The epidemiology of Wegener’s granulomatosis and microscopic polyangiitis in a Southern Hemisphere region

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Objective. To determine the prevalence of Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) in the province of Canterbury, New Zealand.

Method. Three hospital clinical databases and the immunology laboratory database were searched and case notes reviewed for patients fulfilling either the 1990 American College of Rheumatology (ACR) criteria for WG or a modification of those criteria that allowed for antineutrophil cytoplasmic antibody (ANCA) positivity in the absence of granulomatous vasculitis. MPA was defined by the Chapel Hill consensus definition; however, in the absence of histological evidence of pauci-immune glomerulonephritis, ANCA positivity in association with evidence of active glomerular disease was included as a criterion. The point prevalence at 31 December 2003 and the 5-yr period prevalence for the interval 1 January 1999 to 31 December 2003 were calculated.

Results. Seventy-three patients with WG and 28 patients with MPA fulfilled the inclusion criteria. A 5-yr period prevalence of 152 WG cases/million [95% confidence interval (CI) 117–186] and 58 MPA cases/million (95% CI 37–80) was calculated using 2001 census data as denominator. Nineteen patients with WG died and 10 patients with MPA died during the study period, resulting in a point prevalence for survivors at 31 December 2003 of 112 cases/million (95% CI 82–142) and 37 cases/million (95% CI 20–55), respectively. Apart from respiratory tract involvement, which formed part of the case definition of WG, organ involvement was similar in both diseases.

Conclusion. The prevalence of WG and MPA in Canterbury is the highest reported to date. Restricting the case definition of WG to the ACR classification criteria we found a prevalence equivalent to that described in northern Norway. The clinical severity and serological characteristics were similar to descriptions in other WG and MPA patient cohorts. Studies of disease prevalence in other Southern Hemisphere centres will determine if the observed north–south negative disease gradient in the Northern Hemisphere is reciprocated.

KEY WORDS: Wegener’s granulomatosis, Microscopic polyangiitis, Epidemiology, Southern Hemisphere.

Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) are systemic vasculitides of medium and small vessels with overlapping clinical and serological features.

WG produces granulomatous inflammation of the upper and lower respiratory tract and a necrotizing, pauci-immune glomerulonephritis. Patients presenting with an indistinguishable renal lesion and non-granulomatous vasculopathy are considered to suffer from MPA. WG and MPA are associated with a high prevalence of proteinase-3 (PR3) and myeloperoxidase (MPO) antineutrophil cytoplasmic autoantibodies (PR3-ANCA, MPO-ANCA), respectively. These antibodies are now established as a useful diagnostic test. In clinical practice, and given a high clinical suspicion of small vessel vasculitis, specific ANCA are often used as a confirmatory diagnostic test in the absence of histological confirmation. While it is acknowledged that there are difficulties in classification and case definition [1], recent epidemiological studies have included ANCA as one of the inclusion criteria [2].

The aetiology of WG is unknown; however, involvement of the upper airway points toward an environmental trigger, possibly an inhalant. The potential importance of an environmental risk factor(s) is also supported by epidemiological studies from the Northern Hemisphere suggesting a north–south negative disease gradient [3]. No epidemiological studies have been conducted in the Southern Hemisphere.

Our study aimed to determine the prevalence and clinical features of WG and MPA in the province of Canterbury, New Zealand.

Patients and methods

Ethical approval was obtained from the Upper South Regional Ethics Committee. The Christchurch Hospital in-patient database was searched for all patients fulfilling the inclusion criteria for WG or MPA between 1 January 1999 and 31 December 2003. This database uses the International Classification of Diseases...
ICD coding system for discharge diagnosis. We searched on ICD 9 and ICD 10 codes (446.0, 446.20, 446.21, 446.29, M30.0, M30.1, M31.8, M31.9 plus N00 to N08.5) that included the specific diagnoses plus non-specific diagnostic codes that maybe used to describe important clinical features of WG and MPA. One-third of each of the patient groups given a non-specific diagnostic code had their case notes reviewed for evidence of ANCA positivity. If no positive results were found no further patients given that code were reviewed. In addition, the databases of the Department of Nephrology and the Department of Rheumatology, Immunology and Allergy were searched for patients given a specific diagnosis of WG or MPA.

