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Full Review

Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

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ABSTRACT

It is now 25 years since the first European studies on vasculitis—the anti-neutrophil cytoplasmic antibody (ANCA) standardization project. Over that period of time, there have been major developments in the classification of the vasculitides, which has permitted the conduct of high-quality epidemiology studies. Studying the epidemiology of rare diseases such as the ANCA-associated vasculitides (AAV) poses considerable challenges to epidemiologists. The first is the need for a clear definition of a case with good differentiation from similar disorders. The second is case capture. The vasculitides are rare, and therefore, a large population is required to determine the incidence and prevalence, and this poses questions of feasibility. A large population increases the risk of incomplete case detection but permits a reasonable number of cases to be collected in a practicable time frame, whereas a smaller population requires a much longer time frame to collect the necessary cases, which may also not be feasible. Statistical methods of capture–recapture analysis enable estimates to be made of the number of missing cases. The third is case ascertainment. The AAV are virtually always managed in secondary care, and therefore, hospital-based case ascertainment may be appropriate. Fourthly, the rarity of the conditions makes prospective case–control studies investigating risk factors difficult to conduct because the population size required to achieve statistical confidence is in excess of that which is readily available. Thus, much of the data on risk factors are derived from retrospective studies with inherent potential bias.

Keywords: ANCA, classification, epidemiology, vasculitis

INTRODUCTION

It is now 25 years since the first European studies on vasculitis—the anti-neutrophil cytoplasmic antibodies (ANCA) standardization project [1]. Over that period of time, there have been major developments in the classification of the vasculitides, which has permitted the conduct of high-quality epidemiology studies.

Studying the epidemiology of rare diseases such as the ANCA-associated vasculitides (AAV) poses considerable challenges to epidemiologists. The first is the need for a clear definition of a case with good differentiation from similar disorders. The second is case capture. The vasculitides are rare, and therefore, a large population is required to determine the incidence and prevalence, and this poses questions of feasibility. A large population increases the risk of incomplete case detection but permits a reasonable number of cases to be collected in a practicable time frame; whereas a smaller population requires a much longer time frame to collect the necessary cases, which may also not be feasible. Statistical

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methods of capture–recapture analysis enable estimates to be made of the number of missing cases. The third is case ascertainment. The AAV are virtually always managed in secondary care, and therefore, hospital-based case ascertainment may be appropriate. Fourthly, the rarity of the conditions makes prospective case–control studies investigating risk factors difficult to conduct because the population size required to achieve statistical confidence is in excess of that which is readily available. Thus, much of the data on risk factors are derived from retrospective studies with inherent potential bias.

CLASSIFICATION

In 1989, the field was still in the pre-American College of Rheumatology (ACR) Classification criteria era, as these seminal studies were published only in 1990 [2]. The ACR proposed criteria for the classification of vasculitides based on an analysis comparing the clinical features of patients with established vasculitis and included granulomatosis with polyangiitis (Wegener's, GPA), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome, EGPA) and polyarteritis nodosa (PAN) [3–5]. The ACR (1990) criteria provided, for the first time, a framework for conducting epidemiological and clinical studies of using validated classification criteria. There are a number of criticisms of the ACR criteria, mainly that they did not include microscopic polyangiitis (MPA) and ANCA [6]. The latter is not surprising, as the association with vasculitis had only recently been described [7]. The absence of MPA from the criteria resulted in poor discrimination between MPA and GPA. In 1994, definitions were produced by the Chapel Hill Consensus Conference (CHCC) for the major types of vasculitis and introduced the concept of surrogate markers and took into account the fact that relevant histological data were not always available. These were revised and expanded in 2012 to include ANCA and a broader range of vasculitides [8, 9]. The small vessel group was subdivided into ANCA associated (EGPA, GPA, MPA) and immune complex mediated (Table 1). In addition, there was a move away from eponyms towards a more aetiopathological-based nomenclature.

Because of the absence of classification criteria for MPA, which could be used in epidemiological studies, in 2007 a consensus algorithm was produced with the aim of providing a harmonized system for classifying EGPA, GPA, MPA and PAN into distinct categories with a minimum of unclassifiable patients [10]. This was validated initially in European populations but has subsequently been shown to be reliable in Chinese and Indian populations [11].

