Incidence of Wegener's granulomatosis in Finland 1981-2000

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ABSTRACT

Objective. *To determine the incidence and clinical presentation of Wegener's granulomatosis (WG) in Finland during the 20-year period 1981-2000.*

Methods. *We performed a study with retrospective data retrieval using the hospital discharge register in Finland. All available hospital case reports were reviewed. We included those patients diagnosed with and treated for WG. Demographic and clinical data at diagnosis were recorded.*

Results. *Of the 492 patients diagnosed with WG, 49% were male. Mean age at diagnosis was 53.2 years (SD 18.1). The highest rate of incidence occurred in men and women aged 65-74 years. The annual incidence per million of the population increased from 1.9 (95% CI 1.4 to 2.6) during 1981-1985 to 9.3 (95% CI 8.1 to 10.6) during 1996-2000 with gender age-adjusted incidence rate ratio 4.5 (CI 3.6 to 5.7). Only minor changes in the signs and symptoms at diagnosis occurred during the 20-year span. In 83% of cases, the ACR criteria (≥2 criteria) were fulfilled. The mean age at diagnosis rose from 45.8 to 55.0 years and the median diagnostic delay decreased from 17 to 4 months during the two decades.*

Conclusion. *The incidence of WG has increased during the last two decades with little change in clinical symptoms at presentation. At the same time, the mean age of the patients has increased and the diagnostic delay has considerably shortened.*

Introduction

Wegener's granulomatosis (WG), a rare vasculitis disease of unknown aetiology, is characterized by systemic, necrotising, granulomatous, small vessel vasculitis with predilection for upper and lower respiratory tracts and the kidneys (1).

Clinical symptoms and signs, along with the presence of granulomatous vasculitis in histological samples, confirm the diagnosis of WG.

Immune markers have facilitated the diagnostic of systemic vasculitides. Davies *et al*. (7) first reported vasculitis-associated anti-neutrophil cytoplasmic antibodies (ANCA) in1982, of which the diffuse cytoplasmic pattern of ANCA (C-ANCA) has proved highly specific to WG (8). Since then, C-ANCA have been increasingly used in the diagnostics of WG (9) and even as a guide in the treatment of WG.

While WG is still considered a rare disease, some studies have indicated that its incidence has increased during the last few decades, with a two-fold increase in incidence and a three-fold increase in prevalence over a 15-year period. (10-12).

The purpose of the present study is to estimate the incidence of WG in Finland from 1981 to 2000 and to analyze the spectrum and possible changes in clinical symptoms at presentation during this 20-year period.

Patients and methods

Patients

We screened hospital discharge registers (National Research and Development Centre for Welfare and Health, STAKES) nationwide for patients with a discharge diagnosis of WG during 1981-2000 (1981-1986 based on ICD8, 1987-1995 on ICD9, and 1996-2000 on ICD10). We then gathered information on the hospital(s) where patients received treatment, as well as on the duration of the patient's hospital stay. After that, one of us (JT) systematically perused all these available patient files in the hospitals. The patients that were treated only in health care centres were not included in this study because they were very few (n=45) and scattered all over the country.

Finland's population growth has remained quite stable throughout the 20-year period from 1981 to 2000. The number of inhabitants rose from 3.8 million in 1981 by 380,000 to about 4.2 million in 2000. The ratio of men

to women has risen from 0.93 to 0.95. During this same period, the proportion of elderly citizens over 65 years has risen from 12.1% of the population in 1981 to 14.9% in 2000. On average, women outlived men during this period.

Methods

In the process of data collection, we applied the following definitions:

Symptom onset: the time the first WG-related symptom appeared. Persistence of WG-related symptoms subsequently led to the suspicion of WG.

