Increasing Incidence of Wegener's Granulomatosis in Sweden, 1975–2001

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ABSTRACT. ***Objective.*** Studies of Wegener's granulomatosis (WG) since the late 1980s indicate a probable increase in incidence of unknown cause and significance, possibly related to antineutrophil cytoplasmic antibody (ANCA) testing. To extend these observations and to include calendar periods before ANCA was introduced, we assessed time trends in the incidence of WG in Sweden in the period 1975-2001.

Methods. In the population-based Swedish Inpatient Register, we identified 1938 individuals diagnosed with WG in the period 1975-2001, and calculated the annual age and sex adjusted incidences.

Results. The incidence increased from 0.33 (95% CI 0.28–0.39) in the period 1975-85 to 0.77 (95% CI 0.69–0.85) in 1986-90, to 1.19 (95% CI 1.12–1.26) in 1991-2001, resulting in a mean incidence of 0.78 (95% CI 0.74–0.82).

Conclusion. WG displays a strong temporal trend. While the increase coincides to some extent with the implementation of ANCA testing, suggestive of increased disease recognition, ANCA testing remains an incomplete explanation as increasing incidences were noted before as well as after their introduction.

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Key Indexing Terms:
WEGENER'S GRANULOMATOSIS — INCIDENCE
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Studies of Wegener's granulomatosis (WG) have indicated increasing incidence over the last decades, as well as a north-south gradient[1-5]. It has been proposed that this increase might reflect an increasing awareness of WG among physicians as the result of the introduction of antineutrophil cytoplasmic antibody (ANCA) testing in clinical practice. Previous investigations have, however, mainly emanated from referral centers, and encompassed relatively few individuals, in all some 320 patients[1-10], including a recent prospective population-based study from northern Germany[11], summarized in Table 1.

Introduced in the mid 1980s, testing for ANCA represented a new diagnostic tool[12] that, although not included in the American College of Rheumatology (ACR) criteria for the diagnosis of WG[13], may have had an effect on the diagnostic intensity and clinical classification of vasculitides. Since existing incidence studies have almost exclusively included patients diagnosed with WG after the late 1980s, we know little about the underlying time trends onto which any ANCA related effect might have been added. To assess the longterm time trends of WG in a large number of patients, we calculated its incidence in Sweden from 1975 through 2001.

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MATERIALS AND METHODS

In Sweden inpatient care is public and population-based. Referral to hospital is based on geography rather than financial capacity or insurance. In the Swedish Inpatient Register, individual-based information on all inpatient care, irrespective of diagnosis, has been recorded by the county since 1964, and nationally since 1987[14]. For each hospital discharge, the national registration number (a 10-digit number unique for each Swedish resident[15]) is recorded together with date of admission and discharge, the main diagnosis and up to 5 contributory diagnoses, coded according to the International Classification of Diseases (ICD) version 7-10. In previous validations (register codes vs available information in the medical files) of the discharge diagnosis of WG we retrieved the medical files of 81 out of 92 patients discharged with WG, and confirmed diagnosis against the ACR criteria in 72 patients (89%)[16,17]. We also observed that all 72 patients with WG were diagnosed with the disease in conjunction with their first hospitalization listing this diagnosis[16,17]. Validation surveys of other medical conditions also indicate a register correctness close to 90%[14]. For the present incidence analysis, we identified all individuals registered in the Inpatient Register with a discharge diagnosis of WG between January 1, 1968, and December 31, 2001 (n = 1938). Since polyarteritis nodosa (PAN) was previously used as a generic term for systemic vasculitides, we similarly identified all individuals discharged with PAN or any other discharge code for defined (Goodpasture, Churg-Strauss, polyangiitis, midline granulomas) or undefined small or medium-vessel vasculitides during the same period (n = 5306).

To minimize the risk of cases with WG diagnosed before the start of our study period being mistaken for incident cases by having their first hospitalization during our study period (and cause an apparent spike in incidence during the first year(s) of our study period), we used a 3 year washout period so that no patients diagnosed with WG during the 3 years that preceded our study could be included. However, testing for different washout periods (1–5 yrs) had little influence on the appearance of the incidence curve. Since a unique ICD code for WG was first introduced in ICD 8, implemented in 1968-69, and since the population-based coverage of the inpatient register exceeded 50% of

Table 1. Incidence studies of Wegener's granulomatosis, 1980-2001.

