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Diagnosis of Wegener’s Granulomatosis in the ANCA Era

Wegener’s granulomatosis (WG) is a chronic granulomatous necrotizing vasculitis predominantly affecting the upper and lower respiratory tracts and the kidneys. Other organs less commonly involved include the skin, joints, eyes, heart, and peripheral and central nervous systems. The disease is closely associated with circulating antineutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 (PR3), and less commonly against myeloperoxidase. The etiology of WG remains unknown. Although a genetic predisposition is thought to contribute to the development of the disease, the relevance of the genetic variations reported to date is unclear.

The disease is more common in Caucasian populations, but familial cases are very rare and the disease has not been reported in homozygous twins.

A number of environmental factors have been associated with WG. These include respiratory infections, farming, occupational silica and solvent exposures, prior history of allergy to a drug, and history of allergy overall. Rare clusters of cases have been reported, which also suggests environmental factors may contribute to the etiology of the disease. Whether the higher prevalence of WG seen in Northern Europe and in New Zealand compared with Southern Europe reflects the role of environmental influences remains unclear.

In recent years, several studies have suggested that the incidence of WG may be increasing. For example, the annual incidence per million population in northern Norway of 5.2 (95% CI 2.7–9.0) during 1984-88 increased to 12.0 (95% CI 8.0–17.3) during 1994-98. Similar trends of a lesser magnitude were seen in the UK, with an incidence of 8.7 (95% CI 5.2–13.8) during 1988–92 and 10.3 (95% CI 6.4–15.5) during 1993-97.

In this issue of *The Journal*, Knight, *et al* report on the largest published study on the incidence of WG. Using the population-based Swedish Inpatient Register, which records individual-based information on all hospitalizations nationwide, they identified 1636 individuals discharged with a diagnosis of WG between 1975 and 2001, corresponding to a mean incidence per million of 8.6 among men (95% CI 8.0–9.1) and 7.0 among women (95% CI 6.5–7.6). Of interest, the authors observed a statistically significant increase in the incidence of the disease over the study period from 3.3 (95% CI 2.8–3.9) in 1975-84 to 7.7 (95% CI 6.9–8.5) in 1985-90, and to 11.9 (95% CI 11.2–12.6) in 1991-2001. The time trend was similar among men and women, and the age of the patients at the time of discharge remained stable over the study period.

ANCA testing was introduced in some parts of Sweden in 1988, and in the rest of the country in the early 1990s. This raises the question of whether ANCA testing is the main or even the sole explanation for the very significant time trend observed in this and previous studies. Or are we witnessing a true rise in the incidence of the disease? Knight, *et al* maintain that ANCA testing cannot be the only explanation, since an increase in the incidence of the disease was noted 3 years before the introduction of testing in 1988. Thus the annual incidence of WG was stable until 1985 (4 per million in 1975, and 3/million in 1977, 1979, 1981, and 1983); incidence rose slightly between 1985 and 1987 (5/million in 1985, 7/million in 1986, and 7/million in 1987), and then considerably more after 1988 (9/million in 1989, 12/million in 1995, and 15/million in 2001).

Although ANCA testing was not available in Sweden until 1988, increased physician awareness of WG following the discovery of ANCA in 1982 could certainly explain the rise in the incidence of the disease observed between 1985 and 1987. A Medline search using the key term Wegener’s granulomatosis yielded a significant increase in the number of articles on WG published between 1982 and 1987 (540) versus 1969-75 (385).

Further, if we conclude that the rise in the incidence of the disease can be explained entirely by the introduction of ANCA testing and increased physician awareness, the next question is what diagnosis did patients with true WG erroneously receive prior to 1985? It doesn’t appear that patients were misdiagnosed as having polyarteritis nodosa (PAN) because the incidence of PAN was at a similar if not lower level in the decade prior to introduction of ANCA versus the
decade after\textsuperscript{9}. As suggested by the authors, it is certainly possible that the low incidence of WG observed in the early time period may be due to patients dying of multi-organ failure from their disease before being diagnosed and properly treated. In support of this hypothesis is the observation of a significantly longer delay between symptom onset and diagnosis in earlier series (median 15 mo)\textsuperscript{11} than in more recent ones (median 3 mo)\textsuperscript{12}. Also, knowledge about therapy was not as widespread as it is today: The first publication on the use of cyclophosphamide in WG appeared in the early 1970s and the US National Institutes of Health case series of 85 patients was published more than a decade later\textsuperscript{13}.

Since WG diagnosis based on American College of Rheumatology (ACR) criteria by chart audit was confirmed in 89\% of a patient sample, it is unlikely that individuals being misdiagnosed with WG can explain the trend observed. As the authors included only patients who received inpatient care, it is probable that the true incidence of WG in the general population is significantly higher than reported so far. In contrast to the authors’ experience, we have followed a number of ANCA-positive patients with limited WG who have never been hospitalized. These patients present with chronic nasal, sinus, and/or otologic symptoms and have positive ANCA by indirect immunofluorescence (IIF) and ELISA. However, because nasal and sinus biopsies have less than a 30\% chance of showing granulomatous inflammation due to the small size of the specimens obtained\textsuperscript{14}, many of these patients do not meet the ACR classification criteria but are still considered to have the disease. This being said, it is important to emphasize the need to rule out other etiologies in these patients, including chronic infection and cocaine use. This was emphasized in a recent report from the Mayo Clinic describing 25 patients with cocaine-induced midline destructive lesions\textsuperscript{15}. With the exception of one patient, none had histopathologic evidence of WG. Despite this, 19 of these patients (76\%) had positive ANCA by IIF (mostly perinuclear-ANCA) and 12 (57\%) were PR3 ANCA-positive using at least one assay. In cocaine users, human neutrophil elastase, which is structurally and functionally related to PR3, is the target for ANCA, as suggested by the observation of human neutrophil elastase-ANCA in 84\% of these patients.

The discovery of ANCA has increased physicians’ awareness of WG and facilitated diagnosis. It is likely that ANCA testing is responsible for the observed increase in the incidence of the disease in the last 20 years. Unless unidentified environmental factors also contribute to the observed trend, one would expect incidence of the disease to stabilize over the next several years. Stabilization in the incidence of WG already seems to be apparent in Germany, but further observation is needed to confirm this hypothesis\textsuperscript{12}.

**REFERENCES**


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