulocytes in the wall of small arterioles/venules	Purpura or petechia (mandatory) with lower limb predominance[a] plus 1 of 4: -Abdominal pain -Histopathology (predominant IgA deposit in a biopsy) -Arthritis or arthralgia -Renal involvement
Polyarteritis nodosa	≥3 of the following 10 criteria: -Granulocyte or mixed leukocyte infiltrate in an arterial wall on biopsy -Arteriographic abnormalities -Livedoreticularis -Myalgia -Diastolic blood pressure >90 mmHg -Mono- or polyneuropathy -Elevated blood urea nitrogen or creatinine -Testicular pain/tenderness -Hepatitis B reactants -Weight loss >4 kg	Histopathology or angiographic abnormalities (mandatory) plus 1 of 5: -Skin involvement -Myalgia/muscle tenderness -Hypertension -Peripheral neuropathy -Renal involvement
Granulomatous polyangiitis/WG	≥2 of the following: -Abnormal urinary sediment (red cell casts or >5 red blood cell per high power field) -Abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates) -Oral ulcers or nasal discharge -Granulomatous inflammation on biopsy	At least 3 of 6 -Histopathology (granulomatous inflammation) -Upper airway involvement -Laryngo-tracheo-bronchial stenosis -Pulmonary involvement (chest X-ray or CT showing the presence of nodules, cavities, or fixed infiltrates) -ANCA positivity -Renal involvement
Takayasu arteritis	≥3 of the following: -Arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal, upper or lower extremities -Decreased brachial artery pulse -Claudication of an extremity ->10 mmHg difference in systolic blood pressure between arms -A bruit over subclavian arteries or the aorta -Age at disease onset ≤40 years	Angiography (conventional, CT or MRI) of the aorta or its major branches and pulmonary arteries showing aneurysm/dilatation, narrowing, occlusion or thickened arterial wall (mandatory) plus 1 of 5: -Pulse deficit or claudication -Four limbs blood pressure discrepancy >10 mmHg -Bruits -Hypertension (>95 percentile for height) -Elevated acute phase reactants

ACR, American College of Rheumatology; CT, computed tomography; MRI magnetic resonance imaging

[a] For purpura with atypical distribution, a demonstration of an immunoglobulin A deposit in a biopsy is required

Takayasu arteritis

Since the development of the ACR criteria, radiological techniques have advanced significantly. MRA and CTA have similar diagnostic performance for TA and are less invasive when compared to conventional angiography [45, 46]. Thus, during the revision process, the angiographic abnormalities became mandatory criteria and modified with the imaging modalities, such as MRA, CTA and conventional angiography. The age criterion was deleted, and hypertension was included since almost all of the childhood cases had this clinical feature [10]. Elevated acute phase reactants were added as a new criterion, although not all patients have elevated acute phase response. This criterion was added to aid in the differential diagnosis with fibromuscular disease in children. With all of these modifications, the criteria had a sensitivity of 100 % and a specificity of 99 % in children.

Conclusion

Advances in diagnostic technology and improvement in our understanding of etiopathogenesis, mainly through GWAS and other genetic studies, have provided physicians with more detailed data on vasculitis in recent years. The definitions and classification criteria have also evolved with these advances. However, there are still no diagnostic criteria for the primary

systemic vasculitides, necessitating a reliance on disease definitions and physician experience for a differential diagnosis. Collaborative multicenter studies such as DCVAS are needed to develop diagnostic criteria while improving the existing classification criteria. However, with the availability of classification criteria, the pediatric agenda should focus on multicenter studies to define better management and treatment programs for patients with these rare diseases.

Key summary points

1. Classification criteria are used for defining more homogeneous patients groups for research purposes and would facilitate diagnosis by ruling out mimicking conditions.
2. The updated CHCC 2012 definitions provide a classification tree which forms a basis for future classification and diagnostic criteria for vasculitis in both children and adults.
3. Vasculitis in children differs from that in adults in specific aspects, particularly in the frequency of vasculitis subcategories, the predominant presenting features and disease course.

Questions (answers are provided following the reference list)

1. Which of the following is false for the CHCC 2012 classification and diagnostic criteria?

   a) They have redefined the diseases using new data for the respective pathogenesis.
   b) They cannot be relied upon for the diagnosis of an individual patient.
   c) They provide strict criteria to diagnose patients.
   d) They are a nomenclature system providing definitions for the diseases.
   e) They are not a revision of the ACR 1990 criteria.
2. For PAN, which of the following is correct?

   a) Glomerulonephritis is the usual renal manifestation.
   b) Hepatitis B serology is usually positive in children with PAN.
   c) ANCA positivity is an important feature of PAN distinguishing it from MPA.
   d) Designating the typical histopathology or angiographic abnormalities is a mandatory criterion for PAN based on Ankara 2008 criteria.
   e) PAN predominantly affects the arterioles, venules and capillaries.
3. Which of the following is false regarding ANCA?

   a) ANCA plays a role in the pathogenesis of some MVV.
   b) ANCA can activate the neutrophils and monocytes to mediate an inflammatory process.
   c) There are animal models for AAV caused by MPO- and PR3-ANCA.
   d) GPA (WG), MPA and EGPA (CSS) are major categories of AAV.
   e) Approximately 40 % of EGPA (CSS) patients have ANCA.
4. A 10-year-old boy has repeated sinus infections, nasal septum perforation, nodular masses in the lungs, red blood cell casts in urine and PR3-ANCA positivity. Which one is the most likely diagnosis?

   a) IgAV (HSP)
   b) PAN
   c) MPA
   d) EGPA (CSS)
   e) GPA (WG)
5. According to the Ankara 2008 criteria, elevated acute phase reactants is a criterion for classifying:

   a) IgAV (HSP)
   b) TA
   c) KD
   d) GPA (WG)
   e) PAN

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Answers

1. c. The diagnostic criteria are used to diagnose individual patients by ruling out mimicking conditions. Nomenclature systems such as CHCC 2012 are not used for this purpose [7].

2. d. Designating the typical histopathology or angiographic abnormalities became a mandatory criterion for PAN during the revision process of vasculitis criteria at the 2008 Ankara Consensus Conference [10].

3. a. ANCA plays a role in the pathogenesis of AAV which is a category of SVV [6].

4. e. The child presents with upper respiratory system, lung and renal involvement. It is difficult to distinguish between GPA (WG) and MPA. However, PR3-ANCA positivity makes GPA (WG) the most likely diagnosis [26].

5. b. The Ankara 2008 criteria for TA are angiographic abnormalities of the aorta and its main branches and pulmonary arteries showing aneurysm/dilatation (mandatory criterion) plus one of the following five: pulse deficit or claudication, four limb blood pressure discrepancy, bruits, hypertension and elevation of acute phase reactants [10].