Date of diagnosis: the time when the treating physician suggested WG in the patient's files was interpreted as time of diagnosis. The diagnosis of WG was ascertained by one of the authors (JT) based on cumulative clinical features such as indications of generalized inflammatory disease as well as symptoms and signs consistent with the presentation of WG affecting the ear, nose and throat region (ENT), renal and pulmonary organ groups and suitable laboratory findings. The indicators of systemic inflammatory disease were malaise, fatigue and fever. Suitable laboratory findings included anaemia, high erythrocyte sedimentation rate (ESR) and high level of C-reactive protein (CRP) as well as positive ANCA test. Based on the cumulative information available, we tested how well the patient's characteristics agreed with the ACR classification criteria (4).

The study period covered hospital admissions from 1 January 1981 to 31 December 2000. This period of time was divided into the following four five-year segments: 1981-1985, 1986-1990, 1991-1995, and 1996-2000. For a patient to be included in the study the diagnosis had to be made between 1981-2000.

Statistics

The results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR), and 95 % confidence intervals (95% CI). We evaluated the statistical significance between groups with an analysis of variance (ANOVA), the Kruskall-Wallis test or the Jonckheere-Terpstra test and the chi-square test with a Monte Carlo *p*-value when appropriate. Patients with WG and the population at risk were stratified by gender and age (5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+), and we calculated crude and adjusted incidence rates with 95% CI. Standardized estimates of WG incidence rate ratios (IRR) were calculated by using Poisson regression models.

Ethical aspects

The ethics committee of the of Helsinki University Central Hospital, the Kajaani Central Hospital and the National Advisory Board on Health Care Ethics approved the study protocol.

Results

According to the hospital discharge register, 661 patients diagnosed with WG were treated at Finnish hospitals 1981-2000. Of them, 45 patients had received treatment only in health care centres. Of the 616 patients treated at hospitals of specialized medical care, at least some information was available on 585 patients, and 72 of them had received an erroneous code for WG or adequate information was unavailable for diagnostic confirmation. In 513 cases, the hospital clinicians diagnosed patients with WG. Of them, 492 patients had been diagnosed in 1981-2000, 243 men and 249 women; mean age at diagnosis: 53.7 years; range 9-91 years. Judging from the case histories, 410 (83%) of the 492 patients met the ACR diagnostic criteria for WG (≥2 criteria) (Table I).

The 17% of patients not fulfilling the ACR criteria were slightly more often male than female (55 *vs*. 45%), they were some five years older at diagnosis (mean age 57.2 *vs*. 52.4 years), and only five per cent of them had a histological confirmation of their disease.

The crude incidence of WG rose from 1.9 in the period 1981-1985 to 9.3 per million in 1996-2000. The corresponding age-adjusted incidence rate ratio (IRR) for men was 5.2 (95% CI: 3.2 to 8.4), $p<0.001$, and for women 4.0 (95% CI: 2.5 to 6.2), $p<0.001$. These data indicate a slight predominance among males in the last five-year period (men/women ratio 1.14) whereas in the former periods, the female patients outnumbered the male (Table II).

The least frequently affected age group was the youngest (5-14), with an annual incidence of 0.6 per million among males (95% CI: 0.17 to 1.56) and 1.6 (95% CI: 0.77 to 2.93) per million among females. Incidence peaked in the age group 65-74 among both sexes, with an incidence of 14 (95%CI:10.2 to 18.7) per million among males and 11.7 (95% CI: 8.86 to 15.2) per million among females (Fig. 1).

From 1981 to 2000, the mean age at diagnosis rose from 45.8 to 55.0 years

Table I. The progress in diagnosis of Wegener's granulomatosis over the 4 five-year periods in relation to gender ratio, age at diagnosis, diagnostic delay, erythrocyte sedimentation rate (ESR) and the proportion of patients meeting the ACR criteria.

