

# Annals of the Rheumatic Diseases

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## Leader

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### Systemic vasculitis: epidemiology, classification and environmental factors

The systemic vasculitides continue to present the practising clinician with many challenges. The spectrum and severity of disease is broad from life or sight threatening fulminant disease to relatively minor skin disease. There has been over the past five years steady progress in our understanding of pathogenesis but still the precise nature of the triggering event or events remains elusive. The aetiology is clearly multifactorial; among the potential influences on disease expression are ethnicity, genes (HLA and others), sex, and environment (ultraviolet light, infections, toxins, drugs, smoking and surgery). There are sufficient differences even within the limited epidemiological data available to suggest that not all these influences work in the same direction in the various described vasculitis syndromes. This editorial will concentrate on recent developments in the classification, epidemiology, and role of environmental factors in pathogenesis.

The classification of vasculitis remains controversial. Although the American College of Rheumatology (ACR) in 1990 produced classification criteria for the major conditions<sup>1</sup> and the Chapel Hill Consensus Conference (CHCC) in 1994 developed definitions,<sup>2</sup> there are still a number of difficulties. The ACR criteria perform reasonably well when used to compare one type of systemic vasculitis with another; they perform less well when the clinical syndrome is poorly defined, some patients without vasculitis may fulfil ACR criteria for vasculitis.<sup>3</sup> The criteria were of course designed for comparing groups of patients (for example, for therapeutic studies) but not for the diagnosis of individual patients and should only be used for that purpose with caution. The CHCC definitions provide the only working definition of microscopic polyangiitis (MPA). MPA was not included as a diagnostic category by the ACR and hence the CHCC definition is increasingly being used for classification; again this was not the original purpose but is the best available. A revision of the ACR criteria based on the CHCC definitions, tested not only against patients with clear cut vasculitis but also patients with less well defined vasculitic syndromes and other connective tissue diseases is desperately needed.

The evolution of classification systems has permitted the comparison of epidemiological data from different parts of the world. So far the majority of studies have been from Europe. There have recently been completed four studies of primary systemic vasculitis (two prospective) conducted over 5-25 years from England,<sup>4</sup> Spain<sup>5</sup> and Scandinavia.<sup>6,7</sup>

The broad conclusions from these studies is that the overall annual incidence of primary systemic vasculitis is approximately 20/million. Wegener's granulomatosis has an incidence of 5-10/million, MPA 6-8/million and Churg Strauss syndrome 1-3/million. It has been previously suggested that the incidence of vasculitis is increasing,<sup>8,9</sup> the most recent studies completed in the late 1990s, generally report higher figures than earlier reports. In our own prospective study over 10 years there was no clear evidence for a change in incidence, although there was an upward trend.<sup>4</sup> It is likely that most, if not all the reported increase in incidence is attributable to an increase in physician awareness.

Two studies have now observed an age specific increase in incidence. In our study, the maximum incidence was in the 65-74 year age group whose annual incidence was 60/million,<sup>4</sup> whereas Tidman and colleagues noted a maximum incidence in men aged 55-64.<sup>6</sup> A similar age specific increase in giant cell arteritis has long been observed with the highest incidence in those aged over 80 years.<sup>10</sup>

The best data on geographical variation in incidence are for giant cell arteritis where the incidence increases with latitude in the northern hemisphere, with a twofold to threefold increase in incidence in Scandinavia compared with Spain.<sup>11</sup> Two populations with a high incidence of polyarteritis nodosa (PAN) and MPA have been described. McMahon reported a very high frequency of PAN (77/million) in Alaskan Indians.<sup>12</sup> The population was, however, small (14 000) and all the cases were positive for hepatitis B surface and e antigen at diagnosis. Whether this reflects geographical/ethnic differences or a high infection rate with hepatitis B is unclear but this contrasts with other studies from the USA and Europe reporting an incidence of 2-9/million (reviewed by Watts and Scott<sup>11</sup>). A higher incidence of PAN (16/million) and MPA (24/million) has also been reported in the ethnic Kuwaiti population in Kuwait.<sup>13</sup> Although incidence figures were only calculated for Kuwaitis, both MPA and PAN occurred in other ethnic groups, including patients from the Indian subcontinent, Philippines, Indonesia, Somalia, Egypt, Iraq and Syria, suggesting any environmental factor can operate in people of different ethnic origin. PAN has also been reported in isolated case reports from sub-Saharan Africa (Zimbabwe and Nigeria) but not from elsewhere in Africa (reviewed by Mody<sup>14</sup>).

Information on geographical variation of Wegener's granulomatosis and Churg Strauss syndrome is scarce. Prevalence studies suggest that the Wegener's granulomatosis is less common in the USA (26/million)<sup>15</sup> compared with Europe (40–60/million).<sup>4 7 16</sup> Case series from India suggest that Wegener's granulomatosis is being more frequently recognised.<sup>17</sup> Reviews of patients attending rheumatology clinics in both urban and rural Africa do not include patients with Wegener's granulomatosis but do include other forms of autoimmune disease, indirectly implying that the condition might be very rare. In areas where tuberculosis is common, patients presenting with pulmonary disease are liable to be misdiagnosed with tuberculosis.

