

EPIDEMIOLOGY OF WEGENER'S GRANULOMATOSIS IN NORTHERN NORWAY

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Objective. To determine if changes in the incidence, prevalence, and clinical presentation of Wegener's granulomatosis (WG) have occurred in the stable population of northern Norway during a 15-year period.

Methods. We performed a retrospective cohort study using hospital discharge records from all 11 hospitals in the region and the databases of the 2 pathology departments in the area. Only patients fulfilling the American College of Rheumatology 1990 criteria for WG were included in the study, and demographic and clinical data at diagnosis were recorded. Incidence, point prevalence, and period prevalence rates were estimated for three 5-year periods.

Results. Fifty-five patients (62% male) with a median age at diagnosis of 50 years (range 10–84 years) fulfilled the inclusion criteria. The annual incidence/million population increased from 5.2 (95% confidence interval [95% CI] 2.7–9.0) during 1984–1988 to 12.0 (95% CI 8.0–17.3) during 1994–1998. The point prevalence/million increased from 30.4 (95% CI 16.6–51.0) to 95.1 (95% CI 69.1–129.0). The highest incidence rate occurred in men ages 65–74 years. There were no significant period differences in age, first organ involved, delay of diagnosis, or disease activity, but fewer patients had malaise and renal insufficiency during the earliest time period. No seasonal variation in the onset of WG was present, although we noted a pattern of annual fluctuation.

Conclusion. The prevalence of WG has tripled in northern Norway over the last 15 years. While more efficacious therapy may explain part of this increase, we

also found a significant trend toward increased incidence over that period. The incidence rate over the last 5 years is the highest reported so far, while the clinical presentation has remained unchanged.

In Wegener's granulomatosis (WG), a systemic, necrotizing, granulomatous, small vessel vasculitis occurs, with predilection for both the upper and lower respiratory tract and the kidneys. While still considered a rare disease, some authors (1,2) have described an increasing incidence of WG. Whether this reflects a genuine increase or just increased awareness, facilitated by the availability of antineutrophil cytoplasmic antibody (ANCA) testing, is not clear.

The etiology of WG is still unknown, although environmental factors, such as inhaled agents or respiratory infections, are suspected to be precipitating agents (3–7). Geographic differences have been suggested, with WG being more common in northern Europe than in southern Europe (8,9). This may be related to the finding that the onset of WG is most common in winter (2,10). In addition, a recent study from Sweden (11) reported a periodic fluctuation in the annual frequencies of ANCA-associated vasculitides, suggesting a possible relationship to periodic viral infections.

The purpose of the present study was to estimate the incidence and prevalence of WG over a 15-year period in a stable population in the most northern part of Europe, where winters last as long as 6 months. Moreover, we wanted to determine possible changes over time in the incidence rate, demographic and clinical features, and seasonal or annual presentation of WG.

PATIENTS AND METHODS

The study area covers the 3 northernmost counties in Norway (Figure 1), which is a predominantly coastal, rural region of 113,000 km², where fish is the main industrial product. The population in 1998 was 464,000, the largest city

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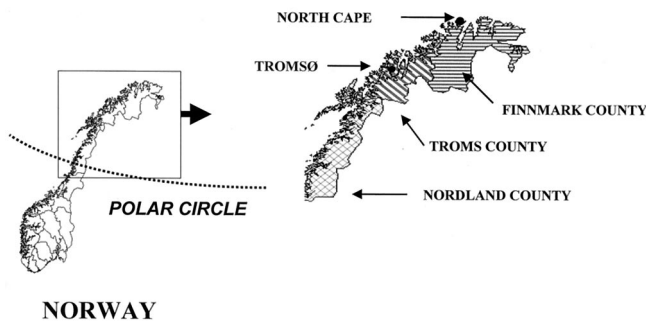


Figure 1. Map showing the study region.

having 50,000 inhabitants. The population (95% Caucasian) represents 11% of the total Norwegian population and decreased by 5,096 inhabitants (1.1%) from 1984 to 1998. The mean annual in-migrations and out-migrations are 2.0% and 2.6%, respectively. The percentage of children (<15 years of age) decreased from 20.8 to 20.0, while the ratio of adult males to adult females decreased from 1.023 to 1.002, from 1986 to 1996 (12).

