Antineutrophil cytoplasm antibody–associated vasculitis: recent developments

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Antineutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV) is a group of vasculitides characterized by small-to-medium-sized blood vessel vasculitis and the presence of ANCA. Although our understanding of the causes of AAV remains limited, new information supporting an autoimmune basis is emerging. This review highlights recent progresses in etiology, pathogenesis, classification, and treatment. A genome-wide association study has confirmed a role for genetic susceptibility in AAV, and links between environmental factors and AAV induction through abnormal neutrophil extracellular traps has been demonstrated. Ongoing international consensus initiatives have revised approaches to the classification of vasculitis that has been enhanced by the analysis of large-scale prospective clinical data sets. New autoantibodies to human lysosome–associated membrane protein-2 antibody, moesin, and plasminogen have been detected in AAV sera and a prognostic classification of renal biopsies developed. Clinical trial networks have extended the evidence base for the treatment of AAV, and rituximab has emerged as an alternative to cyclophosphamide for remission induction. Long-term outcomes following current treatment strategies have been determined and increased risks for cardiovascular and malignant disease reported.

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Antineutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV) is a grouping of multisystem diseases characterized by a pauci-immune small-vessel vasculitis and the presence of circulating autoantibodies. AAV has an annual incidence of 20 per million. Its outcomes are often poor with a mortality of 25% at 5 years. Renal involvement is frequently seen and is strongly associated with outcomes.

CLASSIFICATION OF VASCULITIS

The nomenclature of the primary systemic vasculitis syndromes was defined by the 1994 Chapel Hill Consensus Conference (CHCC). The American College of Rheumatology (ACR) had previously proposed classification criteria for seven vasculitis syndromes including Wegener's granulomatosis (WG), Churg–Strauss syndrome (CSS), and polyarteritis nodosa (PAN) on the basis of analysis of a large retrospective cohort. The ACR criteria were developed before widespread ANCA testing, and PAN and microscopic polyangiitis (MPA) were not differentiated. The CHCC definitions were based on the expert opinion in order to standardize the nomenclature and were based on the predominant size of blood vessel involvement in tissue biopsies. MPA and PAN were defined as two different vasculitides, a small-to-medium-sized blood vessel vasculitis and a medium-sized blood vessel vasculitis, respectively. An association between WG, CSS, MPA, and ANCA due to the common finding of a pauci-immune microscopic vasculitis was emphasized. These three syndromes were subsequently grouped together as AAV.

Application of the ACR criteria alone results in frequent overlaps between syndromes of WG, CSS, and PAN, and the CHCC system was limited by its requirement for histology resulting in many unclassified cases. The absence of MPA in the ACR criteria has led to the use of the ACR criteria and the CHCC definitions in parallel. Resolving these problems, European Medicines Agency developed a stepwise algorithm for diagnosing AAV and PAN in patients with suspected vasculitis in 2007. This algorithm categorizes cases with suspected vasculitis using the ACR and Lanham criteria for CSS, surrogate markers for WG and renal vasculitis, and the CHCC definitions. The deficiencies in these systems and the need for newer approaches to the classification and diagnosis of vasculitis were reviewed by the European League Against Rheumatism/ACR working group in 2010.[1] This led to the launch of a large, prospective, observational study, Diagnosis

and Classification of Vasculitis Study, to develop both revised classification criteria and a validated set of diagnostic criteria.

The CHCC definitions were revised in 2012 to take an account of recent advances, to cover a more complete spectrum of vasculitis, and to begin the replacement of eponyms with descriptive titles for vasculitis syndromes (Table 1).[2] New categories included single-organ vasculitis and variable-vessel vasculitis. In the 2012 CHCC system, small-vessel vasculitis was subdivided into AAV and immune complex small-vessel vasculitis. An AAV was officially defined as a group of necrotizing vasculitides with few or no immune deposits, predominantly affecting small vessels, associated with ANCA. AAV included MPA, granulomatosis with polyangiitis (GPA) renamed from WG, and eosinophilic granulomatosis with polyangiitis (EGPA), renamed from CSS.