During the study period the Canterbury Health Laboratories immunology section provided PR3-ANCA and MPO-ANCA testing for the entire South Island and part of the North Island of New Zealand (Fig. 1). Serum ANCA were screened by indirect immunofluorescence (IIF) of ethanol-fixed normal human neutrophils. All positive samples irrespective of IIF pattern were analysed for specific antibodies directed against PR3 or MPO by two in-house enzyme-linked immunosorbent assays (ELISAs). All patients with a value above the laboratory cut-off for PR3-ANCA and/or MPO-ANCA living in the province of Canterbury during the study period were identified.

From these searches a list of potential patients was generated and their case notes reviewed. To be included, patients had to fulfil either the American College of Rheumatology (ACR) classification criteria for WG or a modification of those criteria that allowed for ANCA positivity. The ACR criteria for WG state that the patient must have at least two of the following: (i) nasal/oral inflammation, (ii) abnormal chest X-ray, (iii) abnormal urinary sediment, and (iv) granulomatous inflammation on biopsy. Where a biopsy was not taken, was inadequate or did not show granulomatous vasculitis the presence of elevated levels of either PR3-ANCA or MPO-ANCA was added as a fifth criterion. The ACR criteria do not allow for a diagnosis of MPA and were developed prior to the widespread use of ANCA. The Chapel Hill Consensus Conference (CHCC) definition of MPA was therefore used but again allowance was made for ANCA positivity. Where a renal biopsy was not taken, or proved inadequate, patients were classified as having MPA if MPO-ANCA or PR3-ANCA were positive and there was evidence of acute glomerular disease (red cell casts and/or haematuria).

Along with demographic information, the case note audit allowed for the collection of information on potentially life-threatening organ involvement. Case notes were searched for evidence of the following: (i) significant proteinuria defined as at least 1 g/24 h, (ii) creatinine ≥0.14 mmol/l, (iii) an active urinary sediment (haematuria or red cell casts), (iv) serious bowel involvement (ischaemia, infarction or perforation), (v) cardiomyopathy, (vi) central nervous system disease (clinical evidence of persistent CNS deficit), (vii) inflammatory lesions of the upper airway, ear, nose or throat (nasal ulcers, epistaxis, subglottic stenosis), (viii) symptomatic lower respiratory involvement (haemoptysis or mention of pulmonary infiltrates and/or cavities on X-ray following diagnosis).

![NEW ZEALAND](image.png)

**Fig. 1.** Map of New Zealand showing the study region and the catchment of Canterbury Health Laboratories shaded area. New Zealand lies between latitudes 34° and 48°S.
The province of Canterbury in the South Island of New Zealand had a population of 481000 at the 2001 census [6]. There were 48.8% males, 20.3% <15 yr and 13.8% >65 yr. Of these, 91.8% identified themselves as New Zealand European (as opposed to Maori, Pacific Islander, Chinese, Indian or other ethnicity). The province lies between latitudes 42°S 44°S. Christchurch (43.5°S) is the main urban centre within the region where 66% of the regional population reside (Fig. 1). Christchurch Hospital is the major provincial referral centre and public hospital. The health system in New Zealand is structured such that the majority of non-surgical patients is seen in the public health system. Furthermore, during the period of the study, the immunology laboratory (Canterbury Health Laboratories) servicing Christchurch Hospital was the only laboratory providing MPO-ANCA and PR3-ANCA testing in the Canterbury province. This allowed for the identification of all patients positive for serum PR3-ANCA or MPO-ANCA.

The period prevalence was calculated using the number of Canterbury residents who fulfilled the inclusion criteria for WG and MPA, respectively, as the numerator and the 2001 census population as the denominator. The calculation of 95% confidence intervals (95% CIs) assumed the number of cases followed the Poisson distribution.

Results

Prevalence

A summary of the search strategy and results is shown in Fig. 2. The search of the ICD coding system yielded 111 patients. The Nephrology and Rheumatology Department databases yielded 34 additional patients given a diagnosis of WG and 27 additional patients given a diagnosis of MPA. An additional 141 patients were identified from the immunology laboratory search as having a positive PR3-ANCA or MPO-ANCA during the 5-yr study period. Therefore a total of 313 potential patients had their case notes reviewed against the inclusion criteria.

Seventy-three patients (28 males) fulfilled the inclusion criteria for WG [mean age 66 yr (range 27–91 yr); 19 (26%) died during the study period]. When restricted to the ACR classification criteria for WG, 63 patients were identified, of whom 18 (28%) died during the study period. One WG patient fulfilled only the ACR criteria. Twenty-eight patients (17 males) fulfilled the inclusion criteria for MPA [mean age 70.5 yr (range 41–94 yr); 10 died during the study period]. Thus the 5-yr period prevalence in Canterbury, New Zealand was 152/million (95% CI 117–186) for WG [131/million (95% CI 99–163) when restricted to ACR classification criteria] and 58/million (95% CI 37–80) for MPA.

