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The kidneys and ANCA-associated vasculitis: from pathogenesis to diagnosis

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Abstract
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of pauci-immune small vessel vasculitides that often affect the kidneys manifesting as rapidly progressive glomerulonephritis. Although the exact pathogenesis of AAV is not fully known, evidence from *in vitro*, *in vivo* and clinical studies all point to the involvement of ANCA in the pathogenesis of AAV. In this review, we highlight the contributory roles played by various factors (e.g. genetics, environment, B and T-regulatory cells, toll-like receptors, etc.) in the pathogenesis of AAV. Furthermore, we discuss renal involvement in AAV in terms of clinical features and the various histopathological classification patterns, which are also known to be of prognostic importance. We also present information on useful imaging techniques for localizing kidney and other organ system involvement in AAV, and also on novel laboratory methods and assays useful for rapid and more specific determination of patients' ANCA status. Finally, we demonstrate evidence on novel serum biomarkers that have been shown to correlate with disease activity in AAV.

Keywords: antineutrophil cytoplasmic antibody-associated vasculitis; immunoassays; pathogenesis; renal histopathology; serum biomarkers

Introduction

The kidneys are highly vascularized visceral organs and are therefore commonly affected by various vasculitic syndromes [1, 2].

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of small vessel vasculitides that are described as pauci-immune (i.e. they are associated with few or no immune deposits) [1, 3]. They are characterized by the presence of ANCA in the circulation. It must be stated here that some AAV patients are ANCA-negative (i.e. they have no circulating ANCA) but still have similar disease manifestations as those who are ANCA-positive [4]. AAV can affect different blood vessels in the body leading to the damage of critical organs such as the heart, lungs, kidneys, nervous system, gastrointestinal system, skin, etc.; but for the purpose of this article, we shall focus on AAV as it affects the kidneys.

According to the International Chapel Hill Consensus Conference (CHCC) on the Nomenclature of vasculitides [5], AAV can be categorized into the following types:

(i) Microscopic polyangitis (MPA): a pauci-immune non-granulomatous necrotizing small vessel vasculitis that is frequently accompanied by necrotizing glomerulonephritis, pulmonary capillaritis and sometimes by the presence of necrotizing arteritis of small- and medium-sized arteries.
(ii) Granulomatosis with polyangitis (GPA, formerly called Wegener's granulomatosis): a small vessel vasculitis characterized by the presence of necrotizing granulomatous inflammation of the respiratory tract, necrotizing vasculitis of small- to medium-sized vessels and by the frequent occurrence of necrotizing glomerulonephritis.
(iii) Eosinophilic granulomatosis with polyangitis (EGPA, formerly Churg–Strauss syndrome): a small vessel vasculitis characterized by the presence of granulomatous and eosinophil-rich inflammation of the respiratory tract, necrotizing vasculitis of small- to medium-sized vessels and an association with asthma and blood eosinophilia.
(iv) A fourth type of AAV called 'renal limited vasculitis' (RLV) or 'idiopathic rapidly progressive glomerulonephritis' (RPGN) also occurs and is characterized by the occurrence of pauci-immune crescentic glomerulonephritis in the absence of other systemic involvements [1].

Table 1. Clinical guide for the diagnosis of renal AAV[a]

1. Clinical features of renal involvement (e.g. haematuria, proteinuria, active urinary sediment, renal failure)
2. Serological assessment (ANCA testing)
3. Histopathological evidence (positive renal biopsy)

[a]This does not represent a diagnostic criteria for renal AAV but rather serves as a guide; at present, there are no validated diagnostic criteria for AAV.

Table 2. Differential diagnosis of AAV and ANCA-associated GN

AAV	ANCA-associated GN
Henoch–Schonlein purpura	Lupus nephritis
Cryoglobulinaemic vasculitis	Anti-GBM disease
Drug-induced vasculitis	Other causes of rapidly progressive GN
Systemic infection	Thrombotic microangiopathies
Cholesterol embolization	
Malignancies	
Atrial myxoma with emboli	

GBM, glomerular basement membrane; GN, glomerulonephritis.