	Period years				All periods	*p*-value between periods
	1981-1985	1986-1990	1991-1995	1996-2000		
Number	43	83	141	225	492	
Male patients (%)	19 (44)	40 (48)	64 (45)	120 (53)	243 (49)	0.42
Age at diagnosis (years), mean (SD)	45.8 (16.5)	51.1 (17.4)	53.7 (17.6)	55.0 (18.6)	53.2 (18.1)	0.014
Time from symptom onset to diagnosis (months), median (IQR)	17 (3,44)	8 (3,41)	5 (1,17)	4 (1,12)	5 (2,20)	<0.001
ESR at diagnosis, mm/h, median (IQR)	80 (55,102)	78 (48,105)	61 (34,95)	80 (50,100)	75 (45,100)	0.11
ACR classification criteria present ≥2 (%)	40 (93)	71 (86)	115 (82)	184 (82)	410 (83)	0.27

Table II. Incidence per million of Wegener's granulomatosis in Finland 1981-2000.

	Period years				
	1981-1985	1986-1990	1991-1995	1996-2000	*p* for linearity
Male					
Number of patients	19	40	64	120	
Crude incidence (95% CI)	2.0 (1.3 to 3.0)	3.6 (2.6 to 4.3)	6.3 (5.0 to 7.9)	8.4 (6.9 to 10.2)	<0.001
Age adjusted Incidence rate ratio (95% CI)	Indicator (1)	2.0 (1.2 to 3.5)	3.0 (1.8 to 5.0)	5.2 (3.2 to 8.4)	<0.001
Female					
Number of patients	24	43	77	105	
Crude incidence (95% CI)	1.7 (1.0 to 2.7)	3.6 (2.6 to 4.9)	5.6 (4.3 to 7.1)	10.2 (8.4 to 12.2)	<0.001
Age adjusted Incidence rate ratio (95% CI)	Indicator (1)	1.8 (1.1 to 2.9)	3.0 (1.9 to 4.8)	4.0 (2.5 to 6.2)	<0.001
Total					
Number of patients	43	83	141	225	
Crude incidence (95% CI)	1.9 (1.4 to 2.6)	3.6 (2.9 to 4.4)	6.0 (5.0 to 7.0)	9.3 (8.1 to 10.6)	<0.001
Age and sex adjusted Incidence rate ratio (95% CI)	Indicator (1)	1.9 (1.4 to 2.4)	3.0 (2.4 to 3.8)	4.5 (3.6 to 5.7)	<0.001

(p for linearity = 0.014). At the same time, the median delay from the appearance of the first symptoms and signs to the confirmation of the diagnosis had shortened from 17 to 4 months (p for linearity <0.001) (Table I).

At the onset of WG, the most frequent manifestations were symptoms and signs of ENT and lung system involvement and symptoms of systemic inflammatory disease (Table III). From the first to the last five-year period, the proportion of systemic symptoms prior to diagnosis tended to grow (p=0.0048), whereas ENT (p=0.0046), skin (p=0.033), eye (p=0.022) and kidney (p=0.0081) involvement as primary manifestations at diagnosis tended to be less frequent with time (Table III).