Study	Country	Period	Case Recruitment	Patients, n	Population	Study Period, yrs	Incidence per 100,000
Andrews[1]	UK	1980–89	Referral center	18	1,300,000	10	0.15, 0.6
Carruthers[6]	UK	1988–93	Referral center	21	500,000	6	0.85
Tidman[9]	Sweden	1975–86	Referral center	19	200,000	20	1.6
Koldingsnes[4]	Norway	1984–98	Hospital discharge register + pathology register	55	460,000	15	0.5, 1.2
Watts[5]	UK and Spain	1988–98	Referral center	48+11	600,000	10	1.0 and 0.5
Reinhold-Keller[8]	Germany	1998–99	Hospital register, pathology + immunology lab register	33/28	4,900,000	2	0.95
Gonzalez-Gay[3]	Spain	1988–2001	Referral center	12	200,000	14	0.3
Watts[10]	UK	1988–97	Referral center	40	430,000	10	1.0
Reinhold-Keller[11]	Germany	1998–2002	Hospital + pathology + immunology lab register	120	2,780,000	5	0.6, 1.2
Present study	Sweden	1975–2001	National inpatient register	1638	8,000,000	26	0.3, 0.8, 1.2

the entire country in the mid 1970s, we started the study period in 1975. Taking into account that some individuals may initially have switched their vasculitis diagnosis, we defined date of onset in such individuals (5.8%) as the date of first discharge listing any vasculitic condition, but used the latest discharge to define the vasculitis diagnosis. From national statistics, we collected information on the annual size and sex- and age-distribution of the Swedish population covered by the Inpatient Register[14]. Incidences were standardized to the Swedish population as of 1990, and evaluated using Poisson regression.

RESULTS

During the study period and after the washout, we identified 1636 incident cases (885 men and 751 women, mean age at diagnosis 59.4 and 62.1 years, respectively) of individuals discharged with WG, corresponding to a mean incidence per 100,000 of 0.78 (95% CI 0.74–0.82): 0.86 among men (95% CI 0.80–0.91) and 0.70 among women (95% CI 0.65–0.76). The incidence increased during the study period, from 0.33 (95% CI 0.28–0.39) in 1975-84 to 0.77 (95% CI 0.69–0.85) in 1985-90 to 1.19 (95% CI 1.12–1.26) in 1991-2001 (Figure 1). Overall and within each of these time periods, the annual increase in incidence was statistically significant (all p values < 0.05). This time trend was similar among men and women, and the age at first discharge listing WG remained constant during the study period, as did the proportion of patients whose first discharge with WG was preceded by at least one discharge listing another vasculitis (data not shown).

When the incidence curve for WG (Figure 1) was compared to and combined with that of PAN (Figure 2), the increase in incidence of WG before the mid 1980s was mirrored by a declining incidence of PAN, resulting in a stable combined incidence. Between the mid-1980s and the late 1990s, the increase in incidence of WG was not clearly reciprocated by that of PAN and the combined incidence. After the late 1990s, the incidence of PAN declined, resulting in a decline in the combined incidence of WG and PAN, despite the continued increase in the former. A similar pattern was observed when the incidence of WG was instead contrasted to all other small or medium-vessel vasculitides combined (data

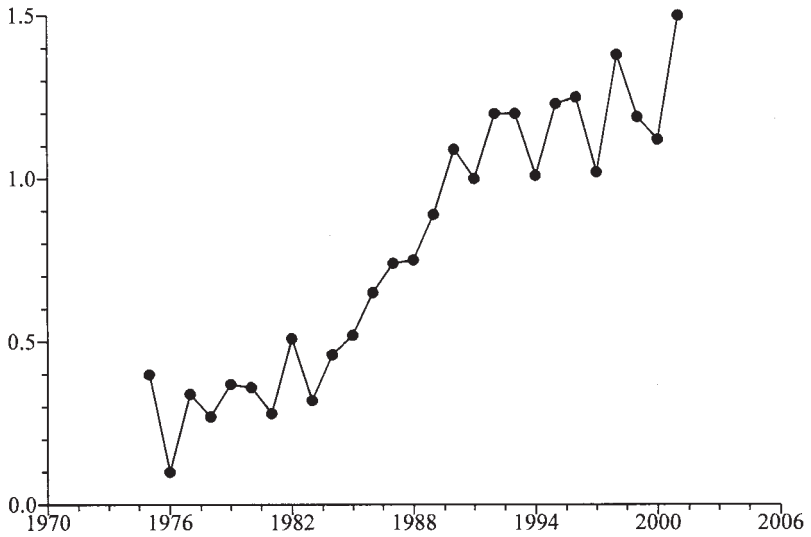

Figure 1. Age-standardized incidence of Wegener's granulomatosis per 100,000 in Sweden 1975-2001.