At present, there are no validated diagnostic criteria for AAV [6] and the definitions of the different vasculitic syndromes presented above are not intended for disease classification or diagnosis but rather to provide a working description of the different syndromes that make up the AAV clinical spectrum. A clinical guide for the diagnosis of renal AAV is presented in Table 1.

AAV occur more frequently in Caucasians than in people of African descent, with the incidence being slightly greater in males than in females [1, 7]. Although AAV may occur at any age, the typical age of disease onset is between the fifth and the seventh decades of life [1, 7]. The estimated disease incidence is 15–23 per million population [8]. The specific vasculitic syndromes comprising AAV also appear to show geographical variation. For instance, in Northern Europe, GPA occurs more commonly than MPA while EGPA is the least predominant in this region [9]. However, in Southern Europe and Japan, MPA occurs more frequently than GPA [9]. Results from epidemiological studies in one region of Northern Germany showed a doubled rate of prevalence of AAV in this region over a period of ∼12 years [10].

ANCA and other antibodies associated with AAV

ANCAs are autoantibodies targeted against antigens present in the cytoplasm of neutrophils and monocytes. The most common target antigens for ANCA are proteinase-3 (PR3) and myeloperoxidase (MPO). These antigens bind ANCA to form PR3-ANCA [cytoplasmic ANCA (C-ANCA)] or MPO-ANCA [perinuclear ANCA (P-ANCA)], respectively [1–3, 7]. ANCA-positive patients usually have either PR3-ANCA or MPO-ANCA. The occurrence of both complexes in an individual patient is extremely rare and may be due to infection- or drug-induced vasculitis which must also be considered in the differential diagnosis of AAV (Table 2) [1, 3, 11]. PR3-ANCA is most common in GPA patients (75% frequency) and least common in EGPA (5% frequency) while MPO-ANCA occurs more frequently in patients with RLV (70% frequency) and less frequently in GPA patients (20% frequency) [2]. The frequencies of occurrence of MPO-ANCA, PR3-ANCA and ANCA negativity in MPA are 50, 40 and 10%, respectively [1, 2]. In addition, MPO-ANCA has been shown to exhibit epitope-specificity which was found to be different for people with ANCA-positive disease, ANCA-negative disease and disease-free individuals [12].

ANCA is a diagnostic tool for AAV and ANCA-associated glomerulonephritis. Its presence in the circulation is detected using indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) methods [13, 14]. A recently published study by de Joode *et al.* [15] has shown that urgent determination of a patient's ANCA status is possible using the Dotblot and Phadia ELiA on anti-PR3 and anti-MPO methods with results obtained being similar to those obtained using the routine ELISA method. Results can be obtained within 2 h upon the use of the Dotblot method. This rapid method of determination is especially useful in establishing a quick diagnosis in patients with life-threatening renal and pulmonary manifestations who are suspected of having AAV, thereby enabling the immediate introduction of immunosuppressive therapy where necessary. In addition, both the Dotblot and the Phadia ELiA are also capable of rapid detection of anti-GBM antibodies [15].

In AAV, ANCA testing is characterized by a high degree of sensitivity but varying degrees of specificity depending on the patient population and the type of assay being used [1, 16]. For instance, one study assessing the specificity of three PR3 assays, namely a combination of human native and human recombinant (hn + hr) PR3; human native ELISA (hn ELISA) PR3 and human native chemiluminescence assay (hn CIA) PR3 in the detection of PR3-ANCA in GPA, showed that individual hn ELISA and hn CIA had greater specificity than the combined hn + hr PR3 assay [16]. This study also indicated that there exists a positive correlation between the antibody titres detected by individual human native (hn) PR3 assays and the Birmingham Vasculitis Activity Score (BVAS) [16]. Standardization of test assays may help reduce the problem of varying test specificity between laboratories. Another issue with ANCA testing that poses a challenge is the present lack of reference values for normal range [17].