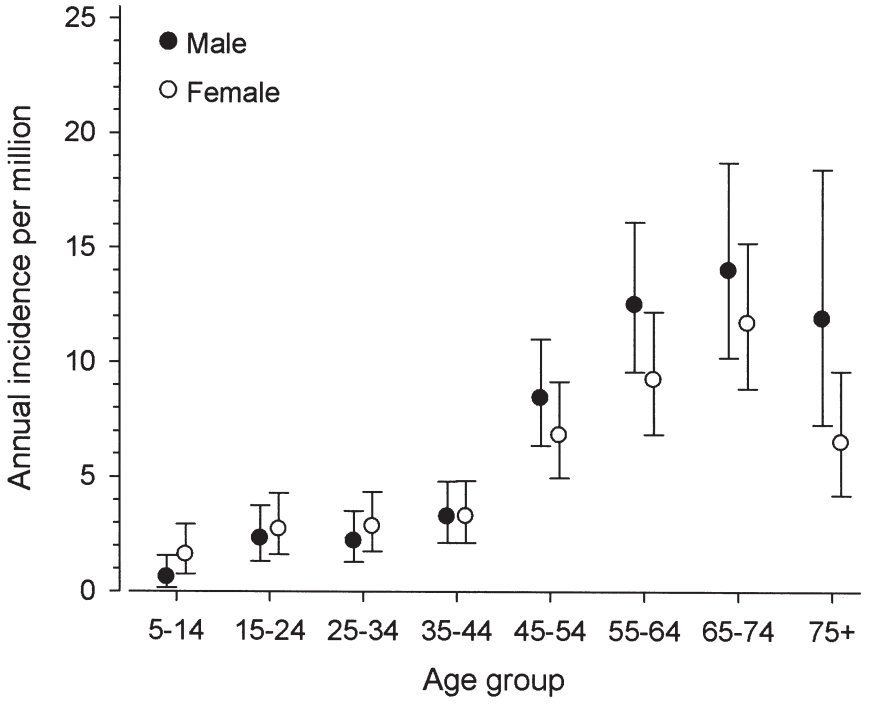

Fig. 1. The annual incidence of Wegener's granulomatosis in relation to gender and age group.

Discussion

The annual incidence of WG in the Finnish population was 1.9 per million in the five-year period 1981-1985, and rose to 9.3 per million by 1996-2000. Thus, incidence rose 4.5-fold. These incidence figures agree with those of previous European studies: a variance in the annual incidence of WG has been from 5.3 in Spain (13) to 12.0 per million of the population in Norway (11). In Sweden, Knight *et al*. observed the incidence of WG to triple from 3.3 per million in 1975-85 to 11.9 per million in 1991-2001 (12). Watts *et al*. (14) reported an increased incidence of WG from 9.7 to 10.6 per million in UK from 1988-1997. In line with our results, the incidence of WG increased two-fold over a 15-year period (1984-1998) in Norway (11). In another study, the incidence of WG 1988-1998 was 10.6 in the UK and 4.9 in Lugo, Spain, with neither an increase nor a fluctuation in the incidence of systemic vasculitis during the 11-year period (13). Reinhold-Keller *et al*. also found in Germany a stable incidence rates for all primary systemic vasculitides in 1998-2002 (15).

The differential diagnosis between various forms of vasculitides is often difficult, which might also slightly contribute to the differences between incidence figures. The American College of Rheumatology (ACR) classification criteria (1990) (4), the Chapel Hill Consensus Conference definitions for nomenclature of systemic vasculitides (1994) (5) and the diagnostic criteria for WG by Sørensen *et al*. (2000) (6) are all being used in the diagnosis of WG.

This rise in incidence of WG may result from increased awareness of the disease among physicians. They may suspect WG more often and therefore refer patients for additional consultation more readily. Thus, even milder

Table III. Organ involvement and systemic signs (number of patients, %) at diagnosis in patients with Wegener's granulomatosis.

Organ system	Period Years				Total	*p*-value between periods
	1981-1985 (n=41) n (%)	1986-1990 (n=83) n (%)	1991-1995 (n=141) n (%)	1996-2000 (n=224) n (%)	(n=489) n (%)	
Muscle/joint	21 (51)	39 (47)	72 (51)	105 (47)	237 (48)	0.84
CNS	2 (5)	8 (10)	15 (11)	24 (11)	49 (10)	0.70
ENT	35 (85)	70 (84)	113 (80)	154 (69)	372 (76)	0.0046
Gastrointestinal	4 (10)	18 (22)	31 (22)	36 (16)	89 (18)	0.20
Gynaecological	0 (0)	0 (0)	2 (1)	1 (0)	3 (1)	0.58
Skin	15 (37)	27 (33)	40 (28)	45 (20)	127 (26)	0.033
Lung	31 (76)	64 (77)	107 (76)	173 (77)	375 (77)	0.99
Kidney	26 (63)	64 (77)	82 (58)	126 (56)	298 (61)	0.0081
PNS	1 (2)	2 (2)	10 (7)	8 (4)	21 (4)	0.25
Psychiatric	0 (0)	1 (1)	0 (0)	0 (0)	1 (0)	0.25
Eye	18 (44)	27 (33)	38 (27)	50 (22)	133 (27)	0.022
Cardiovascular	6 (15)	7 (8)	16 (11)	20 (9)	49 (10)	0.63
Systemic signs	30 (73)	60 (72)	123 (87)	193 (86)	406 (83)	0.0048

