Epidemiology of Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome

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The primary systemic vasculitides (PSV—Wegener's granulomatosis [WG], Churg-Strauss syndrome [CSS], microscopic polyangiitis [MPA], polyarteritis nodosa [PAN]) are a group of uncommon diseases. The etiology of vasculitis is unknown but is clearly multifactorial; among the influences on disease expression are ethnicity, genes (HLA and others), gender, and environment (infections, toxins, drugs, allergy, smoking, UV light). There are sufficient differences, even with the limited epidemiological data available, to suggest that not all these factors work in the same direction in the various vasculitic syndromes described.

The lack of any clear understanding of the etiology of the systemic vasculitides and universally accepted classification systems hampered accurate epidemiological studies until the 1990s.

CLASSIFICATION OF VASCULITIS

The American College of Rheumatology (ACR), in 1990, proposed criteria for the classification of seven types of vasculitis.[1] The ACR criteria are not perfect. They were established by comparing patients with different types of vasculitis, but not with patients prior to the diagnosis of vasculitis, or with other systemic diseases or even with other connective tissue diseases. The reliability of these criteria when used in patients in whom vasculitis is suspected but not yet diagnosed is poor.[2]

In 1994, consensus definitions were proposed at the Chapel Hill Consensus Conference (CHCC). These provided important and useful definitions of disease but were not considered appropriate for diagnosis or classification of patients as no specific criteria were produced.[3] Microscopic polyangiitis (not included by the ACR study) was defined for the first time. We have shown, for example, that the currently available criteria/definitions often identify different patients.[4] The implication of these developments is that any study must identify the criteria/definitions on which the diagnosis has been based. Furthermore, the ACR classification criteria and the Chapel Hill Consensus definitions did not specifically include ANCA.

EPIDEMIOLOGY

Most studies are hospital-based from tertiary/university referral centers with ill-defined denominator populations and hence referral bias. Patients seen in tertiary hospitals may not be representative of those seen either at district hospitals or in the community, especially in terms of disease severity or age spectrum. Prospective population-based estimates of incidence and prevalence are few.

The epidemiology of PSV has been studied in the Norwich Health Authority (England) with data collected prospectively from 1988. Incidence rates adjusted for age and sex to the 1992 population show an overall annual incidence of primary systemic vasculitis of 19.8 per million. The point prevalence on December 31, 1997 was 144.5 per million. Primary systemic vasculitis was more common in males (23.3 per million) than females (16.4/million). The age- and sex-specific incidence showed a clear increase with age with an overall peak in the 65-to-74-year age group (60.1 per million).[5]

GEOGRAPHICAL FACTORS

A study using the same classification criteria (ACR [1990] and CHCC) in three populations—Norwich; Tromsø (North Norway); and Lugo (North-West Spain), confirmed the older age at onset (compared with previous studies) and showed a similar overall incidence and pattern of vasculitis in terms of age and sex distribution. Microscopic polyangiitis was more common (11.6/million) in Spain compared with Norway (2.7/million), while WG was less common in Spain (4.9/million) compared with Norway (10.5/million). Churg-Strauss syndrome appeared to be more common in Norwich

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(3.1/million) compared with the other two populations.[6] Comparative data from well-defined populations may provide further insights into the role of environmental or genetic factors in the pathogenesis of vasculitis.

There are two studies which reported a particularly high annual incidence of PAN. McMahon and colleagues reported a high frequency of PAN (77/million) in Alaskan Indians.[7] The population was small, and all the cases were positive for hepatitis B surface and e antigen at diagnosis. Detailed hepatitis serology was not available in the other studies. Whether these data reflect geographical and ethnic differences or a high infection rate with hepatitis B is unclear as no other comparable study has been reported. The second population with an apparently high incidence of MPA and PAN is the Kuwaiti national population, where the incidence of classical PAN was 16/million and MPA 24/million. Although incidence figures were only calculated for Kuwaitis, both MPA and PAN occurred in other ethnic groups, suggesting any environmental factor operates irrespective of ethnic origin.[8]

TIME TRENDS

The incidence of Wegener's granulomatosis (WG) may be increasing. Andrews and colleagues (1990) in Leicester (UK) reported an increase in the annual incidence of WG from 0.7/million (1980–1986) to 2.8/million (1987–1989).[9] This was partially attributed to an increase in diagnostic awareness following the introduction of assays for ANCA in 1987. The incidence of Wegener's granulomatosis has, however, increased in Tromsø, Norway, from 5/million to 12.5/million over the last 15 years.[10] We have observed a small but not significant increase during the 10-year period of our study.