Of the remaining cases, 15 patients identified from the immunology laboratory search were excluded as they were not from Canterbury. No further information could be obtained for another six patients. The remaining 191 patients had a variety of diagnoses including inflammatory bowel disease, bronchiectasis, interstitial lung disease, glomerulosclerosis, infection, systemic lupus erythematosus, Goodpasture’s disease and Churg–Strauss syndrome (two patients). While no cases of polyarteritis nodosa were identified using this search strategy, at least four patients with idiopathic mesenteric arteritis were recorded on the rheumatology database.

Clinical features

As outlined in Table 1, upper respiratory tract/ear, nose and throat (ENT) involvement was the most common clinical feature in the WG cohort (63/73, 86%). Lower respiratory tract involvement was present in 38/73 (52%). One patient with MPA had upper respiratory tract involvement whilst another had lower respiratory tract involvement. However, these disease manifestations were not a prominent feature of the disease and therefore these patients were considered to have MPA rather than WG.

Serious renal involvement was more prominent in the MPA group, with significant proteinuria and/or elevated serum creatinine present in 82% compared with 34% in the WG group (these summative figures are not shown in the table). In addition, two patients with WG and four with MPA were on dialysis while one patient with WG and one with MPA had received a renal transplant.

There was a clear bias in antibody specificity, with 82% of WG patients PR3-ANCA positive and 15% MPO-ANCA positive. The antibody specificity was reversed for MPA with 3.5% PR3-ANCA positive and 89% MPO-ANCA positive. Two patients with WG were both PR3-ANCA and MPO-ANCA positive, while 4/73 (5.4%) WG and 2/28 (7%) MPA patients were MPO-ANCA and PR3-ANCA negative.

Forty-five (61%) of the WG cohort had a biopsy from a variety of sites including kidney, lung, skin and nasal mucosa. Of these, 35 (78%) revealed granulomatous inflammation. Renal biopsy
was performed in 22 (79%) of the MPA patients, all of whom had pauci-immune glomerulonephritis except for one patient whose biopsy was inadequate for interpretation. One patient was admitted with rapidly progressive renal failure and died with post-mortem findings consistent with MPA.

### Mortality

During the study period, 19/73 (26%) patients with WG died, giving a point prevalence for WG survivors at 31 December 2003 of 112 per million (95% CI 83–142) [using ACR criteria only 93.5/million (95% CI 66–121)]. The mean age of the deceased was 72.6 yr (WG cohort mean age 66.7 yr) with a male:female ratio of 10:9. Six of the 19 had a serum creatinine ≥0.14 mmol/l, two were on dialysis and one had a renal transplant. One patient had bowel involvement, three proteinuria, five central nervous system disease and three cardiomyopathy.

During the study period, 10/28 (36%) patients with MPA died, giving a point prevalence for survivors at 31 December 2003 of 37 per million (95% CI 20–55). The mean age of the deceased was 74 yr (MPA cohort mean age 70.5 yr) with an equal male:female ratio. One patient suffered bowel involvement, two central nervous system involvement, four cardiomyopathy, six had a serum creatinine ≥0.14 mmol/l, two were on renal replacement therapy and six had proteinuria ≥1 g/24 h.

### Discussion

There is accumulating evidence that in some regions of the world the prevalence of small vessel vasculitis has increased over the past two decades whereas in others it appears to have remained static [9–11]. In a well-conducted study from Tromso, northern Norway, using ACR classification criteria, Koldingnes and Nossent [3] showed that the point prevalence of WG successively increased from 30.4 cases/million in 1988, to 49.3 cases/million in 1993, to 95.1 cases/million in 1998. This increase was not likely to be due to ascertainment bias or improved survival as the inclusion criteria were designed to apply equally across the three quinquennia. In addition over the same 15-yr period the incidence increased from 5.2 cases/million/yr to 12.0 cases/million/yr. Using the ACR classification criteria we found that the point prevalence for WG in Canterbury in 2003 (93.5/million) was the same as that in northern Norway (95/million).

Two studies from the UK have also recorded an increasing prevalence, although of a lesser magnitude [7, 8]. In Norwich, England the point prevalence of WG in 1997 was 63/million [7] while in Paris the prevalence in 2000 [2] was lower at 23.7/million a figure similar to that found in the USA (30/million) [11]. These studies give support to a Northern Hemisphere north–south negative disease gradient that is of interest as it hints at a latitude-dependent predisposition. It would be of interest to know if a reciprocal gradient for WG is present in the Southern Hemisphere.