The health care system in Norway is based on free access to both primary (family physician) and secondary (specialist) health care. All counties have administrative and financial responsibility for providing health care for their inhabitants, who may receive free medical care outside their county of residence only after prior evaluation at the referral center. The study area has 9 district hospitals, 1 regional referral center, and 1 tertiary care center. The starting point for this retrospective study was January 1, 1984 and the study period spanned 15 years. The study period was arbitrarily divided into three 5-year periods, as follows: period 1 encompassed 1984–1988, period 2 1989–1993, and period 3 1994–1998 (all January 1st of the beginning years through December 31st of the ending years).

We used 2 supplementary retrieval sources for case ascertainment. First, we used computerized discharge diagnosis indices from the departments of internal medicine, rheumatology, pediatrics, and ear, nose, and throat (ENT) at all hospitals. International Classification of Diseases, Ninth Revision (ICD-9) codes 446, 446.0, 446.2, and 446.4, and ICD-8 codes 446, 446.00, 446.10, 446.20, 446.99 (corresponding to WG, polyarteritis nodosa [PAN], and PAN-like diseases or allergic vasculitis) were used as search terms. Second, we used computerized diagnosis lists from the 2 departments of histopathology in the region, searching for all cases with a histologic diagnosis of WG, PAN, or granulomatous inflammation in the upper airways. In addition, private specialists in rheumatology (1) and ENT (5) as well as the departments of rheumatology and nephrology in the neighboring county were contacted and asked if they had treated patients with WG who had not been treated at the study hospitals. Ascertainment of WG diagnosis and data collection were done by one of us (WK), a rheumatologist, using a predefined form. When in doubt about how to interpret information in the medical records, a consensus was sought between both investigators.

For the study of incidence and prevalence, WG was diagnosed at the time point when patients cumulatively ful-

Table 1. Middle population in the study region of northern Norway*

	Total population	Adult population	Adult male population	Adult female population
Period 1 1984–1988	464,610	367,804	186,030	181,744
Period 2 1989–1993	460,809	371,142	186,546	184,596
Period 3 1994–1998	467,964	374,275	187,333	186,945
Total study period 1984–1998	460,809	371,142	186,546	184,596

* Subjects ≥ 15 years old were counted in the adult population. The middle population is the population in the middle of each period (January 1st of 1986, 1991, and 1996).

filled ≥ 2 of the American College of Rheumatology (ACR) 1990 classification criteria for WG (13). In studying seasonal variation, we used the date of onset of the first symptom attributable to WG in an attempt to be closer to a possible triggering factor.

For each patient, we recorded demographic data, organ involvement at the onset of symptoms attributable to WG, as well as organ involvement at the time of diagnosis. All information on the extent and severity of the disease was based on documentation in the record and was supplanted when needed by information from the surviving patients ($n = 43$ at a followup examination performed in 1998–1999, 5 of which were by telephone interview).

Organ involvement was defined according to the Disease Extent Index (DEI) (14) and disease activity according to the Birmingham Vasculitis Activity Score (BVAS) (15). The following laboratory data were obtained from the records: complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, serum creatinine level, and findings of urine dipstick test and microscopy of the urine sediment. Tests for ANCA were first introduced in the study region in 1987, and since the study goes back to 1984, ANCA was not used as a search term. Results of ANCA tests were recorded as positive or negative, since different methods (indirect immunofluorescence to identify cytoplasmic ANCA and perinuclear ANCA and/or enzyme immunoassays for antibodies against proteinase 3 or myeloperoxidase) were being used in the study period.

