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VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Classification of ANCA-Associated Vasculitis

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Abstract Classification of the ANCA-associated vasculitides remains controversial. Existing systems, developed by the American College of Rheumatology (ACR) in 1990, the Chapel Hill Consensus Conference (CHCC) in 1994 and updated in 2012, and the European Medicines Agency algorithm, all have deficiencies, especially when applied to unselected patients. The ACR system did not include ANCA or microscopic polyangiitis, and the CHCC (1994) included MPA but not ANCA (this was rectified in the 2012 revision). These systems were developed as classification criteria and not as diagnostic criteria. There are currently no validated diagnostic criteria for AAV. The Diagnostic and Classification Criteria for Vasculitis (DCVAS) study is a global study with the objective of developing and validating diagnostic criteria.

Keywords Vasculitis · Classification · ANCA · Criteria · Chapel Hill Consensus Conference · Granulomatosis with polyangiitis · Microscopic polyangiitis · Eosinophilic granulomatosis with polyangiitis · Polyarteritis nodosa

Introduction

The vasculitides are a group of systemic disorders characterized by inflammation of blood vessels leading to end organ tissue injury. The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA; Wegener's), eosinophilic granulomatosis with polyangiitis (EPGA; Churg–Strauss Syndrome), and microscopic polyangitis (MPA). Polyarteritis nodosa (PAN) was previously often considered with this group but is now generally considered not to be associated with ANCA.

Classification of systemic vasculitis remains controversial. It is important both for researchers to have agreed classification criteria, to enable studies to be conducted using homogenous patient populations, and for physicians to have agreed diagnostic classification criteria, to enable prediction of future outcome of the disease and provide appropriate treatment.

Various classification systems have been proposed for systemic vasculitis but none provides comprehensive diagnostic and classification criteria for the diseases. Classically the vasculitides have been classified on the basis of the size of the blood vessels involved (Fig. 1); this approach has stood the test of time and was continued by the Chapel Hill Consensus Conference (CHCC) in 2012 [1••]. The CHCC also, for the first time, produced clear definitions of vessel size (Fig. 1).

In 1990, the American College of Rheumatology (ACR) proposed classification criteria for seven types of vasculitis [2] including GPA, EGPA, and PAN, which are widely accepted. The criteria do not work well for diagnostic purposes and indeed were not designed for that purpose. The ACR (1990) criteria described the differences between the different types of vasculitis but failed to differentiate vasculitis from other diseases. MPA was not included. ANCA was not used in the classification process, because it was not widely tested in the 1980s during the period when the criteria were being developed. Better understanding of pathogenesis, and routine use of immunology, for example ANCA, has limited use of the ACR criteria.

In 1994, the first CHCC proposed new nomenclature based on the size of the blood vessels. It provided definitions for 10 different types of vasculitis but did not give any diagnostic or

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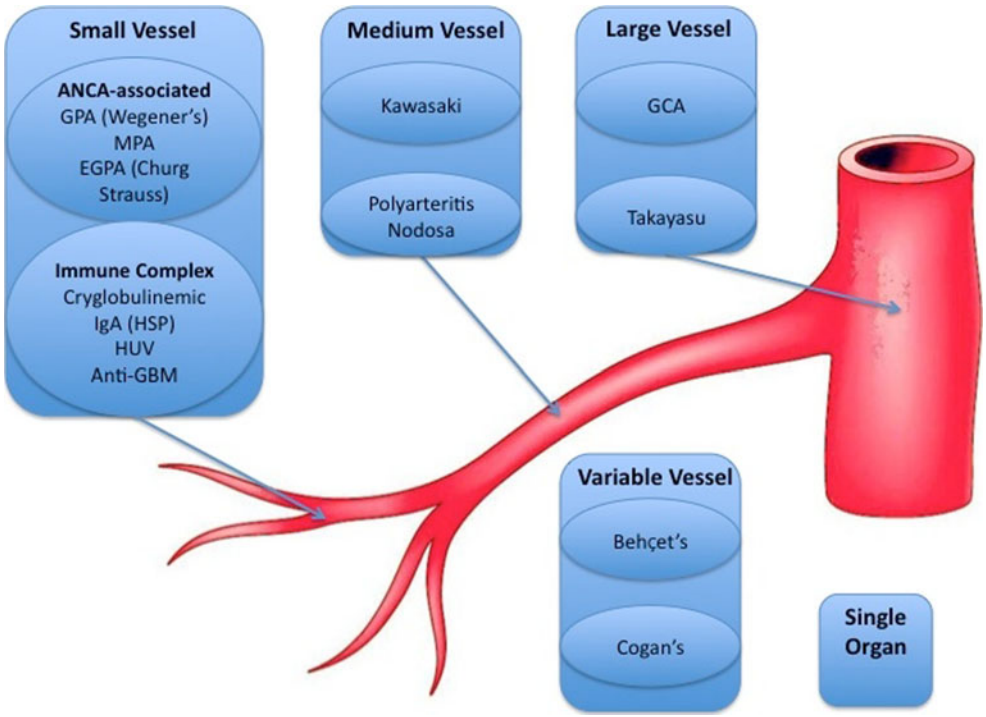