Prevalence data on MPA are less comprehensive as it has only recently been distinguished from polyarteritis nodosa, so comparisons between studies are difficult. We found a 5-yr period prevalence of 58/million and point prevalence at 31 December 2003 of 37/million for MPA. In our study the prevalence of MPA was about one-third that of WG. Data from Leicester and Norwich, England [7, 8] suggest an increasing incidence of MPA. The Norwich study identified 33 new cases in the 10-yr period January 1988 to December 1997. Because of the retrospective nature of our study and the difficulty in identifying the time of disease onset we did not feel it was possible to provide reliable incidence statistics. Mahr and colleagues reported a prevalence of 25.1/million for MPA in a Paris-based study for the calendar year 2000 [2]. Interestingly in this Paris study (latitude 49°N) the prevalence of MPA and WG was near equal, while in Lugo, Spain (latitude 43°N) the annual incidence of MPA was over 2.5 times that of WG [12].

Our WG cohort had clinical features not dissimilar to those recorded in the last 5-yr period of the Norwegian study [3]. Involvement of the upper respiratory tract occurred in 86 vs 75%, the lower airway in 52 vs 68% and renal disease in 78 vs 79%. Involvement of the lower respiratory tract in our cohort may be an underestimate as chest X-rays were not reviewed. The difference in the frequency of heart disease (13.7 vs 21%) and gastrointestinal disease (9.6 vs 0%) and other low-frequency organ involvement is unlikely to represent a true difference as it is evident that there is considerable variability in organ involvement between time periods [3].

Descriptions of ANCA positivity vary between different prevalence and incidence studies and the specificity is not always described. Overall the positivity for one or other ANCA specificity in our combined disease cohort was high (95%), supporting disease homogeneity. This was also reinforced by the bias in ANCA specificity between the two diseases, a difference that has been recognized previously [13].

Because of the methodology used and the structure of the medical and laboratory services in the Canterbury region we believe our data are as close to a census as can be achieved. It is possible, although we believe unlikely, that we may have missed a small number of potentially classifiable patients. These patients would have had to have been PR3-ANCA and MPO-ANCA negative and never have been admitted to Christchurch Hospital with a diagnosis of WG or MPA or any disease with similar clinical features. Because ANCA is now almost a sine qua non for two of the ANCA-associated vasculitides (WG and MPA) our laboratory coverage has allowed us to identify all ANCA-positive WG and MPA patients tested in the region. It is possible that patients already diagnosed and entering our region from overseas or entering from other New Zealand regions not covered by our laboratory may have been missed. However, for that to have been the case such patients would not have had any further ANCA testing or have been an in-patient at Christchurch Hospital or attended the rheumatology or nephrology services. Our respiratory and ENT services do not have readily searchable databases. An informal survey of these specialist colleagues did not reveal any additional patients and also emphasized that a diagnosis of either disorder was unlikely to be made in the absence of ANCA.

New Zealand lies between latitudes 34°S and 47°S with a notable diversity of geographical and climatic conditions. It is a legislative requirement for all New Zealand public hospitals to code in-patient discharges using the ICD system. This information is retained in a national registry, which it may be possible to search for evidence of a geographical disease gradient.

### Table 1. Summary of clinical and laboratory features in WG and MPA

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>WG, n = 73 (%)</th>
<th>MPA, n = 28 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 yr</td>
<td>47 (63)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Upper respiratory tract/ENT</td>
<td>63 (86)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>38 (52)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CNS</td>
<td>15 (20)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Heart</td>
<td>10 (14)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Bowel</td>
<td>7 (10)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Haematuria/red cell casts</td>
<td>55 (75)</td>
<td>28 (100)</td>
</tr>
<tr>
<td>Creatinine &gt;0.14 mmol/l</td>
<td>19 (25)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Proteinuria &gt;1 g/day</td>
<td>15 (20)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>PR3-ANCA positive</td>
<td>60 (82)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>MPO-ANCA positive</td>
<td>11 (15)</td>
<td>25 (89)</td>
</tr>
<tr>
<td>Both ANCA positive</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Both ANCA negative</td>
<td>4 (5)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Tissue biopsy consistent</td>
<td>35 (48)</td>
<td>21 (75)</td>
</tr>
</tbody>
</table>
Acknowledgements

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References