There remains a major need for better classification criteria for the AAV, which have been appropriately validated in populations of different ethnicities. The diagnostic and classification of vasculitis (DCVAS) project aims to recruit >2000 patients with primary systemic vasculitis and >1500 controls with other types of autoimmune disease that may mimic vasculitis from Europe, the Americas, Japan and Australasia [12, 13].

EPIDEMIOLOGY

Incidence studies

In 1989, there were very little data on the incidence and prevalence of the AAV. During the last 25 years, studies on the epidemiology of AAV have been reported from Europe, Japan, the USA, New Zealand and Australia (Tables 2 and 3). The overall incidence rates of AAV in Europe are reported to be in the range from 13 to ~20/million (Tables 2 and 3). The incidence of GPA has increased since the 1980s. The combined annual incidence of GPA and MPA was reported to be 1.5/million in the beginning of 1980s in the UK and significantly increased to 6.1/million by the end of the 1980s [14]. Similarly, during the same time period, the incidence of GPA increased in Sweden from 3 to 8/million [21]. This increment could be due to several factors including (i) increased awareness among physicians, (ii) the introduction of ANCA or iii) a genuine increase in incidence rates. However, the incidence has been stable since the early 2000s, suggesting that the likely explanation was increasing physician awareness following the introduction of routine ANCA testing (Table 2). Geographical factors may also play a role. A comparison study from three regions in Europe showed overall incidence rates of all AAV to be quite similar, about 19/million [20]. There were, however, differences in the incidence of GPA and MPA between northern and southern Europe; GPA is more common in the north, while MPA is more common in the south of Europe [20] (Table 2). However, the north–south gradient was not evident in southern Sweden with an incidence rate of MPA comparable with the reported rate from southern Europe [22]. Studies from New Zealand and Australia showed quite similar incidence rates of GPA, comparable with the incidence rate in northern Norway [38, 48]. In contrast, the proposed latitudinal gradient was observed in New Zealand [39]. Using the International Classification of Disease, patients coded as GPA were more frequent in southern New Zealand latitudes. EGPA has been previously studied within the PAN group. In France, the disease represented 20% of the systemic vasculitides group of PAN [52]. The highest incidence rate was reported from Norwich (UK), 2.7/million [53], and recently from Australia, 2.3/million [38].

The gender distribution of AAV is fairly similar in most studies with a slight male predominance. The age-specific incidence for the whole group of AAV shows a clear increase with age. However, some variation has been reported between studies; the peak incidence in the age group was reported to be 55–64 [28], 65–74 [53] and ≥75 years [22].

There is a need for studies in other regions and in other ethnicities. There is only one study from central and Latin America as opposed to Europe and more recently Asia and Oceania. In a Peruvian population, MPA was more frequent than GPA, an observation that would need confirmation in populations with such diverse ethnic origins [36].

Prevalence

There are relatively few prevalence estimates compared with incidence studies of AAV. The prevalence of AAV is estimated

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Table 1. Chapel Hill definitions as revised in 2012. From Jennette *et al.* (2013). With permission [9]