ANCA-negative renal AAV patients have similar clinicopathological disease manifestations and prognosis as those who are ANCA-positive [4]. Statistics vary but between 10 and 20% of patients with AAV and glomerulonephritis will be ANCA-negative [1, 2, 4, 18]. Although the pathogenesis of ANCA-negative disease remains unknown [2], some possible explanations for this phenomenon are as follows:

(i) ANCA-negative patients might indeed have an autoantibody capable of neutrophil activation just like their ANCA-positive counterparts, but current assays are not capable of detecting them [2].
(ii) ANCA negativity might be associated with the phase, extent and severity of disease. The following observations give credence to this point. ANCA negativity occurred more commonly in less severe disease such as localized GPA (i.e. disease limited to the upper or lower airways without other systemic involvements or constitutional symptoms) [6, 19, 20]. This is further supported by the observation that ANCA-negative patients tend to have a shorter prodromal period and fewer systemic upsets than their ANCA-positive counterparts [21]. In *some* patients who were ANCA-positive prior to treatment, ANCA was shown to disappear following immunosuppressive therapy with its disappearance

being associated with an absence of disease activity [22].

(iii) ANCA negativity might be more characteristic of certain vasculitic syndromes (e.g. EGPA) and/or certain systemic involvements. Epidemiological data indicate that up to 55% of untreated EGPA patients are ANCA-negative [2]. Also in EGPA, there are differences in disease manifestation based on ANCA status; for instance, ANCA-positive patients were more likely to have necrotizing glomerulonephritis (75% of EGPA patients with glomerulonephritis are ANCA-positive) while ANCA-negative patients tend to develop cardiac and lung involvements [2, 23]. Based on these observations, we hypothesize that some EGPA patients who were ANCA-negative at diagnosis possibly undergo seroconversion to ANCA positivity at some point upon the development of glomerulonephritis or some other specific systemic involvement. This hypothesis however requires verification.

There is increasing evidence that ANCA plays a role in the pathogenesis of AAV [24], and this will be examined in the next section of this article. Besides ANCA, other antibodies found in the circulation of AAV patients have also been linked to the pathogenesis of AAV. For instance, studies in MPO-AAV patients have demonstrated the presence of serum anti-moesin autoantibodies that are thought to be involved in the secretion of inflammatory cytokines and chemokines and also in the pathogenesis of AAV [3, 25].

Also anti-plasminogen antibodies found in some AAV patients have been linked to increased susceptibility to venous thromboembolic events and greater severity of renal and systemic involvements in these patients [26, 27]. Another likely reason for the increased susceptibility to venous thromboembolic events in AAV may be due to the presence of hypercoagulability (as indicated by an elevated endogenous thrombin potential) and endothelial dysfunction/activation (as indicated by an increased level of factor VIII) found in AAV patients even in remission [28].

Studies have demonstrated the presence of antibodies against lysosome-associated membrane protein-2 (LAMP-2) in the circulation of patients with ANCA-associated glomerulonephritis [29–31]. It has been suggested that anti-LAMP-2 antibodies are a new ANCA subtype [29]. However, the prevalence and pathogenicity of these antibodies in AAV patients are still debatable [29–32]. Some authors have noted that anti-LAMP-2 antibodies are prevalent in AAV patients [29, 32] while other authors did not confirm such observations [31]. Recent reports suggest that the contrasting results obtained by these authors may perhaps be due to differences in the patient selection criteria and in the assays used [32]. In another recently published study involving ANCA-associated glomerulonephritis patients who were ANCA-negative, anti-LAMP-2 antibodies were shown to selectively bind native glomerular LAMP-2 instead of neutrophil LAMP-2, thereby suggesting a role in disease pathogenesis [18].

Pathogenesis of AAV

The exact pathogenesis of AAV is not fully known [33, 34], but *in vivo* studies in animal models, *in vitro* and clinical studies all point to the involvement of ANCA in the pathogenesis of AAV [35]. These findings are summarized in the following sections:

In vitro *studies demonstrating the mechanism of ANCA-mediated vascular injury*

In vitro studies have demonstrated that ANCA plays a role in the stimulation of cytokine-primed neutrophils, thereby inducing the degranulation of neutrophils, the release of oxygen free radicals and lytic enzymes which results in the lysis and disruption of endothelial cells [1, 2, 34, 36–38]. Similar events occurring *in vivo* would result in vasculitis via the same mechanism [1, 2]. Studies in rats and in AAV patients have shown that simvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, is capable of inhibiting ANCA-induced degranulation of neutrophils, thereby making it a potential therapeutic option for use in AAV patients [39].