Prevalence was calculated as the point prevalence at the end of each period (December 31st of 1988, 1993, and 1998) and as 5-year period prevalence. Seasons were defined as follows: winter was from December through February, spring was from March through May, summer was from June through August, and autumn was from September through November. The population in the middle of each period (January 1st of 1986, 1991, and 1996) (Table 1) was used as the denominator when incidence rates were calculated for the 3 periods. For the total period and for age-specific incidence rates, the population in 1991 was used as the denominator. Breakdowns of the population data by age and sex were provided by the Statistical Central Bureau, Statistics Norway.

Data are presented as the median and range unless stated otherwise. The nonparametric Kruskal-Wallis test was used to compare continuous variables between groups, and

Table 2. Incidence/million/year (95% confidence interval) of Wegener's granulomatosis in northern Norway, according to sex and study period*

	Period 1, 1984–1988	Period 2, 1989–1993	Period 3, 1994–1998	Total, 1984–1998
Total population				
No. of patients	12	15	28	55
Incidence	5.2 (2.7–9.0)	6.5 (3.6–10.7)	12.0 (8.0–17.3)	8.0 (6.0–10.4)
Adult population				
No. of patients	11	14	27	52
Incidence	6.0 (3.0–10.7)	7.5 (4.1–12.7)	14.4 (9.5–21.0)	9.3 (7.0–12.2)
Adult female population				
No. of patients	3	4	11	18
Incidence	3.3 (0.7–9.6)	4.3 (1.2–11.1)	11.8 (5.9–21.1)	6.5 (3.8–10.3)
Adult male population				
No. of patients	8	10	16	34
Incidence	8.6 (3.7–16.9)	10.7 (5.1–19.7)	17.1 (9.8–27.7)	12.2 (8.4–17.0)

* Subjects ≥ 15 years old were counted in the adult population. Adult patients include 1 patient with onset of Wegener's granulomatosis at the age of 15 years.

chi-square, chi-square for linear trend, and Fisher's exact test were used when comparing categorical data. Patients with missing data (for CRP 16, ANCA 15, platelets 5) were omitted from the analyses. In the estimation of incidence rates and 95% confidence intervals (95% CI), the Poisson distribution was assumed. *P* values less than 0.05 were considered significant.

RESULTS

Demographics and epidemiology. A total of 55 patients, 34 men (62%) with a mean \pm SD age of 51.3 ± 16.5 years and 21 women (38%) with a mean \pm SD age of 45.2 ± 22.0 years fulfilled the ACR classification criteria for WG during the study period. Fifty patients (91%) were recruited from the 2 referral hospitals, 36 of whom (65% of all patients) had been seen at the tertiary care unit. Of the remaining 5 patients, 4 (7%) were recruited from district hospitals and had not been seen at referral centers, 1 (2%) was recruited from the lists of the departments of pathology, and none were recruited through private specialists or hospitals in the neighboring county.

Twelve patients fulfilled the ACR 1990 criteria for WG during period 1 (years 1984–1988), 15 during period 2 (years 1989–1993), and 28 during period 3 (years 1994–1998), giving an overall incidence rate for the whole study period of 8.0/million/year (95% CI 6.0–10.4). There was a linear trend toward an increase in the incidence rate ($P < 0.01$), from 5.2/million/year (95% CI 2.7–9.0) in period 1 to 12.0 (8.0–17.3) in period 3. The annual incidences of WG over time for the entire study group and for the adult population, categorized according to sex, are shown in Table 2.

Four patients, all girls, were ≤ 15 years of age at disease onset. In males, there was a peak in age-specific

annual incidence in the 65–74-year age group of 29.0/million (95% CI 12.5–57.1), while in females, no distinct peak was seen, and the highest incidence occurred in the 45–54-year age group, at 13.2/million (4.3–30.9) (Figure 2).