CHCC 2011 name	CHCC 2011 definition
Large-vessel vasculitis	Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected.
Takayasu arteritis	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50.
Giant cell arteritis	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid artery. Often involves the temporal artery. Onset usually in patients older than 50 and often associated with polymyalgia rheumatica.
Medium-vessel vasculitis	Vasculitis predominantly affecting medium-sized arteries defined as the main visceral arteries and their branches. Any size artery may be affected. Inflammatory aneurysms and stenoses are common.
Polyarteritis nodosa	Necrotizing arteritis of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules and not associated with ANCA.
Kawasaki disease	Arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium-sized and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children.
Small-vessel vasculitis	Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries and venules. Medium-sized arteries and veins may be affected.
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-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 tracts, 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.
Immune complex small-vessel vasculitis	Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e. capillaries, venules, arterioles and small arteries). Glomerulonephritis is frequent.
Anti-GBM disease	Vasculitis affecting glomerular capillaries, pulmonary capillaries or both, with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary haemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents.
Cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules or arterioles) and associated with cryoglobulins in serum. Skin and glomeruli are often involved.
IgA vasculitis (Henoch–Schönlein)	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules or arterioles). Often involves skin and gut, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur.
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e. capillaries, venules or arterioles), and associated with anti-C1q antibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease and ocular inflammation are common.
Variable vessel vasculitis	Vasculitis with no predominant type of vessel involved that can affect vessels of any size (small, medium and large) and type (arteries, veins and capillaries).
Behçet's disease	Vasculitis occurring in patients with Behçet's disease that can affect arteries or veins. Behçet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis and arterial aneurysms may occur.
Cogan's syndrome	Vasculitis occurring in patients with Cogan's syndrome. Cogan's syndrome is characterized by ocular inflammatory lesions including interstitial keratitis, uveitis, and episcleritis and inner-ear disease including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis.
Single-organ vasculitis	Vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis. The involved organ and vessel type should be included in the name (e.g. cutaneous SVV, testicular arteritis, central nervous system vasculitis). Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. Some patients originally diagnosed with SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides (e.g. cutaneous arteritis later becoming systemic polyarteritis nodosa).
Vasculitis associated with systemic disease	Vasculitis that is associated with and may be secondary to (caused by) a systemic disease. The name (diagnosis) should have a prefix term specifying the systemic disease (e.g. rheumatoid vasculitis, lupus vasculitis).
Vasculitis associated with probable aetiology	Vasculitis that is associated with a probable specific aetiology. The name (diagnosis) should have a prefix term specifying the association (e.g. hydralazine-associated microscopic polyangiitis, hepatitis B virus-associated vasculitis, hepatitis C virus-associated cryoglobulinemic vasculitis).

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Table 2. Reported annual incidence of granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis

Place	Period	Criteria	Population	Incidence GPA[a]	Incidence MPA[a]	Incidence EGPA[a]	Reference
Europe							
Leicester, UK	1980–86	Fauci		0.7	0.5	NA	Andrews *et al.* 1990 [14]
Leicester, UK	1987–89	Fauci		2.8	3.3	NA	Andrews *et al.* 1990 [14]
Norwich, UK	1988–10	EMEA	459 000	11.3	5.9	NA	Watts *et al.* 2012 [15]
Norwich, UK	2005–09	EMEA	459 000	NA	NA	0.9	Fujimoto *et al.* 2011 [16]
UKGPRD, UK	1990–05	ACR	2 500 000	8.4	NA	NA	Watts *et al.* 2009 [17]
Kristiansand, Norway	1992–96	ACR	150 426	6.6	NA	NA	Haugeberg *et al.* 1998 [18]
Tromso, Norway	1984–98	ACR	371 100	9.3	NA	NA	Koldingsnes *et al.* 2000 [19]
Tromso, Norway	1988–98	ACR	371 100	NA	2.7	0.5	Watts *et al.* 2001 [20]
Sweden	1975–85	ICD	8 000 000	3.3	NA	NA	Knight *et al.* 2006 [21]
Sweden	1986–90	ICD	8 000 000	7.7	NA	NA	Knight *et al.* 2006 [21]
Sweden	1991–00	ICD	8 000 000	11.9	NA	NA	Knight *et al.* 2006 [21]
Lund, South Sweden	1997–06	EMEA	641 000	9.8	10.1	0.9	Mohammad *et al.* 2009 [22]
Finland	1980–85	ACR	NS	1.9	NA	NA	Takala *et al.* 2008 [23]
Finland	1986–90	ACR	NS	3.6	NA	NA	Takala *et al.* 2008 [23]
Finland	1991–95	ACR	NS	6.0	NA	NA	Takala *et al.* 2008 [23]
Finland	1996–00	ACR	NS	9.3	NA	NA	Takala *et al.* 2008 [23]
Heidelberg, Germany	1984–89	MPA[b]	NS	NA	1.5	NA	Andrassy *et al.* 1991 [24]
Schleswig-Holstein, Germany	1998–02	CHCC	2 777 275	8.6	2.6	1.1	Reinhold-Keller *et al.* 2005 [25]
Vilnius, Lithuania	1990–99	ACR	468 500	2.1	3	1.3	Dadoniene *et al.* 2005 [26]
Crete, Greece	1995–03	ACR	369 430	6.6	10.2	0	Panagiotakis *et al.* 2009 [27]
Lugo, Spain	1988–01	CHCC	208 270	2.95	7.9	1.31	González-Gay *et al.* 2003 [28]
Malaga Spain	1994–10	ACR/CHCC	379 330	2.1	2.3	0.64	Romero-Gomez *et al* 2013 [29]
Reggio Emilia, Italy	1995–09	ACR	519 480	2.4	NA	NA	Catanaaso *et al.* 2014 [30]
Greenland (Inuit)	1992–11	ACR	56 000	1	NA	NA	Faurschou *et al.* 2013 [31]
Faroes (Danes)	1992–11	ACR	48 000	6.4	NA	NA	Faurschou *et al.* 2013 [31]
Burgundy, France	1998–08	ACR	1 631 000	NA	NA	1.2	Vinit *et al.* 2009 [32]
Edirne, Turkey	1994–13	NS	616 000	3.3	1.1	0.6	Pamuk *et al.* 2013 [33]
Americas							
Western Montana, USA	1993–06	ACR	319 640	9.1	1.25	NA	Zeft *et al.* 2010 [34]
Sasketchwan, Canada	2007–11	ACR/CHCC	562 882	4.6	7.1	NA	Anderson *et al.* 2013 [35]
Lima, Peru	1990–04	CHCC	930 306	0.5	4	0.14	Sanchez *et al.* 2006 [36]
Australasia							
South Australia	2001–05	ACR, ICD	1 500 000	11.2	NA	NA	Hissaria *et al.* 2008 [37]
Capital Territory,+ SE NSW, Australia	1995–99	ACR	433 000	8.8	2.3	2.3	Ormerod *et al.* 2008 [38]
Capital Territory, + SE NSW, Australia	2000–04	ACR	451 337	8.4	5.0	2.2	Ormerod *et al.* 2008 [38]
New Zealand (Upper North Island)	1999–03	ICD 10 M313	1 949 091	5.8	NA	NA	O'Donnell *et al.* 2007 [39]
New Zealand (Lower South Island)	1999–03	ICD 10 M313	326 877	25	NA	NA	O'Donnell *et al.* 2007 [39]
Japan	2005–09	EMEA	759 000	2.1	18.2	NA	Fujimoto *et al.* 2011 [16]
Taiwan	1997–08	EMEA	23 000 000	0.37	NA	NA	Wu *et al.* 2014 [40]
Arabia							
Kuwait	1993–96	CHCC	291 926	NA	24.0	NA	El-Reshaid *et al.* 1997 [41]

EMEA, European Medicines Agency Algorithm; ACR, American College of Rheumatology criteria (1990); CHCC, Chapel Hill Consensus Conference definition (1994); ICD, International Classification of Diseases; UKGPRD, United Kingdom General Practice Research Database. From Fauci *et al.* 1983 [42]

[a]Incidence expressed per million population.

[b]Renal involvement only.

to be 46–184/million [38, 44]. The prevalence of AAV has generally increased over the last 20 years, and this could reflect improved patient survival and also improved case identification, for example, by using multiple retrieval sources (Table 3).

The prevalence of GPA doubled in north Germany from 58 in 1994 to 98/million in 2006 [45]. A study from an urban multi-ethnic population from Paris has also shown a low prevalence of GPA, 23.7/million [43]. In Northern Europe, the prevalence of GPA in Norway increased from 30.4/million in 1988 to 95.1/million in 1998 [19] and was 160/million in Sweden in 2003 [47]. From the southern hemisphere, the prevalence of GPA was estimated to 112/million in New Zealand and 95/million in Australia [38, 48].