In vivo *studies in animal models demonstrating the pathogenicity of ANCA*

In vivo studies in mice have also shown that MPO-ANCA is capable of inducing the development of pauci-immune vasculitis and glomerulonephritis [34, 37]. Injection of mouse anti-MPO immunoglobulin G (IgG) into immune-competent wild-type recipient mice or immune-deficient Rag2−/− mice produced pauci-immune necrotizing and crescentic glomerulonephritis in these mice [40–42]. The transfer of anti-MPO lymphocytes into immune-deficient mice has also resulted in necrotizing glomerulonephritis with glomerular immune deposits [40–42].

Clinical studies demonstrating the pathogenicity of ANCA

Transplacental transfer of maternal MPO-ANCA IgG is reported to have resulted in the development of glomerulonephritis and pulmonary haemorrhage in a neonate [43, 44].

Contribution of complement alternative pathway to the pathogenesis of AAV

Studies involving human subjects have shown that the activation of the complement alternative pathway plays a role in the pathogenesis of AAV [35, 36, 45–47] and that factors released by neutrophils after their stimulation by ANCA are believed to be involved in this complement alternative pathway activation [45]. The presence and level of factor B (Bb—a product of alternative complement pathway activation) in the plasma, glomeruli and urine of patients with active AAV have been linked to the severity of renal injury in these patients [46, 48].

Contribution of environmental factors to the development of ANCA and AAV

Studies have also shown the possible involvement of environmental factors such as drugs, air pollutants (e.g. silica) and infectious organisms like *Staphylococcus aureus* and Gram-negative bacteria in the development of ANCA and AAV [4, 35, 44, 49]. For instance, drugs such as propylthiouracil, hydralazine, cocaine-containing levamisole, minocycline, isoniazid and tumour necrosis factor-alpha inhibitors have been shown to induce AAV [4, 49–54]. In experimental studies, propylthiouracil-induced MPO-AAV and glomerulonephritis were linked to propylthiouracil-induced abnormalities in the structure and degradation of neutrophil extracellular traps (NETs) [55]. NETs induce cell death in neutrophils, and this process involves the release of chromatin fibres and intracytoplasmic proteins including PR3, MPO, lactoferrin, etc. [55].

In vivo studies in animal models have demonstrated the role of toll-like receptors (TLRs) in different aspects of disease pathogenesis (such as at level of tissue damage and also in the stimulation of autoimmune response) [56, 57]. TLRs are a class of receptors that are capable of recognizing microbial molecular patterns, thereby playing an important role in the innate immune system [58]. TLRs are increasingly expressed by leucocytes [58, 59]. TLR4 ligation has been shown to play a role in AAV induction and also in the stimulation of T helper 17 (Th17) and Th1 responses via TLR2 and TLR9 activation [56].

Contribution of genetic factors to the development of ANCA and AAV

Results from a large genome-wide association study involving Northern European GPA and MPA patients have confirmed the role of genetic factors in the pathogenesis of AAV [33]. This study demonstrated that,

(i) AAV had both major histocompatibility complex (MHC) and non-MHC associations;
(ii) GPA and MPA were genetically distinct disease entities;
(iii) HLA-DP, SERPINA 1 [the gene that encodes for α(1)-antitrypsin] and PRTN3 (the gene that encodes for PR3) were associated with PR3-ANCA in GPA with their specific loci and single-nucleotide polymorphism (SNP) being given as follows: HLA-DP (chromosome 6, SNP rs3117242), SERPINA 1 (chromosome 14, SNP rs7151526), PRTN3 (chromosome 19, SNP rs62132295);
(iv) HLA-DQ (on chromosome 6, SNP rs5000634) was associated with MPO-ANCA in MPA;
(v) Genetic associations were stronger for ANCA specificity than for specific AAV clinical syndromes.