CNS: central nervous system; ENT: ear, nose and throat; PNS: peripheral nervous system; Systemic signs: malaise, fatigue, fever, anaemia, high erythrocyte sedimentation rate (ESR) and high levels of C-reactive protein (CRP).

forms of the disease are currently more likely to be properly diagnosed.

Another possible explanation may be an improvement in diagnostic facilities and by the availability of more accurate, sensitive, and specific laboratory methods *e.g.*, ANCA and its subclasses. ANCA was first described in association with vasculitis in 1982 (7). It has been increasingly applied in the diagnostics since 1985 in Finland. Table I indicates a decrease in diagnostic delay and in the number of patients fulfilling ACR criteria from the pre-ANCA era. This probably means that nowadays positive results in ANCA testing in the presence of relevant clinical symptoms and laboratory findings give additional support to the diagnosis. Improvements in endoscopic equipment and biopsy processing methods may also facilitate obtaining diagnostic biopsies.

A third possibility is that the incidence of Wegener's granulomatosis has actually increased. Interestingly, increased incidences have been independently reported for three Scandinavian countries (11, 12), including our present results. The availability of ANCA test does not, at least totally, explain the increases in the incidence figures, as similar trends have not been reported from central or south European countries (13-15).

Although the aetiology of WG remains unknown, researchers suspect various aetiological or precipitating agents, such as inhaled substances and respiratory infections (16, 17, 19). Cold climate may be a factor in increased incidence of WG, which is more common in northern Europe than southern Europe (13). Tidman *et al*. (18) have reported periodic annual fluctuation in the incidence of ANCA-associated vasculitides in 1998, indicating perhaps the role of viral infections as etiologic or precipitating factors. Other studies, however, have failed to confirm this finding (11, 15, 20).

The strengths of this study are that the hospital discharge register covers the whole country of Finland, and that the hospital records of all patients with a discharge diagnosis of WG and treated at hospitals of specialized medical care were reviewed and their diagnoses confirmed. On the other hand, this study only includes patients with the correct diagnosis code of WG in their discharge records. Some patients may have been excluded from the study if they were diagnosed not during their hospital stay, but afterwards, or if the patient underwent treatment only as an outpatient. Still, given the seriousness of WG and its considerable morbidity and mortality rate, most WG-patients have likely received diagnostic or therapeutic treatment at some point in a hospital of specialized medical care, as also discussed by Knight *et al*. (12). Thus, the number of patients excluded this way would be quite small. In an epidemiological study from Norway, only 7% of the patients were recruited from district hospitals and 2% were identified only from the lists of the departments of pathology (11).

A weakness of this study is that we included only patients that were treated at a hospital ward, at least once. We reasoned that no patient with a *de novo* diagnosis of WG during the study period would have been treated only at a health care centre. Therefore, we excluded such patients from this incidence study. Furthermore, the information was gathered retrospectively from patient files. Diagnostic criteria must have varied with district and time. Also, we have probably missed some cases with only a limited form of the disease.

WG was introduced as early as the1930s and has been fairly well-known among physicians over the last two decades. It is probable that most WG-patients have been properly diagnosed at some point.