There is a paucity of data on the prevalence of MPA. The prevalence of MPA varied from 25.1 to 94/million (Table 3). The prevalence of EGPA is as expected much lower than

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Table 3. Reported prevalence rates for granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis

Place	Period	Criteria	Population	Prevalence GPA[a]	Prevalence MPA[a]	Prevalence EGPA[a]	Reference
Europe							
Norwich, UK	31/12/2008	EMEA	459 000	146	63	NA	Watts *et al.* 2012 [15]
UKGPRD, UK	1990	ACR	2 500 000	28.8	NA	NA	Watts *et al.* 2009 [17]
UKGPRD, UK	2005	ACR	2 500 000	64.8	NA	NA	Watts *et al.* 2009 [17]
Paris, France	2000	ACR	1 093 515	23.7	25.1	10.7	Mahr *et al.* 2004 [43]
Burgundy, France	1998–08	ACR	1 631 000	NA	NA	11.3	Vinit *et al.* 2009 [32]
Germany, North	1994	CHCC	449 500	58	9	7	Reinhold-Keller *et al.* 2000 [44]
Germany, North	2006	EMEA	469 000	98	28	24	Herlyn *et al.* 2014 [45]
Germany, South	1994	CHCC	426 500	42	0	2	Reinhold-Keller *et al.* 2000 [44]
Denmark	1977–2001	ICD	5 472 000	100	NA	NA	Eaton *et al.* 2007 [46]
Southern Sweden	1/1/2003	ACR/CHCC	287 500	160	94	14.0	Mohammad *et al.* 2007 [47]
Norway	1996	ACR	150 000	53	NA	13	Haugeberg *et al.* 1998 [18]
Tromso, Norway	1998	ACR	371 100	95.1	NA	NA	Koldingsnes *et al.* 2000 [19]
Reggio Emilia, Italy	2009	ACR	519 480	34.3	NA	NA	Catanaso *et al.* [30]
Australasia							
Canterbury, New Zealand	1999–2003	ACR/CHCC	481 000	131	58	NA	Gibson *et al.* 2006 [48]
Canterbury, New Zealand	31/12/2003	ACR/CHCC	481 000	93.5	37	NA	Gibson *et al.* 2006 [48]
Capital Territory, + SE-NSW, Australia	1995–99	ACR CHCC	433 000	64.3	17.5	11.7	Ormerod *et al.* 2008 [38]
Capital Territory, + SE-NSW, Australia	2000–04	ACR CHCC	451 337	95.0	39.1	22.3	Ormerod *et al.* 2008 [38]
Japan	2002	NS	NS	2.3	13.8	1.0	Fujimoto *et al.* 2006 [49]
Japan	2008	NS	NS	NA	NA	17.8	Sada *et al.* 2013 [50]
Americas							
New York, USA	1986–90	ACR	NS	32.0	NA	NA	Cotch *et al.* 1996 [51]
Nationwide, USA	1986–90	ACR	NS	26.0	NA	NA	Cotch *et al.* 1996 [51]
Western Montana, USA	2006	ACR	319 640	91	13	NA	Zeft *et al.* 2010 [34]

[a]Prevalence rates expressed per million population.
EMEA, European Medicines Agency Algorithm; ACR, American College of Rheumatology criteria (1990); CHCC, Chapel Hill Consensus Conference definition; ICD, International Classification of Diseases; UKGPRD, United Kingdom General Practice Research Database.

either GPA or MPA, with the highest estimate being 45.7/million (Table 3).

Genetic factors are clearly important, and it has long been observed anecdotally that the AAV are relatively rare in non-Caucasian populations. The first study to show differences in the occurrence of AAV in different ethnic groups came from Paris, which reported that GPA was less common in people of non-European ancestry than MPA [43]. A study directly comparing two ethnically different populations—white Caucasian from the UK with Japan—showed that the incidence rate of AAV overall was similar but that GPA and PR3-ANCA vasculitis was much less common in Japan than in Europe [16]; in Japan, MPA and MPO-vasculitis was the much predominant form of AAV; and in Latin America (Peru), MPA is more common than GPA [36]. In New Zealand, GPA was twice as common in Europeans than in Maoris or Asians [39]. Large case series from China suggest that MPA is more common than GPA [11]. According to a study in a multi-ethnic series from Chapel Hill in the USA, GPA is relatively uncommon in African Americans [54]. These differences might reflect global variation in the frequency of the allele HLA DPB1*0401, which has been associated with GPA [55]. The north–south gradient in Europe might also reflect genetic differences between northern and southern Europeans [56]. The clinical phenotype of systemic lupus erythematosus (SLE) has been shown to differ between northern and southern Europeans [57], and it is possible that the different clinical phenotypes of the AAV in northern and southern European populations may also reflect their different genetic background.