The CHCC definitions are based on histology and clinical manifestations, but newer insights for classification have emerged from large cohort and genetic studies. Mahr *et al.*[3] using a cluster analysis approach demonstrated the importance of ANCA subtypes, myeloperoxidase (MPO)/proteinase 3 (PR3)-ANCA, in deriving novel subgroups. Lyons *et al.*[4] demonstrated in their genome-wide association study that associations with the particular genes were primarily aligned with ANCA subtypes rather than diagnostic subgroups. Their results have suggested the classification of AAV into MPO-ANCA-positive angiitis and PR3-ANCA-positive angiitis.

ANCA AND OTHER ANTIBODIES

The major autoantigens of ANCA are MPO and PR3. MPO-ANCA is the predominant serotype in MPA patients, whereas PR3-ANCA is usually found in GPA. True dual positivity is rare and raises suspicion of a drug-induced vasculitis. In addition to being a diagnostic marker, a pathogenic role for ANCA is supported by experimental data and associations of ANCA with disease activity. However, vasculitis can occur in AAV without ANCA, and ANCA levels do not correlate well with disease activity. Differences in the functional effects of ANCA epitopes may explain differing clinical associations but recently described autoantibodies in vasculitis may also be important.

In 1995, Kain *et al.* found antihuman lysosome–associated membrane protein-2 (hLAMP-2) antibody in 16 of 17 patients with pauci-immune focal necrotizing glomerulonephritis. They subsequently reported a higher prevalence in pauci-immune renal vasculitis (80/84 by immunofluorescence assay and 70/84 by ELISA), compared with ANCA (38/84 with MPO-ANCA and 39/84 with PR3-ANCA). LAMP-2 is a membrane protein in both the lysosome and cellular membrane; it is coexpressed in neutrophil granules with MPO and PR3, and it is also expressed in glomerular endothelial cells. Anti-hLAMP-2 antibodies activate neutrophils and induce apoptosis of human microvascular endothelium *in vitro* and cause renal vasculitis when injected into rats. There is cross-reactivity and 100% homology of LAMP-2 with the bacterial adhesion protein FimH. In 2012, Kain *et al.*[5] showed a high prevalence again of 84% in 64 newly diagnosed, untreated AAV patients with three different methods, immunofluorescence, ELISA, and western blot. However, Roth *et al.*[6] found only 21% of ANCA-positive renal vasculitis patients ($n = 329$) and 28% of ANCA-negative patients ($n = 104$) to have anti-hLAMP-2 as compared with 16% of controls with urinary tract infection ($n = 104$). The rapid fall in anti-hLAMP-2 antibody that appears to occur with the therapy and difference in subjects, assays, and the LAMP-2 substrates may explain differences in results between the studies.

In 2011, a Japanese group revealed that MPO-ANCA–activated glomerular endothelial cells directly in a murine model. They identified a new target antigen of MPO-ANCA, moesin, on the glomerular endothelium. Moesin has partial amino-acid sequence homology with an epitope of MPO-ANCA.[7] They found a high prevalence of anti-moesin antibodies in MPA patients (not published).

An increased prevalence of thromboembolic disease occurs in AAV, and autoantibodies have now been described to plasminogen and tissue plasminogen activator in the sera of one quarter of PR3-ANCA-positive AAV patients. The presence of antiplasminogen antibodies correlated with venous thrombosis and with the severity of renal vasculitis.[8]

Table 1 | Definitions of ANCA-associated vasculitis according to the Chapel Hill consensus conference in 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 indicating ANCA reactivity. e.g., PR3-ANCA, MPO-ANCA, and 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 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 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 vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present

Abbreviations: ANCA, antineutrophil cytoplasm antibody; MPO, myeloperoxidase; PR3, proteinase 3.
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