At the end of the 3 periods, 14, 23, and 44 patients, respectively, were still alive and residing in the region, giving a point prevalence for WG of 30.4/million (95% CI 16.6–51.0) in 1988, 49.3/million (95% CI 31.2–73.9) in 1993, and 95.1/million (95% CI 69.1–129.0) in 1998. The 5-year period prevalence/million during period 1 was 30.1 (95% CI 16.5–50.6), 62.9 (95% CI 42.1–90.4) during period 2, and 109.0/million (95% CI 81.1–143.3) during period 3.

Seasonal and annual variations. There was no clear seasonal variation in the onset of WG in this cohort. Onset occurred during summer in 16 patients (29%), during spring in 13 (24%), during autumn in 13 (24%), and during winter in 13 (24%). There was no

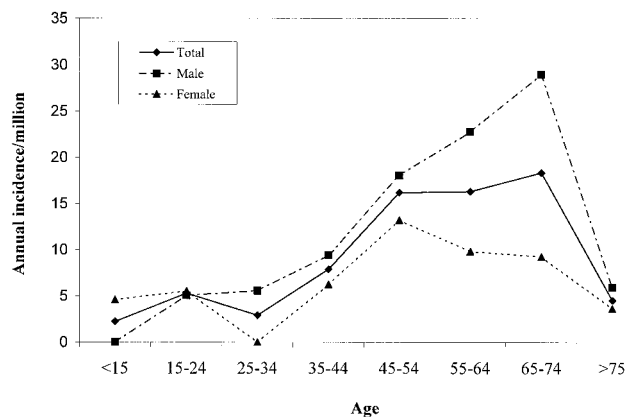


Figure 2. Age-adjusted annual incidence/million of Wegener's granulomatosis in the population of northern Norway, by sex and by age group.

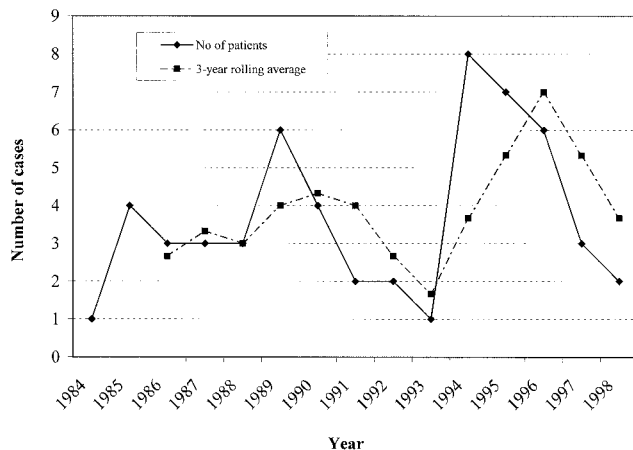


Figure 3. Incidence of Wegener's granulomatosis in the population of northern Norway, 1984–1998, by year of symptom onset and by 3-year rolling average.

increase in disease onset during the 6 months of real winter in the area (20 with disease onset from November to April, versus 35 for the rest of the year).

The number of incident cases per year varied from 1 to 8 (Figure 3), giving the impression of increased incidences every 4–5 years. The fluctuation in annual incident cases was still present when 3-year rolling averages were calculated, which showed peaks in 1990 and 1996 (4.3 and 7.0, respectively), a trough in 1993 (1.7), and falling again to 3.7 in 1998 (Figure 3).

Clinical features. The median age at the onset of WG symptoms in the total group was 50 years (range 10–84 years; median of 52 years excluding the 4 pediatric cases). The median time from first symptom to diagnosis was 6 months, which did not change significantly during

Table 4. Organ involvement at diagnosis in patients with Wegener's granulomatosis*