Results from another study suggests that HLA-DRB1*15 alleles play a role in the pathogenesis of PR3-ANCA disease, especially among African Americans with an allele frequency of 94% [60].

Contibutions of endogenous inflammatory mediators to the pathogenesis of AAV

One study has demonstrated the presence of endogenous antimicrobial peptide cathelicidin LL37 and interferon-alpha (IFN-α) in AAV patients, with their levels being more elevated in those with crescentic glomerulonephritis than in those without it, thereby suggesting the contribution of local and systemic inflammation to disease pathogenesis [61]. LL37 has also been shown to play a role in the pathogenesis of autoimmune disorders [61].

Role of B and T cells in the pathogenesis of AAV

B and T cells are believed to contribute to the pathogenesis of AAV. For instance, the existence in the normal immune system of a special subpopulation of B regulatory (Breg) cells that produce interleukin (IL)-10 and which may help regulate the action of the T-cell population [including T-regulatory (Treg) cells and T-helper (Th) 1 cells] has been demonstrated [62–64]. A study by Wilde *et al.* [64] has shown that there is a reduction in the number of Breg cells in both active and quiescent AAV. This study further went on to show that there was a positive correlation between Breg and Treg in quiescent AAV and suggests that Th1 cell suppression by Breg may be inadequate in active AAV [64]. Other studies in AAV patients have demonstrated the occurrence of impaired Treg cell functions coupled with the presence of effector T cells that are resistant to suppression by Treg cells [65]. Results from *in vitro* studies also indicate the possible role of a subpopulation of effector T cells called Th17 cells in the pathogenesis of AAV [34, 36, 56]. Also, studies in experimental animal (mice) with crescentic glomerulonephritis have demonstrated that Th17-mediated response and tissue injury is stimulated by microRNA-155 (miR-155) [66]. Also, an increased expression of miR-155 occurs in the kidneys of patients with ANCA-associated glomerulonephritis [66].

Clinical features of AAV

AAV is not a single disease entity but a group of multisystem disorders that share certain features in common. Therefore, the clinical features of AAV can be varied as they are dependent on disease stage, the specific organ system involvement(s), disease activity/severity and the chronicity/extent of damage to organ system involved [1, 67, 68]. Also, patients with GPA and EGPA have additional features that are characteristic of each of these vasculitic syndromes [1].

Patients often present with non-specific constitutional symptoms in addition to symptoms peculiar to the site of organ system involvement. Generalized non-specific symptoms may include a 'flu-like illness' present at disease onset, fever, malaise, weight loss, loss of appetite, myalgias, arthralgias and migratory arthropathy [1, 7]. Prodromal symptoms may be present for weeks to months in the absence of evidence of specific organ system involvement [69].

Renal involvement is one of the most clinically significant manifestations of AAV and perhaps the most severe. It occurs more frequently in MPA (90%) and in GPA (80%) and less frequently in EGPA (45%) [70]. Renal AAV that frequently manifests as RPGN can present with the following features: haematuria, proteinuria, active urinary sediments and renal failure [1, 7, 71]. RPGN in AAV can lead to end-stage renal disease (ESRD) within a very short period if not properly addressed. Renal involvement has been associated with increased morbidity and mortality in AAV [72]. In MPA and GPA, renal disease can also present as subacute or chronic nephritis [1]. With the exception of RLV whose manifestations are limited to the kidneys, the other AAV syndromes could be accompanied by manifestations involving other organ systems as presented below.

Pulmonary (lung) involvement is more frequent in GPA (90%) and EGPA (70%) and less frequent in MPA (50%) [70]. At least half of patients with ANCA-associated glomerulonephritis also have pulmonary disease [7]. Pulmonary involvement has also been associated with increased morbidity and mortality [72]. The extent of pulmonary involvement varies as it can range from transient infiltrates of the alveoli to severe pulmonary haemorrhage [7]. Severe pulmonary haemorrhage has been shown to be more predominant in PR3-ANCA disease, tightly correlated with renal AAV (the so-called pulmonary–renal syndrome) and associated with a higher incidence of long-term mortality despite treatment [73].