Fig. 1 Classification of vasculitis on the basis of vessel size (reprinted from Watts et al. [26]; copyright 2011, by permission of Oxford University Press)

classification criteria. The importance of ANCA in diagnosis of the disease was recognised but it was not included in the definition of any vasculitis [3]. In 2012 this nomenclature was revised and updated (Table 1) [1••]. For the first time ANCA was included to define a group of vasculitis—called ANCA-associated vasculitis. This clearly distinguished the AAV from the other types of small-vessel vasculitis—the immune complex group characterised by marked vessel wall immune deposits (anti-GBM disease, cryoglobulinaemic vasculitis, IgA vasculitis (Henoch–Schönlein), hypocomplementaemic vasculitis). The CHCC recognised the problem of ANCA-negative vasculitis viewing it as analogous to seronegative lupus or seronegative rheumatoid arthritis.

ANCA Associated Vasculitis

ANCA were first reported by Davies, among patients with a necrotising glomerulonephritis in 1982, and then by van der Woude et al. in 1985, in GPA [4]. ANCA antigen is of vital importance in determining the disease process and its prognosis. The AAV have distinct pathological features, with necrotising vasculitis and pauci-immune immunoglobulin deposition with a wide range of clinical presentations.

Sub-classification of AAV into GPA, MPA, and EGPA is complicated and difficult, because of the heterogeneity of the disease and its overlapping clinical features. There has been a long-running debate about whether GPA, MPA, and EGPA are distinct conditions or reflect a range of overlapping conditions [5]. There is evidence suggesting these are distinct conditions.

The factors initiating AAV are unknown in most cases. Current data support the involvement of infection for GPA but not MPA. In the UK, there is evidence that GPA has a cyclical pattern of incidence (often taken as evidence of an infectious aetiology) with seven-year periodicity, in contrast with MPA [6]. The frequency of upper respiratory tract involvement has also led to speculation that infection may be an important initiator. Nasal carriage of *Staph. aureus* has been associated with relapse in GPA [7]. These findings support the idea that GPA, but not MPA, is induced by infection (unknown). EGPA, unlike GPA and MPA, is associated with eosinophilia (both tissue and peripheral blood) and asthma. Drug-induced vasculitis (most commonly secondary to exposure to propylthiouracil and hydralazine) is typically associated with induction of vasculitis similar to MPA with MPO-ANCA. Environmental exposure to silica has been associated with renal vasculitis, and most of these patients also have MPA-type vasculitis with MPO-ANCA [8]. The genetic basis is different, with PR3-ANCA disease being associated with *HLA-DP*, *SERPINA1*, and *PRTN3* whereas MPO-ANCA disease is associated with *HLA-DQ* [9••]. There are significant differences in outcome between GPA and MPA. Walsh et al., in a study of risk factors for relapse of 535 patients with either GPA or MPA, followed for 1,804 patient years in four European studies, reported that PR3-ANCA positivity was associated with a much higher risk of relapse than MPA [10].