In conclusion, the incidence of WG seems to have increased over the study period. We can speculate whether exposure to environmental agents, viral or bacterial infections, immunisation, antimicrobial or other kinds of drugs might have contributed to this increase in incidence.

References

1. FAN PT, DAVIS JA, SOMER T, KAPLAN L, BLUESTONE R: A clinical approach to systemic vasculitis. *Semin Arthritis Rheum* 1980; 9: 248-304.
2. KLINGER H: Grenzformen der Periarteriitis nodosa. *Frankfurter Zeitschrift für Pathologie* 1931; 42: 455-80.
3. WEGENER F: Über generalisierte, septische Gefässerkrankungen. *Verhandlungen der Deutschen Pathologischen Gesellschaft* 1936; 29: 202.
4. LEAVITT RY, FAUCI AS, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990; 33: 1101-7.
5. JENNETTE JC, FALK RJ, ANDRASSY K *et al*.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
6. SORENSEN SF, SLOT O, TVEDE N, PETERSEN J: A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. *Ann Rheum Dis* 2000; 59: 478-82.

7. DAVIES DJ, MORAN JE, NIALL JF, RYAN GB: Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? *BMJ* 1982; 285: 606.
8. VAN DER WOUDE FJ, RASMUSSEN N, LOBATTO S *et al*.: Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985; 1: 425-9.
9. MANDL LA, SOLOMON DH, SMITH EL, LEW RA, KATZ JN, SHMERLING RH: Using antineutrophil cytoplasmic antibody testing to diagnose vasculitis: can test-ordering guidelines improve diagnostic accuracy? *Arch Intern Med* 2002; 162: 1509-14.
10. CARRUTHERS DM, WATTS RA, SYMMONS DP, SCOTT DG: Wegener's granulomatosis--increased incidence or increased recognition? *Br J Rheumatol* 1996; 35: 142-5.
11. KOLDINGSNES W, NOSSENT H: Epidemiology of Wegener's granulomatosis in northern Norway. *Arthritis Rheum* 2000; 43: 2481-7.
12. KNIGHT A, EKBOM A, BRANDT L, ASKLINGR J: Increasing incidence of Wegener's granulomatosis in Sweden. *J Rheumatol* 2006; 33: 2060-3.
13. WATTS RA, GONZALEZ-GAY MA, LANE SE, GARCIA-PORRUA C, BENTHAM G, SCOTT DG: Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. *Ann Rheum Dis* 2001; 60: 170-2.
14. WATTS RA, LANE SE, BENTHAM G, SCOTT DG: Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom. *Arthritis Rheum* 2000; 43: 414-9.
15. REINHOLD-KELLER E, HERLYN K, WAGNER-BASTMEYER R, GROSS WL: Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. *Arthritis Rheum* 2005; 53: 93-9.
16. SOMER T, FINEGOLD SM: Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; 20: 1010-36.
17. DUNA GF, COTCH MF, GALPERIN C, HOFFMAN DB, HOFFMAN GS: Wegener's granulomatosis: role of environmental exposures. *Clin Exp Rheumatol* 1998; 16: 669-74.
18. 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.
19. MAHR AD, NEOGI T, MERKEL PA: Epidemiology of Wegener's granulomatosis: Lessons from descriptive studies and analyses of genetic and environmental risk determinants. *Clin Exp Rheumatol* 2006; 24 (Suppl. 41): S82-91.
20. MAHR A, ARTIGUES N, COSTE J *et al*.: Seasonal variations in onset of Wegener's granulomatosis: increased in summer? *J Rheumatol* 2006; 33: 1615-22.
21. GIBSON A, STAMP LK, CHAPMAN PT, O'DONNELL JL: The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. *Rheumatology* (Oxford) 2006; 45: 624-8.
22. LANE SE, WATTS RA, BARKER TH, SCOTT DG: Evaluation of the Sorensen diagnostic criteria in the classification of systemic vasculitis. *Rheumatology* (Oxford) 2002; 41: 1138-41.