Upper airway involvement (disease of the ear, nose and throat) is more common in GPA (90%) and less common in MPA (35%) and EGPA (50%) [70]. It can manifest as sinusitis, rhinitis, subglottic stenosis or ocular inflammation (such as episcleritis, uveitis, iritis) [1, 7]. The presence of

upper airway involvement in AAV patients has been associated with an increased risk of relapse [74, 75].

Neurologic involvement occurs more frequently in EGPA (70%) and less frequently in GPA (50%) and MPA (30%) [70]. It usually manifests as peripheral neuropathy (mononeuritis multiplex). Central nervous system involvement (most often in the form of granulomatosis meningeal inflammation) is less common [1, 7].

Cardiovascular involvement occurs less frequently in GPA or MPA and more frequently in EGPA (with a greater predominance in ANCA-negative EGPA patients than in their ANCA-positive counterparts) [1, 76]. Cardiovascular manifestations could include hypokinesis of the ventricles, temporary heart blocks, myocardial infarction, pericarditis, endocarditis or severe myocarditis [1]. Cardiovascular involvement has also been identified as a risk factor for relapsing AAV [77].

Gastrointestinal involvement has an equal frequency of occurrence (50% respectively) in the three main types of AAV. It could manifest as abdominal pain, haematochezia or perforation, all resulting from vasculitic ulceration of the small and large intestines [1, 7]. There could also be liver or pancreatic involvement [1].

Cutaneous involvement is very common and usually presents as purpura (especially in the lower extremities) [1, 7]. Other cutaneous lesions that could occur include nodules, petechiae, ecchymoses, ulcers, bullae, etc. [1, 7].

Renal biopsy as both a diagnostic and prognostic tool in renal AAV

Renal biopsy is the gold standard for the diagnosis of renal AAV [78]. This is especially true in light of the fact that not all patients with AAV are ANCA-positive. The classic histopathological features of ANCA-associated glomerulonephritis include the presence of segmental fibrinoid necrosis, glomerular crescents, and paucity or absence of glomerular immune deposits (pauci-immune glomerulonephritis) [1, 7]. However, some patients with ANCA-positive disease have been shown to demonstrate atypical pathology such as interstitial nephritis with vasa recta vasculitis in the absence of glomerulonephritis [79]. Such patients may eventually develop the classic lesions that characterize pauci-immune necrotizing glomerulonephritis [80].

Renal biopsy not only serves as a diagnostic tool in AAV but often has prognostic value [78]. For instance, Berden *et al.* developed an outcome-based classification system that divided renal histology in ANCA-associated glomerulonephritis into four classes namely: focal, crescentic, mixed and sclerotic based on the proportion of normal, cellular crescentic and sclerotic glomeruli present [78]. The focal class was defined by the presence of ≥50% of normal glomeruli and was associated with a good renal outcome. The crescentic class consisted of ≥50% glomeruli with cellular crescents and was associated with the possibility for the recovery of renal function. The mixed class consisted of <50% normal, <50% crescentic and <50% globally sclerotic glomeruli and was associated with an intermediate risk for non-recovery of renal function. The sclerotic class consisted of ≥50% of globally sclerotic glomeruli and was associated with the poorest prognosis (a high probability of advancement to ESRD and death within a year of disease diagnosis) [78]. This classification system was found to have a predictive value for 1- and 5-year renal outcomes [78, 81]. In another study involving Chinese patients with renal AAV, this outcome-based classification system was also found to be useful to some degree in predicting renal response to treatment [82]. The limited predictability of the outcome-based classification system for response to therapy in this cohort of patients might have been associated with the type of induction treatment used in the study.

The role of imaging techniques in the localization of renal and other organ system involvements in AAV

Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) has been shown to be useful in localizing most organ system involvements in GPA (with the exception of the skin, eyes and nervous system) [83]. Fluorodeoxyglucose (^{18}F-FDG or FDG), a radiolabeled glucose molecule, is the radiotracer used for this imaging technique. ^{18}F-FDG has a radioactivity half-life of ∼110 min (identical to that of fluorine 18 [^{18}F]) and is not known to cause contrast-induced nephropathy [http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=edb15e3c-848d-433d-9f1c-c73a3c72861b (date of access 09 January 2015)]. Further studies are needed to establish the use of this imaging technique in other types of AAV.