Organ system	Period 1 (n = 12)	Period 2 (n = 15)	Period 3 (n = 28)	All patients (n = 55)	P†
ENT	11 (92)	12 (80)	21 (75)	44 (80)	0.48
Lung	5 (42)	9 (60)	19 (68)	33 (60)	0.30
Kidney	7 (58)	13 (87)	22 (79)	42 (76)	0.21
Muscle/joint	7 (58)	8 (53)	20 (71)	35 (64)	0.46
Eye	2 (17)	8 (53)	11 (39)	21 (38)	0.15
PNS	2 (17)	2 (13)	8 (29)	12 (22)	0.46
CNS	3 (25)	2 (13)	2 (7)	7 (13)	0.30
Gastrointestinal	1 (8)	2 (13)	0 (0)	3 (5)	0.16
Heart	1 (8)	1 (7)	6 (21)	8 (15)	0.33
Skin	2 (17)	6 (40)	9 (32)	17 (31)	0.42
Malaise	8 (67)	13 (87)	26 (93)	47 (85)	0.10

* Values are the number (%) of patients. ENT = ear, nose, and throat; PNS = peripheral nervous system; CNS = central nervous system.

† Difference between periods.

the study period. Sixty-two percent of the patients (n = 34) presented with upper airways symptoms, 20% with pulmonary symptoms, 9% with urinary abnormalities, and 5% and 4% presented with musculoskeletal and eye symptoms, respectively. While early death, renal insufficiency, and renal failure were observed less frequently during the first period of study, only renal insufficiency showed a statistical trend toward increasing frequency ($P = 0.03$) during the study period. Disease severity by the BVAS and disease extent by the DEI, although lower during the first period, showed no significant changes over time (Table 3). Limited WG, defined as the absence of renal involvement, was seen in 24% of all patients.

The frequency of specific organ involvement at the time of diagnosis is shown in Table 4. The only

Table 3. Demographic and clinical features of patients with WG in northern Norway*

	Period 1, 1984–1988	Period 2, 1989–1993	Period 3, 1994–1998	All periods, 1984–1998	P†
No. of patients	12	15	28	55	
Sex, male:female ratio	2.0:1	2.0:1	1.3:1	1.6:1	0.77
Age at first symptom, median (range) years	47 (14–73)	57 (10–77)	50 (11–84)	50 (10–84)	0.63
Time from symptom onset to diagnosis, median (range) months	5.5 (1–55)	6.0 (2–35)	6.0 (1–102)	6.0 (1–102)	0.93
BVAS at diagnosis, median (range)	13.5 (4–46)	23 (6–34)	24.5 (4–45)	23 (4–46)	0.08
DEI at diagnosis, median (range)	7 (2–21)	9 (2–13)	9 (2–17)	9 (2–21)	0.12
No. (%) with limited WG at diagnosis	5 (42)	2 (13)	6 (21)	13 (24)	0.21
No. (%) with serum creatinine >150 μ moles/liter at diagnosis	2 (17)	8 (53)	16 (57)	26 (47)	0.05
No. (%) with dialysis dependence at diagnosis	1 (8)	6 (40)	4 (14)	11 (20)	0.07
No. (%) of early deaths (within 3 months of diagnosis)	0 (0)	2 (13)	2 (7)	4 (7)	0.42
No. (%) tested for ANCA at diagnosis	3 (25)	11 (73)	26 (93)	40 (73)	<0.001
No. (%) ANCA positive, of those tested	3 (100)	8 (73)	24 (92)	35 (88)	0.20

* WG = Wegener's granulomatosis; BVAS = Birmingham Vasculitis Activity Score (15); DEI = Disease Extent Index (14); limited WG = no renal involvement; ANCA = antineutrophil cytoplasmic antibodies.

† Difference between periods.

significant change over time was a trend toward an increasing frequency of malaise from period 1 to period 3 ($P = 0.04$).

Results of laboratory testing showed no significant differences in the levels of hemoglobin, white blood cell counts, ESR, CRP, or serum creatinine between the various study periods (data not shown). Eosinophilia ($>500 \times 10^6/\text{liter}$), without a history of allergy or atopy, was found in 13 of the 34 patients who were tested at the time of diagnosis (38%).