ENVIRONMENT

Environmental risk factors

Recent data from genome-wide association studies (GWAS) and ethnic studies clearly support a vital genetic role in the aetiology of AAV [43, 58]. That said, descriptive epidemiology certainly implicates an important environmental contribution as well. The relatively high prevalence of AAV among the middle-aged and elderly people [43, 51] along with their equitable gender balance (quite unlike most systemic autoimmune diseases) [25, 43] favours an environmental rather than genetic attribution. This argument is further enhanced by those studies reporting an apparent temporal and/or seasonal fluctuation of disease occurrence [15, 19, 53, 59, 60] (potentially explained by infectious disease cycles) and latitudinal differences in incidence [implicating factors such as ultraviolet radiation (UVR)] [48, 61]. Several studies have investigated the influence of rural versus urban living. In Australia, there was a significant increase in the incidence of MPA in rural areas (13.9/million) compared with the cities (1.6/million). The trend for GPA was not so marked [38]. Other studies have not shown a convincing difference, and this may reflect difference in the

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definition of an urban area. Studies designed to identify environmental risk factors of a disease will be crucial to the ultimate aetiological solutions, which will likely be framed by key gene–environment interactions. Existing studies have been limited by the excessive heterogeneity of the disease, small sample sizes, inconsistent case ascertainment and issues of recall bias. Nonetheless, a number of worthwhile candidate risk factors have been identified.

Infection

Both physicians and patients frequently note infective-type symptoms to precede disease onset. Furthermore, disease relapse may coincide with infective episodes [62]. Specifically, the role of *Staphylococcus aureus* in pathogenesis has been explored by Tervaert and colleagues. Their work demonstrated an increased nasal carriage of staphylococci, which correlated with relapse [63]. The observation that a patient who received co-trimoxazole (a useful agent for Staphylococcal eradication) for a urine infection had an apparent improvement in their intercurrent GPA led to the antibiotic being tested for induction therapy in GPA. Although this approach may have a role for sino-nasal disease [64], its efficacy is limited and there is no proof that its effect is actually anti-microbial. The sulfasalazine story provides a historical reminder: an agent now known for its intrinsic immunosuppressive nature was initially thought to modify a supposed infective aetiology of rheumatoid arthritis via its anti-bacterial properties [65].

One recent epidemiology study suggested that there was a cyclical occurrence for GPA with a period of 7.6 years, which was not seen for MPA, suggesting that GPA might be associated with a cyclic infection [15]. Case reports have delineated numerous other infections that appear to relate the onset of AAV, which include Rickettsiae [66], Enterococcus [67] and Epstein-Barr virus [68]. More recently, an intriguing finding provided evidence for molecular mimicry between the human LAMP-2 epitope (a common ANCA specificity) and bacterial adhesion FimH (derived from many Gram-negative organisms) [69]. This quite compelling hypothesis remains *in limbo* due to technical difficulties in validating these observations in other laboratories [70].

Ultraviolet radiation

In an attempt to unravel the link between disease and latitudinal gradient, an ecological study was undertaken to examine the relationship between ambient UVR and incident data from several international epidemiological studies. Ambient UVR was obtained from satellite data using the longitude and latitude of the largest urban centre in any given area. The crude incidence rates of both EGPA and GPA increased with latitude, although only GPA achieved statistical significance. Using a negative binomial regression, there was a modest increase in the incidence of both EGPA (3.4%) and GPA (3.5%) per higher degree of latitude. MPA showed no association in either analysis [71]. Although UVR has local effects on the immune system in the skin [72] and as such is of particular importance in SLE, the most plausible explanation for these findings is through the effects on vitamin D synthesis, a hormone that has profound effects on the immune system as observed in a wide range of inflammatory rheumatological conditions [73]. There are, however, no population data on vitamin D from the cohorts for which we have AAV incident data and no series measuring vitamin D in patients and matched controls [74].