INFECTION

The strongest association of infection with vasculitis is PAN with hepatitis B virus infection (HBV); the highest incidence rate for PAN comes from an area endemic for HBV infection. Whether HBV infection results in PAN may be determined by HLA haplotype. In a familial cluster, a father and two sons were infected with HBV through use of a shared razor; however, only the father and one son developed PAN. They shared HLA haplotypes, whereas the other son had a different HLA haplotype.[11]

Tidman and colleagues,[12] in a hospital study of patients with ANCA-associated vasculitis and renal involvement during 1975–1995, noted a periodic fluctuation with peaks every 3 to 4 years, suggesting an infective etiology. This cyclical pattern for ANCA-associated vasculitis has not yet been confirmed.

Wegener's granulomatosis has been linked to parvovirus B19 and *Staphylococcus aureus* infection. The initial studies associating Wegener's granulomatosis and parvovirus B19 infection were case reports, but a detailed study of 42 patients with new-onset disease showed no evidence for this infection.[13] Nasal carriage of *S aureus* has been associated with increased risk of relapse in WG.[14] Over 10 years, we have not been able to demonstrate any periodic fluctuation, nor have we been able to associate onset with mycoplasma, parvovirus, chlamydia, or influenza.

ENVIRONMENTAL FACTORS

A number of other trigger factors have also been reported in association with systemic vasculitis, including silica, solvents, allergy, and vaccination.

A case-control study undertaken in Norfolk showed an association between occupations with high exposure to silica and PSV. In particular, pANCA/MPO-positive patients showed an association rather than cANCA/PR3. It is notable that the incidence of MPA doubled after the Kobe earthquake, when exposure to silica would have been high.[15] Three case-control studies also support the association of silica with ANCA-positive glomerulonephritis, MPA, and WG.[16-18] Our case-control study also found a significant association of occupational exposure to organic solvents with WG and cANCA-positive vasculitis.

We have found an association between farming and PSV (adjusted odds ratios between 2.2 and 6.3). Interestingly, a significant association was not seen for CSS. It was not possible to identify a particular causal exposure, but exposure to livestock showed a stronger association than crop exposures. In particular, exposure to cows, sheep, and chickens showed an association with PSV overall. cANCA and pANCA showed similar associations to farming as a whole, predominantly livestock exposures. Duna and colleagues[19] studied self-reported exposure to heat, fumes, and particulates. There was a higher incidence of exposure in WG patients compared with normal control subjects, but no difference between WG patients and patients with pulmonary disease. They found no association between farming and WG, which may be explained by selection bias of cases.

Clusters of Wegener's granulomatosis occurring in families have been described (reviewed in reference 20). In most clusters, no more than two people have been affected, usually one parent and a child or two siblings. Distant family members are rarely reported. The occurrence of clusters in first-degree relatives and not in more distant family members suggests that environmental triggers play an important role in the etiology, as parents and children or siblings share their environment as well as genetic background.

SEASONALITY

Raynauld and colleagues in 1993 reported a higher rate of onset in winter (29.8%) compared with the summer (14.3%).[21] This trend was also supported by a study of ANCA-associated glomerulonephritis and systemic vasculitis, which showed a higher onset in winter.[22] We have been unable to demonstrate any significant seasonal differences.

DRUGS

Many drugs have been associated with vasculitis; in the majority of cases these have been anecdotal. Propylthiouracil and hydralazine are drugs known to be

associated with vasculitis and propylthiouracil, in particular with high titers of pANCA/MPO.[23]

Wechsler and colleagues[24] reported eight patients with glucocorticosteroid-dependent asthma receiving the sulphidopeptide-leukotriene antagonist zafirlukast who developed CSS associated with corticosteroid withdrawal. Two patients probably had preexisting CSS with asthma, neuropathy, and infiltrates. In the other patients, zafirlukast improved asthma control sufficiently to permit reduction in glucocorticoid dose. CSS became apparent within days or months of the dose reduction. Although allergic vasculitis due to zafirlukast is possible, it is more likely that reduction of steroid dose unmasked underlying CSS.

CONCLUSIONS

The systemic vasculitides are a group of important inflammatory conditions resulting in inflammation and necrosis of blood vessel walls. They are associated with significant morbidity as well as mortality, particularly microscopic polyangiitis. They are commoner than previously believed, with an annual incidence of primary systemic vasculitis of 20/million/year. The primary vasculitides are also seen in a much older population than was previously believed due to the development of vasculitis registers in district hospitals such as Norwich. Classification criteria and disease definitions are now well established, which has led to conformity between different centers, allowing geographical comparisons. The numbers of studies are still relatively small, and further understanding of these diseases, particularly in the Indian subcontinent and the Far East, may be important in areas where other infections are common, particularly TB.

Studies of epidemiology have suggested some important avenues for research in terms of environmental factors, particularly the role of silica and potential infections associated with farming. Data, however, are still essentially descriptive at this stage, but further epidemiological studies will hopefully shed further light on etiopathogenesis.

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