Assessment of disease activity and damage in AAV

Disease activity in AAV can be assessed using the BVAS now in its third version (BVAS v.3) [84, 85]. The BVAS is a checklist of pertinent signs, symptoms and features of active vasculitis and is useful both as a research tool and in aiding clinical decision-making [84]. BVAS v.3 represents an improvement on the two earlier versions and can be freely accessed online [http://vasculitis.org/images/documents/bvas%203.0.pdf (date of access 19 March 2015); http://www.epsnetwork.co.uk/BVAS/bvas_flow.html (date of access 09 January 2015)].

Damage in AAV can be assessed using the Vasculitis Damage Index (VDI) [55, 63, 86]. The VDI quantifies all damage (disease or treatment related) associated with vasculitis [63, 87]. The VDI is also a prognostic tool that is useful in predicting future relapses and mortality in AAV [87, 88]. However, due to concerns that VDI may not adequately indicate the full extent of damage experienced by patients with small- and medium-sized vessel vasculitis, a revised damage assessment tool called the Combined Damage Assessment Index (CDA) is presently being developed [89]. Unlike disease activity that is potentially reversible with the proper immunosuppressive treatment regimen, the damage is irreversible [63, 86].

Biomarkers of disease activity in AAV

At present there are no reliable biomarkers for monitoring disease activity in AAV. ANCA titre has been shown to correlate to some extent with disease activity, but to make therapeutic decisions based solely on ANCA titre is not encouraged. [1, 90, 91]. Research efforts are now focussed on identifying candidate serum proteins that could serve as biomarkers of disease assessments. There are ongoing

studies in different centres worldwide aimed at identifying potential serum biomarkers of disease activity in AAV. One such recently identified serum protein is B-cell activating factor belonging to the tumour necrosis family (BAFF). Serum levels of BAFF have been shown to be elevated in patients with MPO-AAV, with the levels being more elevated during active disease than in remission [92]. Furthermore, BAFF levels have been shown to correlate well with BVAS and erythrocyte sedimentary rate (ESR) levels [92]. In another recently published study involving patients from the RAVE (Rituximab in ANCA-Associated Vasculitis) trial with severe AAV, it was shown that the serum proteins, CXCL13 (BCA-1), matrix metalloproteinase-3 and tissue inhibitor of metalloproteinases-1 were better at distinguishing active disease from remission than most other serum biomarkers including C-reactive protein and ESR [93]. Serum neutrophil gelatinase-associated lipocalin has also been shown to be useful in assessing disease activity in AAV [94]. As these are just research data, there is need for further validation studies of these biomarkers.

Conclusions

ANCA has been implicated in the pathogenesis of AAV. However, the absence of ANCA in the presence of clinicopathological evidences of disease (as seen in ANCA-negative patients) does suggest that other factors besides ANCA also play a role in the pathogenesis of AAV. Furthermore, several serum factors such as anti-moesin antibodies, IFN-α and cathelicidin LL37 have been put forward as possible contributors to disease pathogenesis. However, there is a need to fully establish and validate the roles played by these and other proposed contributory factors in the pathogenesis of AAV. Knowledge gained from such studies could prove useful in the development of target assays and specialized therapies that can further modify the diagnostic and therapeutic landscape of AAV.

Secondly, the present lack of validated diagnostic criteria for AAV does present some challenge. It is known that about a fifth of AAV patients present with an ANCA-negative status. This is further complicated by the fact that some patients will have relative and absolute contraindications to a diagnostic renal biopsy, thereby making the final diagnosis of renal AAV all the more complex. This and other issues further underscore the need for the development of validated diagnostic criteria for AAV.

Thirdly, as there are no reliable biomarkers of disease activity in AAV at present, there is a need for concerted efforts aimed not only at identifying potential serum and urinary biomarkers but also at validating them for routine use in disease assessment.

Conflict of interest statement. None declared.

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