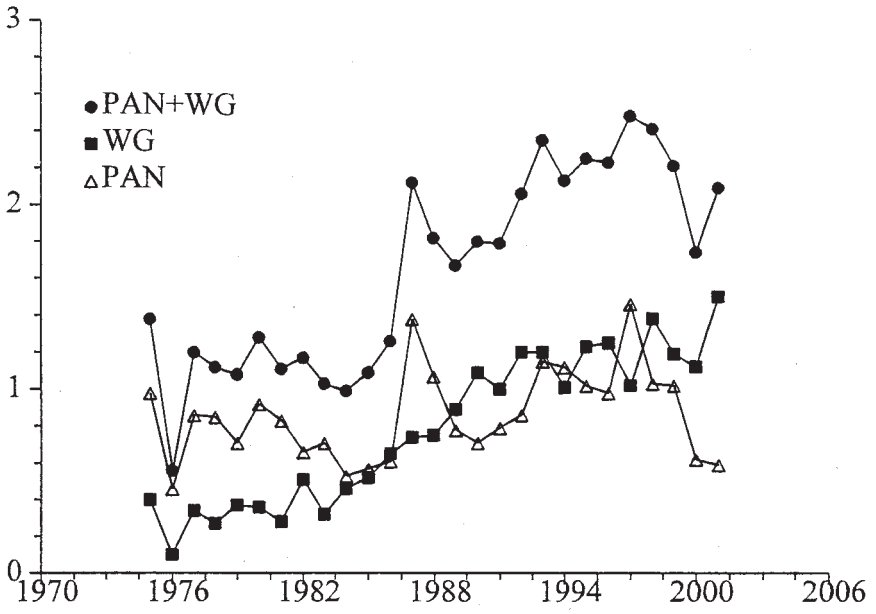

Figure 2. Age-standardized incidence of Wegener's granulomatosis per 100,000 in Sweden 1975-2001 and its relation to the corresponding incidence of PAN.

not shown). (The spikes in the incidence of PAN 1987 and 1997 reflect change of classification, from ICD 8 to 9 and ICD 9 to 10, respectively, and the fact that we did not employ any washout procedures of prevalent cases specifically for these changes in classification.)

DISCUSSION

In our large population-based study, the incidence of WG tripled between 1975 and 2001. Although this increase partly concurred with the introduction of ANCA testing in routine clinical practice in 1987 in some parts of Sweden and on a nationwide basis in the early 1990s, we had already observed an increasing incidence of WG before the introduction of ANCA. This underlying early increasing trend was, however, partly reciprocated by the incidence of other systemic vasculitides such as PAN.

Throughout the study period, we used the same case definition (hospitalization) to define WG. Despite possible differences in case ascertainment between our study and others, our results are remarkably consistent with respect to sex, distribution, mean age at onset, and the level of the observed incidence during the 1990s[4,5,8]. Similarly, estimations of the prevalence of WG based on the data used in our study revealed a dramatic increase in prevalence (from 36 per million in 1993 to 112 per million in 2001), figures that are very similar to those reported from smaller studies from Norway (49 and 95 per million, respectively)[4] and from the UK[10], and most likely reflect increasing survival.

Although our method of case identification may have failed to include individuals with WG never hospitalized (irrespective of cause), this limitation is unlikely to explain the time trends observed. Moreover, in an ongoing study in which we have identified all positive ANCA tests at a large Swedish hospital during the 1990s, no patients with WG (n = 77) had been treated solely in outpatient care (Knight A, personal communication). The result of the most likely change over time — an increasing proportion of patients with WG being diagnosed and managed solely in outpatient settings — would result in attenuation, rather than inflation, of the observed time trends. Similarly, assuming that the proportion of patients erroneously given the diagnosis of WG has decreased over time as the result of increasing diagnostic quality, this would also counteract rather than explain the observed time trends. On the other hand, patients who died early during the course of their true WG disease because of multiorgan failure may never have been correctly diagnosed, more likely so during the early years of the study.

Regarding the introduction of classifications of systemic vasculitides, the ACR classification criteria (1990) and the Chapel Hill Consensus Conference (1994)[18], most vasculitides were likely to have been diagnosed earlier as PAN. A drift from PAN to WG explains some of the time trends of WG, at least in the early part of the study. To assess this, we calculated corresponding incidence curves for PAN and for all other small- or medium-size vasculitides except WG. Our results suggest that the pre-ANCA increase in WG might indeed be attributed to a tendency to use the WG diagnosis in favor of PAN. This phenomenon does not, however, explain the subsequent increase in WG during the late 1980s and 1990s. Our study confirms previous reports of an overall increase over time of the systemic vasculitides[19], and part of this increase is due to WG. In the late 1990s there seemed to

be a decrease in the incidence of PAN (and other vasculitides, data not shown) possibly due to a decrease in hepatitis B[20], and milder cutaneous forms of PAN not requiring hospitalization, etc.

The strength of the study lies in the population-based nationwide setting that allowed us to identify a large cohort of WG over a long period of time. We did not validate the diagnosis of WG in the 1636 subjects in our study, since our previous validations of over 100 medical files from patients with WG identified from the same source revealed a diagnostic specificity high enough to allow this type of time-trend analysis to be performed, and short time intervals from diagnosis to hospitalization[15,16].

Whereas much of the increased incidence of Wegener's granulomatosis in Sweden in 1975-2001 concurred with introduction of ANCA testing, our results suggest that incidence increased before as well as after ANCA testing had become routine practice; also, the early underlying increase occurred to some extent at the expense of other systemic vasculitides. Although our study indicates that increased ANCA-related awareness or diagnostic drift from PAN are not likely to be the only explanations for the observed dramatic time trends in the early years of study, it remains an open question whether the increased incidences observed are a true reflection of a trend.

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