Table 1 Definitions of AAV according to CHCC 2012

ANCA-associated vasculitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add a prefix or suffix indicating ANCA reactivity, e.g. PR3-ANCA, MPO-ANCA, ANCA-negative
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent
Granulomatosis with polyangiitis (Wegener's)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium-sized vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium-sized vessels, and associated with asthma and eosinophilia. ANCA is most frequent when glomerulonephritis is present

Data from Jennette et al. [1••]

The first formal classification criteria for GPA and EGPA were developed by the ACR in 1990; these perform well with sensitivity of 88.2 % and 85.0 %, respectively, and specificity of 92.0 % and 99.7 %, respectively [11, 12]. The criteria for PAN performed less well, with sensitivity of 82.2 % and specificity of 86.6 %. MPA was not included in the classification. Patients with MPA may be classified as either GPA or PAN by use of the ACR (1990) criteria, and this has limited their usefulness [13].

The CHCC (1994) defined GPA, MPA, EGPA, and PAN, recognising the difficulty of obtaining a biopsy for diagnostic purposes, and proposed the idea of surrogate markers for vasculitis [3]. They did not provide a list of surrogate markers, furthermore ANCA was not included in the definition of any vasculitis. The classification was based on the size of the blood vessels. The term PAN was restricted to diseases with involvement of medium-size and small arteries without involvement of smaller vessels. The term GPA was restricted to granulomatous inflammation. Microscopic polyangiitis was defined as a nongranulomatous, pauci-immune, small-vessel vasculitis involving the upper and lower respiratory tract. EGPA was defined as necrotising, granulomatous inflammation involving small to medium-sized blood vessels of respiratory tract associated with asthma and eosinophilia. The CHCC (1994) was a major advance, clearly separating PAN from the AAV, and distinguishing it from MPA. A consequence of this was that PAN has become a relatively rare type of vasculitis.

Sorensen et al., for the first time, incorporated ANCA in the classification of systemic vasculitis [14]. They critically evaluated the CHCC 1994 nomenclature and came to the conclusion that the CHCC failed to adequately distinguish GPA and MPA. They suggested that some clinical findings can be used as a surrogate marker to establish classification criteria for different types of vasculitis. The surrogate markers included glomerulonephritis (proteinurea and haematurea), arteritis in the presence of other signs of vasculitis, radiological evidence of lower respiratory infiltrates or cavitations in the absence of infections and malignancies, and upper airway chronic inflammation with radiological evidence of bone or cartilage destruction.

Lane et al., in 2002 [15], evaluated the diagnostic criteria proposed by Sorensen. Ninety-nine patients with primary systemic vasculitis from a single region of the UK were classified on the basis of the CCHC, ACR, and Sorenson criteria. It was concluded that the Sorensen criteria was a useful classification tool if eosinophilia was excluded. It was noted that this classification system failed to classify MPA, because only a few patients fulfilled the criteria for MPA.

The difficulties in using the ACR and CHCC (1994) criteria and/or definitions to conduct epidemiological studies across different populations led to the development of the EMA algorithm [16]. A consensus group of experts determined that an algorithm approach would enable a harmonised system to be developed. The purpose was to classify patients with AAV and PAN systematically, with a minimum of unclassified patients, by use of a stepwise hierarchical approach: EGPA, GPA, MPA, PAN, and others which were, at the time, unclassified. The ACR criteria were given priority over the CHCC definitions because the former had been validated. The algorithm was validated in a study of 99 patients from a single centre. It was developed and validated initially for Caucasian patients. It has been criticised for placing MPA below GPA and hence potentially has a tendency to over-classify GPA and under-classify MPA. Classification into GPA and MPA is not dependent on ANCA specificity but on the presence or absence of ANCA. Hence it should work for populations among which the association

between GPA and PR3-ANCA is less close than for Caucasian populations. It has subsequently been shown to work well among several non-Caucasian populations [17, 18]. The algorithm is, therefore, a useful tool for epidemiological studies. It was recently reassessed using the CHCC (2012) definitions and the original 99 patients, and the CHCC 2012 definitions and shown to work as well [19]. The algorithm does not provide diagnostic criteria that enable the practising physician to discriminate MPA from GPA.

The classical subdivision of the AAV into GPA, MPA and EGPA has been challenged, primarily because of substantial overlap of clinical phenotypes. Recently, several groups have attempted to divide AAV into different categories depending on the clinical features only. Mahr et al. used cluster analysis to determine whether this approach would yield a different categorisation [20]. The analysis suggested that the AAV could be categorized into five classes with different clinical presentation and outcome. The study involved 673 newly diagnosed patients with AAV which were classified into five classes:

1. renal AAV with PR3 ANCA;
2. renal AAV without PR3 ANCA;
3. non-renal AAV;
4. cardiovascular AAV; and
5. gastrointestinal AAV.