ANCA testing was available in the national referral laboratory from 1987 and in the 2 immunologic laboratories in the study area from 1994. There was a trend toward increasing ANCA testing from period 1 to 3 ($P < 0.001$), but no significant difference between periods 2 and 3. Positive ANCA test results were obtained in 88% of all patients tested, with no significant difference between the 3 study periods.

DISCUSSION

This retrospective study shows an increasing prevalence rate of WG over the last 15 years and suggests that an increased incidence is a major contributor, with the annual incidence rate of 12/million during the latest period of study (years 1994–1998), the highest reported so far. In this study, great effort was put into tracing all suspected cases of WG. We used the ACR criteria for the diagnosis and did not add positive ANCA testing as a search term because this test was not available in the first 3 years of the study, and we wanted to use the same searching method throughout the study.

The homogenous population, the low rate of population migration, and the public health care system in the study area make it well suited for epidemiologic studies. The study area has 11 hospitals; however, there are very few private specialists. One rheumatologist in the area had a part-time private practice, as did 5 ENT specialists; however, all were affiliated with the nearest hospital, and none had treated WG patients who were unknown at the study hospitals. This makes it unlikely that patients with WG were never referred to 1 of the 11 hospitals in the region, since WG is a chronic, progressive/relapsing disease, which even in limited forms, requires cytotoxic therapy (16–18). We therefore believe that the identification of incident WG cases was as complete as possible. However, since the study was retrospective and went back 15 years, we cannot exclude the possibility that some cases were missed, despite the lack of statistically significant changes over time in the

demographic data, diagnostic delay, and clinical findings.

It is nevertheless possible that some WG patients may have died early in their disease course because of multiple organ failure, having never been diagnosed with any of our search-term diagnoses, particularly during the early years of the study. The lower rates of malaise and severe renal involvement and the lower disease activity as measured by the BVAS during that period (see Table 3) could indicate a failure to include more severely ill patients. Various studies have shown the frequency of early death from active WG to be ~6–11% (18–21), as we found in the 2 latest periods of the present study (9.3%). However, no early death occurred during period 1 of our study, and by extrapolating from both the previous data and our own data from the 2 latest study periods, we estimate that no more than 2 early deaths during period 1 may have been missed. Inclusion of 2 such missed cases would increase the incidence rate to 6.0/million in period 1, which is still only one-half of the incidence rate in period 3. Patients with localized disease may experience a long delay in diagnosis (up to 8 years in the present study); however, with a followup extending as long as 15 years, it is likely that such patients from the earliest periods would have been diagnosed later on. Such missing cases from the latest period would strengthen the trend of increasing incidence.

The tripling of the prevalence rate, from 30.4/million in 1988 to 95.1/million in 1998, can be explained by an increased incidence and/or an increased survival, which is most likely due to the efficacy of current treatment regimens, with more early and aggressive therapy (19,22,23). Both the incidence and prevalence rates from the late 1980s and early 1990s in this study are comparable to the rates reported elsewhere (2,24). However, the incidence for the latest period (14.4/million/year in the adult population) is higher than the recently reported rate of 10.3/million/year in Norfolk, UK (25).

This trend toward an increasing incidence of WG is supported by several other studies. Andrews et al (1) found a 4-fold increasing incidence of WG (from 0.7 to 2.8/million/year) in Leicester, UK, from 1980 to 1989. In the most recent Norfolk, UK, study (25), a trend toward an increase in the overall incidence of primary systemic vasculitides from 1988 to 1997 was found. The annual incidence of WG in the adult population in Norfolk increased from 8.7/million (95% CI 5.2–13.8) during the period 1988–1992 to 10.3/million (6.4–15.5) during the period 1993–1997.

The reason for this increasing incidence is un-

clear, and increased diagnostic awareness, especially as a result of earlier case identification following the introduction of ANCA testing, is difficult to exclude. In the present study, ANCA testing first became widely available in 1994, and limited ANCA testing (especially during the first period) may have biased our findings, leading us to identify a spurious increase in incidence. But, this rationale leaves unexplained our finding of an incidence rate during the last period that is the highest described so far. Furthermore, positive ANCA findings are not diagnostic, and Woodrow et al (26) reported an increase in arteritis-related severe renal disease starting 2–3 years before ANCA testing became available, while Tidman et al (11) found no significant increase in ANCA-associated small vessel vasculitides after routine ANCA testing was introduced.