The cyclical occurrence of giant cell arteritis was first noted in Olmsted County (USA) where over a 40 year period peaks occurred every seven years, a finding that would be consistent with an infectious aetiology.<sup>10</sup> In Denmark peak incidences were correlated with the occurrence of epidemics of *Mycoplasma pneumoniae* infection.<sup>18</sup> Using a matched case control method Russo *et al* (1995) showed a correlation between infection and onset of giant cell arteritis but could not identify a specific infection.<sup>19</sup> Recently Tidman noted during 1975–95 a periodic fluctuation in incidence of ANCA associated vasculitis with peaks every three to four years.<sup>6</sup>

Seasonal variations in presentations of Wegener's granulomatosis also suggest an infectious aetiology but the data are inconsistent. Raynauld and colleagues (1993) reported a higher rate of onset in winter (29.8%) compared with summer (14.3%).<sup>20</sup> In Norwich, we also found a more frequent onset in winter (December–February) with 43% of patients first developing symptoms in these months.<sup>9</sup> This trend was also seen in ANCA associated glomerulonephritis and systemic vasculitis.<sup>6 21</sup> The USA prevalence study of Wegener's granulomatosis did not, however, support the notion of seasonality<sup>15</sup> nor did a study of environmental exposure.<sup>22</sup> Part of the difficulty with all these studies is defining accurately the date of onset of symptoms.

Viral infection has been clearly associated with two specific forms of vasculitis. PAN in its classic form is strongly associated with hepatitis B infection and seems to have a different clinical phenotype from MPA. Classic PAN is often a one shot disease responding to anti-viral treatment<sup>23</sup> whereas MPA is a relapsing remitting condition.<sup>23 24</sup> A clear association has also emerged between essential mixed cryoglobulinaemia and hepatitis C infection<sup>25</sup> where anti-viral treatments may be effective.

Case reports of parvo virus B19 occurring in Wegener's granulomatosis, led to a study of 42 patients with new onset disease, however, no association of Wegener's granulomatosis with parvo B19 infection was observed.<sup>26</sup> Other agents with suspected links to vasculitis include Chlamydia, herpes viruses and parainfluenza virus.<sup>27 28</sup> Specific searches for infectious agents and case-control studies have so far been unfruitful. Vaccination against hepatitis B, pneumococci and influenza has been linked to onset of vasculitis in individual case reports but no case-control studies have been performed.<sup>29–32</sup>

Chronic nasal carriage of *Staphylococcus aureus* has been associated with an increased risk of relapse in Wegener's granulomatosis, which is improved by treatment with trimethoprim/sulphamethoxazole.<sup>33</sup>

Other potential environmental factors include inhaled allergens and particulate pollution. The frequency of asthma and allergy in the Churg Strauss syndrome and upper airway involvement in Wegener's granulomatosis has led to a search for potential inhaled allergens. D'Cruz and colleagues were unable to find an association with any specific allergens.<sup>34</sup> Although the majority of cases of Churg

Strauss syndrome are idiopathic, inhaled antigens (hay), vaccination, and desensitisation (candida, microbial), infection (ascaris) and discontinuation of oral corticosteroids have been reported as trigger factors.<sup>35</sup>

Environmental pollution is suggested by differences between rural and urban populations; systemic vasculitis in general was found to be commoner in urban areas of Germany.<sup>16</sup> In New York state, some counties had a higher prevalence of Wegener's granulomatosis but there was no significant difference in prevalence between metropolitan and non-metropolitan counties.<sup>15</sup> Duna and colleagues (1998) studied self reported exposure to fumes and particulates and were unable to demonstrate any significant difference between Wegener's granulomatosis patients and pulmonary controls.<sup>22</sup> In Norfolk, Churg Strauss syndrome seems to be commoner in rural areas.<sup>36</sup> Case-control studies are needed to explore further the possible link between allergy and vasculitis.

Other potentially important non-infectious environmental factors include occupational exposure to silicon. This was initially described in case reports where patients with pulmonary silicosis developed vasculitis. Case-control studies indicate that exposure to silicon containing compounds is associated with development of chronic renal failure and vasculitis (odds ratio 6.5) (reviewed by Cohen *et al*<sup>37</sup>). MPO-ANCA has been described in patients with pulmonary silicosis and nephropathy.

Several drugs have been associated with development of vasculitis in particular propylthiouracil and hydralazine.<sup>38</sup> Recently Wechsler and colleagues (1998) reported eight patients with corticosteroid dependent asthma receiving the sulphidopeptide-leukotriene antagonist Zafirlukast who developed Churg Strauss syndrome associated with withdrawal of corticosteroids.<sup>39</sup> Two patients probably had pre-existing Churg Strauss syndrome with asthma, neuropathy and pulmonary infiltrates. In the other patients Zafirlukast improved asthma control sufficiently to permit reduction in corticosteroid dose. Churg Strauss syndrome became apparent within days or months of the dose reduction. Although allergic vasculitis attributable to Zafirlukast is possible, it is more likely that reduction of corticosteroid dose unmasked underlying Churg Strauss syndrome.

In conclusion, knowledge of the epidemiology of vasculitis is increasing albeit slowly, data are urgently needed from Africa, Asia and the Pacific, and also from Europe and the USA in non-white populations. Studies of the epidemiology of systemic lupus erythematosus in different communities have led to the prevalence gradient hypothesis<sup>40</sup> with migration of sub-Saharan Africans to the Caribbean and USA, and subsequently to the UK. Systemic lupus erythematosus is apparently relatively uncommon in Africans living in sub-Saharan Africa but is much more common in the same ethnic groups living in the Caribbean and USA, and moving subsequently to the UK. The recent observation of cyclical peaks in the incidence of vasculitis and possible differences between urban and rural populations provide pointers towards new avenues for research. A broader search for infectious triggers possibly by using new polymerase chain reaction based techniques is required. Confirmation that the primary systemic vasculitides have geographical and ethnic variations would be a first step in elucidating the interplay between environment and genes in these fascinating diseases.

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