Silica

Silica appears to be a consistently identified risk factor among existing case–control studies, for both GPA and MPA. This is perhaps not surprising given its known association with a number of other autoimmune syndromes [75]. Commonly inhaled, the association with AAV is observed even in the absence of respiratory tract disease and so suggesting impact beyond the immediately exposed airways. These findings are supported by a Japanese study from Kobe. This showed an increased incidence and severity of AAV for 3 years following the devastating 1995 earthquake when compared with the unaffected neighbouring Kyoto prefecture. The authors attribute this to dust and other particulate air pollution, the dust contained silica [60]. Silica of course is often not inhaled alone, and this needs to be borne in mind. Perhaps the most interesting conclusion from the Kobe earthquake is that the environmental influence can be quite proximate in a temporal sense, that is, the effect came and went soon after the original challenge [76].

Others

An excess heavy metal exposure is reported by some studies as are solvents and pesticides, the latter supporting why farming appears as an at-risk occupation in a minority of studies [77–79]. Atopy is also common, but allergies may be over-reported since some of the clinical features, for example, sinusitis, may be seen as part of the phenotype of vasculitis itself [77]. While case–control studies have highlighted a non-specific association with drug allergies, specific relationships have been reported by clinical series, including propylthiouracil, hydralazine and minocycline [80, 81]. Most recently, a growing number of cases in association with levamisole-adulterated cocaine have been noted [82]. Interestingly, the ANCA seen with drug-induced disease [82] appears to be much more heterogeneous with additional specificities such as lactoferrin, human neutrophil elastase, cathepsin G and azurocidin and a long list of less-frequent neutrophil antigens [74, 83].

Finally, tobacco smoke contains multiple active compounds that can potentially interact with the immune system [84]. Any effects could be local in the airways (all three AAV have prominent respiratory tract features) or systemic. The data, however, are less compelling. A small retrospective study showed fewer smokers in patients with AAV than a matched control population [85]. An analysis of patients enrolled in four EUVAS-sponsored controlled trials and repeated in the Vasculitis Quality of Life study indicated that smokers were more likely to have vasculitis-related gastrointestinal disease than non-smokers [86]. This effect of smoking parallels that observed in Crohn's inflammatory bowel disease, but what the observation means in terms of the overall aetiopathogenesis of AAV is unclear. Other lifestyle factors such as physical activity and diet, have been implicated in the mechanisms of other

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autoimmune diseases [87, 88] but have yet to be explored in AAV [74].

Clinical subtyping

The traditional division of the AAV into EGPA, GPA and MPA based on clinical phenotype has recently been challenged on epidemiological, genetic and clinical grounds [89, 90]. Cluster analysis of the clinical features of newly presenting GPA and MPA patients suggested five distinct phenotypes—renal AAV with PR3-ANCA, renal AAV without PR3-ANCA, non-renal AAV, cardiovascular AAV and gastrointestinal AAV—with different outcomes [91]. Patterns of disease expression vary between populations, and GPA may have a cyclical pattern of occurrence, which is not seen in MPA [15]. There are significant differences in the outcome between GPA and MPA. PR3-ANCA positivity is associated with a much higher risk of relapse [92]. The European GWAS in AAV [58] reported that PR3-ANCA disease was associated with *HLA-DP*, *SERPINA1* and *PRTN3*, while MPO-ANCA disease was associated with *HLA-DQ*. *SERPINA1* encodes alpha-1 antitrypsin, a serine protease that has PR3 as one of its substrates. PRTN3 encodes proteinase 3. Thus, the immune response against the autoantigen PR3 is a central aetiological feature of PR3-ANCA-associated vasculitis. These data suggest that perhaps a new classification is required centred around the specificity of ANCA.

CONCLUSION

Considerable strides have been made over the past 25 years. The basic descriptive epidemiology has been well established in white Caucasian populations. There are tantalizing hints emerging from variations between different ethnic and genetic populations, which may give important clues to pathogenesis. More studies are urgently needed from areas currently poorly represented such as Latin America, where there is only a single study [36], and in particular from Africa and India. Investigation of risk factors has proved more difficult, but there is building evidence around the influence of latitude perhaps mediated by the effects of UVR on vitamin D and the immune system. Silica and drugs appear to be more associated with AAV. The long-held view that there is an infectious trigger has not been borne out.

There is, therefore, much to do over the next 25 years, and we hope that by then there will be a much fuller picture of the epidemiology of the AAV.

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CONFLICT OF INTEREST STATEMENT

None declared.

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