It might be that there are considerable fluctuations in the incidence of WG (conceivably in relation to cycles of infectious respiratory diseases), and that the latest period of our study coincided, by chance, with a peak in this fluctuation. An even longer followup period would be needed to clarify this possibility. It should also be noted that the CIs for the incidence rates overlapped (see Table 2), and the data should therefore be interpreted with caution.

Our results provide some support for the idea of a decreasing north–south gradient for WG, as found in a recent study comparing annual incidence rates of ANCA-associated vasculitis in 2 European regions. In Spain, the incidence rate of WG was 4.1/million (95% CI 2.1–7.4) and in England 10.3/million (7.6–13.8) (9). A German study (27) estimated the prevalence of WG to be 51.2/million in the north of the country and 43.2/million in the south. Furthermore, in the Middle East country of Bahrain, which has a population comparable to that in the present study, the very first case of WG has only recently been reported (28). Similar geographic differences have been described for giant cell arteritis (GCA) (8,29,30). Furthermore, in their epidemiologic study of the US, Cotch et al (24) found that WG was overrepresented among Caucasians. Both Cotch and Carruthers and coworkers (2) have discussed the possibility that WG is more prevalent in such rural populations as in our cohort, which is also 95% Caucasian.

Seasonal variations in the onset of WG symptoms have suggested an infectious triggering factor (2,10), but consistent with 2 other studies from the US (6,24), we could not confirm this trend. However, due to the small numbers in our study, the power to detect a seasonal difference was only 0.45. On the other hand, we found a trend toward an annual variation in WG onset, which

was consistently present even when a 3-year rolling average of incident cases was calculated. This phenomenon has also been described for GCA (29,31), and Tidman et al (11) found a fluctuation in annual frequencies of ANCA-associated small vessel vasculitides in central Sweden. For the time being, however, one can only speculate about the role of periodic changes in environmental factors in relation to WG.

The spectrum of clinical features in the present cohort is quite comparable to that of other studies (2,16,18), although we registered more patients with neurologic symptoms and more malaise ($P = 0.03$ for both symptoms; data not shown) than in the study from Norfolk (2). The patients in the present cohort were younger at disease onset (50 years versus 62 years), but as in the most recent studies from Norfolk (25) and Sweden (11), we found WG to be most frequent in middle-aged or elderly men. Peak incidence in females also occurred during middle age (45–54 years), while young females (<25 years) had a higher incidence rate than young males.

The increasing prevalence of WG, as illustrated by this study, has important repercussions for the economics and planning of health care, since most of these patients have chronic and severe disease that requires intensive treatment and life-long followup by specialist health care services (32). Whether the increase in incidence will continue or is a transient phenomenon remains to be seen. Registries that prospectively document all new patients with WG are warranted in different parts of the world so that more information on genetic and environmental factors in the occurrence of WG can be gathered.

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REFERENCES

1. Andrews M, Edmunds M, Campbell A, Walls J, Feehally J. Systemic vasculitis in the 1980s—is there an increasing incidence of Wegener's granulomatosis and microscopic polyarteritis? *J R Coll Physicians Lond* 1990;24:284–8.
2. Carruthers DM, Watts RA, Symmons DP, Scott DG. Wegener's granulomatosis—increased incidence or increased recognition? *Br J Rheumatol* 1996;35:142–5.