The largest groups were the two renal clusters which included 72 % of the patients. The five clusters had distinct death and relapse rates. Prognosis was best for the non-renal AAV cluster and worst for those with cardiovascular or gastrointestinal involvement. On the basis of four variables 97 % of subjects could be classified into one of the five classes.

Lionaki et al. compared the usefulness of existing classification systems for the AAV in predicting clinical outcome, response to therapy, disease relapse, development of end-stage renal disease, and death [21]. They evaluated the CHCC classification system, the EMA algorithm, and a third system based on MPO and PR3 ANCA specificity. The study included 502 patients with biopsy-proved AAV. They were classified into MPA and GPA by CHCC and EMA classification. Significant discrepancies were found in the allocation of patients to GPA and MPA. GPA was felt to be overclassified by the EMA algorithm, most likely because the presence of upper respiratory tract manifestations in the ACR criteria results in any patient with these symptoms being regarded as having GPA. It was found that clinical manifestation correlates strongly with ANCA positivity. Most of the patients with glomerulonephritis, up to 81 %, had MPO ANCA positivity. Patients with destructive upper airway disease had high PR3 ANCA positivity (94 %). Granulomatous disease was strongly associated with PR3 ANCA positivity (79 %). Relapse was found to be independently associated with PR3 ANCA positivity. The CHCC and EMA systems did not predict relapse.

The classification systems and definitions described above have been developed by using adult patient populations. The pattern of vasculitis in children is different. The predominant types of vasculitis in children (Kawasaki disease and IgA vasculitis (Henoch–Schonlein) either do not occur in adults or are much less common. AAV occurs much less frequently and the major differentiation among children is from IgA vasculitis. A separate classification system has therefore been proposed for children. As for adults, the classification is based on vessel size. Small-vessel disease is further divided into granulomatous and non-granulomatous diseases. The classification was developed before the 2012 revision of CHCC and included ANCA and the presence of subglottic, tracheal, or endobracheal stenosis [22]. The EMA approach has also been shown to be valid for a paediatric population [23].

Future Developments

Classification of the AAV still poses problem both for the researcher wanting to accurately classify his or her patients for comparative studies and for the practising clinician, because there is no universally agreed system for diagnostic classification and physicians must rely on experience and disease definitions. There are still no validated diagnostic criteria for the AAV. Updated criteria should improve clinical practice and enable progress to be made in clinical trials.

The Diagnostic and Classification Criteria for Vasculitis (DCVAS) study is a multinational observational study designed to develop and validate diagnostic criteria and to improve and validate classification criteria for six forms of primary systemic vasculitis—GPA, MPA, EGPA, PAN, giant-cell arteritis (GCA), and Takayasu arteritis (TAK) [24•]. The analytical approach will be based on the traditional approach of vessel size for classification of vasculitis but will also incorporate detailed clinical data, evaluation of ANCA, diagnostic testing, biopsy, and imaging data. The study is following the guidelines for the development of classification criteria established by the ACR and the European League against Rheumatism (EULAR) [25]. It is expected that 2,000 patients with primary systemic vasculitis (at least 260 within each of the six main types of vasculitis) and 1,500 patients with autoimmune diseases and other conditions that mimic vasculitis will be recruited. The list of clinical features for inclusion in the dataset was determined by a multidisciplinary expert panel by use of a nominal group technique. For all patients, data from a detailed medical history, physical examination, laboratory testing, radiographic testing (including angiography), biopsy results, treatment, Birmingham Vasculitis Activity Score, and Vasculitis Damage

Index are being collected. One of the major problems with development of criteria is defining the method of choice and avoiding circularity. Use of physicians' opinions to define the method of choice leads to physician bias. The DCVAS study is trying to avoid this by investigating alternative approaches to deriving reference standards by creating data-driven classification algorithms using analytical techniques such as K-means clustering and support vector machine modelling.

Conclusions

Classification of the AAV remains controversial and there are still no validated diagnostic criteria for the AAV. The DCVAS study will provide validated diagnostic criteria for the AAV.

Compliance with Ethics Guidelines

Conflict of Interest Irfan Khan and Richard A. Watts declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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