

Epidemiology of Wegener's granulomatosis: Lessons from descriptive studies and analyses of genetic and environmental risk determinants

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This work was supported by the Vasculitis Clinical Research Consortium (www.rarediseasesnetwork.org/vcrc) through a grant from the National Institutes of Health (National Center for Research Resources and the National Institute of Arthritis and Musculoskeletal and Skin Diseases) (NIH-NCRR: U54 RR019497). Dr. Neogi is supported by the Abbott Scholar Award in Rheumatology and an Arthritis Foundation Postdoctoral Fellowship Award.

Dr. Merkel is also supported by a Mid-Career Development Award in Clinical Investigation (NIH-NIAMS: K24 AR02224).

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Received and accepted on February 9, 2006.

Clin Exp Rheumatol 2006; 24 (Suppl. 41): S82-S91.

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Key words: Wegener's granulomatosis, epidemiology, frequency, genetics, risk factor.

ABSTRACT

During the past 15 years, the epidemiology of Wegener's granulomatosis (WG) has become better understood. Descriptive epidemiological studies carried out primarily in European countries estimate a prevalence of WG ranging from 24 to 157 per million and annual incidence rates from 3 to 14 per million. These studies suggest a North-South declining gradient in disease risk in the Northern Hemisphere and an increase in incidence over time, although the latter is likely largely due to improved diagnostic ascertainment. Data also indicate the presence of potential secular and seasonal variations in WG incidence and a decreasing disease risk among non-Caucasians. Furthermore, analytic epidemiological studies have pointed out putative genetic and non-genetic risk factors for WG. Genetic investigations have identified various candidate genes, with $\alpha 1$ -antitrypsin deficiency being the most consistently reported genetic susceptibility factor to date. Even though much less research has been devoted to environmental risk factors, evidence has grown for a possible relationship between WG and occupational exposure to crystalline silica. Thus far, data support the concept of WG as a multifactorial disease in which genetic and environmental determinants are involved but a major gap in understanding persists regarding the extent to which both factors contribute to its development. This and many other questions remain to be answered by future structured epidemiological research. This review focuses on the current knowledge of descriptive epidemiology and genetic and environmental factors associated with WG.

Introduction

Wegener's granulomatosis (WG) is a necrotizing granulomatous vasculitis primarily involving the upper and lower respiratory tracts and the kidneys but that may also affect multiple other organs or tissues. Originally described as a clinical triad with an almost invariably fatal course if left untreated, it is now apparent that this primary systemic vasculitis may have highly diverse clinical and prognostic profiles. Moreover, WG is characterized by a close association with anti-neutrophil cytoplasm antibodies (ANCA), most commonly giving a cytoplasmic pattern by immunofluorescence (C-ANCA) and directed against proteinase 3 (anti-PR3), that has led to the classification of this disorder together with microscopic polyangiitis and Churg-Strauss syndrome as an "ANCA-associated vasculitis" (AAV). Hypotheses regarding the pathogenesis of WG concentrate on neutrophil-, monocyte- and lymphocyte-dependent mechanisms and a possibly pivotal role of ANCA (1). The etiology of WG remains unknown. Based on a growing number of epidemiologic investigations carried out during the last 15 years, current understanding is that of a complex disease resulting from the interplay among multiple genetic and environmental risk factors. The increased interest in the epidemiology of WG is likely reflective of an overall heightened awareness to WG since the discovery of ANCA (2) but also the result of the development of standardized definitions for primary systemic vasculitides. In particular, publication of the American College of Rheumatology (ACR) classification criteria (3) and the Chapel Hill Consensus Conference (CHCC) definitions of vasculitides (4)

greatly facilitated the separation of WG from other primary systemic vasculitides and had a strong positive effect on epidemiological research.

This article reviews the current data on the descriptive epidemiology and genetic and environmental factors associated with WG.