3. George J, Levy Y, Kallenberg CG, Shoenfeld Y. Infections and Wegener's granulomatosis—a cause and effect relationship? *QJM* 1997;90:367–73.
4. Mandell BF, Calabrese LH. Infections and systemic vasculitis. *Curr Opin Rheumatol* 1998;10:51–7.
5. Cohen Tervaert JW, Popa ER, Bos NA. The role of superantigens in vasculitis. *Curr Opin Rheumatol* 1999;11:24–33.
6. Duna GF, Cotch MF, Galperin C, Hoffman DB, Hoffman GS. Wegener's granulomatosis: role of environmental exposures. *Clin Exp Rheumatol* 1998;16:669–74.
7. Cohen Tervaert JW, Stegeman CA, Kallenberg CG. Silicon exposure and vasculitis. *Curr Opin Rheumatol* 1998;10:12–7.
8. Watts RA, Scott DG. Classification and epidemiology of the vasculitides. *Baillieres Clin Rheumatol* 1997;11:191–217.
9. Watts R, Gonzales-Gay M, Garcia-Porrúa C, Lane S, Bentham G, Scott D. ANCA-associated vasculitis in two European regions [abstract]. *Clin Exp Immunol* 2000;120 Suppl 1:60.
10. Raynauld JP, Bloch DA, Fries JF. Seasonal variation in the onset of Wegener's granulomatosis, polyarteritis nodosa and giant cell arteritis. *J Rheumatol* 1993;20:1524–6.
11. Tidman M, Olander R, Svalander C, Danielsson D. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975–95: organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. *J Intern Med* 1998;244:133–41.
12. Statistics Norway. Annual report 1984–1999. Oslo: Statistics Norway; 1999.
13. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101–7.
14. Reinhold-Keller E, Kekow J, Schnabel A, Schmitt WH, Heller M, Beigel A, et al. Influence of disease manifestation and antineutrophil cytoplasmic antibody titer on the response to pulse cyclophosphamide therapy in patients with Wegener's granulomatosis. *Arthritis Rheum* 1994;37:919–24.
15. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *QJM* 1994;87:671–8.
16. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488–98.
17. Hoffman GS. Immunosuppressive therapy is always required for the treatment of limited Wegener's granulomatosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;13:249–52.
18. Luqmani RA, Bacon PA, Beaman M, Scott DG, Emery P, Lee SJ, et al. Classical versus non-renal Wegener's granulomatosis. *QJM* 1994;87:161–7.
19. Gordon M, Luqmani RA, Adu D, Greaves I, Richards N, Michael J, et al. Relapses in patients with a systemic vasculitis. *QJM* 1993;86:779–89.
20. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *J Am Soc Nephrol* 1998;9:842–52.
21. Pettersson EE, Sundelin B, Heigl Z. Incidence and outcome of pauci-immune necrotizing and crescentic glomerulonephritis in adults. *Clin Nephrol* 1995;43:141–9.
22. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *BMJ* 1958;2:265–70.
23. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983;98:76–85.
24. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis: estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum* 1996;39:87–92.
25. Watts RA, Lane SE, Bentham G, Scott DGI. Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000;43:414–9.
26. Woodrow G, Cook JA, Brownjohn AM, Turney JH. Is renal vasculitis increasing in incidence? [letter]. *Lancet* 1990;336:1538.
27. Reinhold-Keller E, Zeidler A, Mock C, Raspe H, Gutfleisch J, Peter H, et al. Epidemiology of primary systemic vasculitis in North and South Germany [abstract]. *Sarcoidosis* 1996;13 Suppl 3:272.
28. Jamal A, Ebrahim RA, Tammam N, Kanekar S. Wegener's granulomatosis: first case report in Bahrain. *J Laryngol Otol* 1998;112:664–6.
29. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med* 1995;123:192–4.
30. Smith CA, Fidler WJ, Pinals RS. The epidemiology of giant cell arteritis: report of a ten-year study in Shelby County, Tennessee. *Arthritis Rheum* 1983;26:1214–9.
31. Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of *Mycoplasma pneumoniae* infection. *J Rheumatol* 1996;23:112–9.
32. Cotch MF. The socioeconomic impact of vasculitis. *Curr Opin Rheumatol* 2000;12:20–3.