Descriptive epidemiology

The aim of descriptive epidemiological studies is to give insight into the frequencies, geographic variations, temporal trends, and clinical characteristics of diseases. Estimates of disease frequencies, expressed as prevalence or incidence rates, are most reliably derived from population-based studies which additionally offer the opportunity to perform wider investigations within unselected cohorts. However, as is common in the study of rare diseases, many of the investigations, both descriptive and analytic, discussed herein were hospital-based rather than population-based. Hospital-based cohorts

allow for accumulation of larger patient groups but are associated with the potential for serious selection biases.

1. Prevalence and incidence rates

Prior to the publication of the ACR classification criteria and the CHCC nomenclature, only a few population-based studies had estimated the frequency of WG in the USA (5) and UK (6, 7), each using what are now obsolete disease definitions. Since the new classification schemes have become available, prevalence and incidence rates have been published for a variety of populations throughout the world (8-22). Notably, studies from 3 geographic areas provided results derived from prospective longitudinal patient registries (13, 16, 19).

Accordingly, the prevalence of WG is estimated at 23.7-156.5 per million (8, 10, 12-14, 17, 18, 20, 22) and the annual incidence at 3.0-14.4 per million (9, 11-13, 15, 16, 19-21) (Table I, Fig. 1). These variations in occurrence of WG

generate valuable hypotheses for the etiology of WG, but it should be noted that some of the discrepancies may be accounted for by methodological differences. Limitations to comparability result partly from the fact that these studies employed either the ACR classification criteria or CHCC definitions since both sets likely perform differently. Although the CHCC definitions appear conceptually more flexible, there is evidence that in practice they tend to generate lower estimates of the frequency of WG than the ACR criteria (22-24). Moreover, it is probable that among different investigators the instruments have not been used in a uniform manner. Comparisons are further problematic because the incidence and prevalence estimates were, apart from one study (16), crude rates and not age- and sex-adjusted to a common standard population. In some studies, these differences were minimized by providing estimates restricted to the adult population (9, 11-13, 18), but

Table I. Frequency estimates (per million) of WG in various populations (studies are sorted by continents and increasing geographical latitudes from top to bottom).

References	Study area	Inclusion criteria	Prevalence		Annual incidence	
			Study period	Rate (95% CI)	Study period	Rate (95% CI)
<i>Europe</i>						
Gonzales-Gay <i>et al.</i> (16)	Lugo county (Spain)	CHCC			1998-2001	3.0 (1.4-6.1)
Gonzales-Gay <i>et al.</i> (11)	Lugo county (Spain)	ACR			1988-1997	4.8 (1.6-7.9) [¶]
Reinhold-Keller <i>et al.</i> (14)	Breisgau district (Germany)	CHCC	1994	42 (23-62)		
Reinhold-Keller <i>et al.</i> (15)	Baden-Württemberg State (Germany)	CHCC			1998-1999	5.5 (2-12) [*]
Mahr <i>et al.</i> (18)	Seine-St. Denis county (France)	ACR	2000	23.7 (16-31) [†]		
Reinhold-Keller <i>et al.</i> (14)	Segeberg district (Germany)	CHCC	1994	58 (36-80)		
Reinhold-Keller <i>et al.</i> (19)	Schleswig-Holstein State (Germany)	CHCC			1998-2002	8.6 (4-16) [*]
Carruthers <i>et al.</i> (9)	Norwich county (UK)	ACR			1988-1993	10.3 (6.4-15.5) [§]
Watts <i>et al.</i> (13)	Norwich county (UK)	ACR	1997	62.9 (41.5-91.6) [‡]	1988-1997	8.5 (5.2-12.9) [‡]
Mohammad <i>et al.</i> (17)	Lund-Orup district (Sweden)		2003	156.5 (133-182) [*]		NR
Knight <i>et al.</i> (21)	Sweden (nationwide)	Discharge diagnoses			1991-2001	11.9 (11.2-12.6)
Haugeberg <i>et al.</i> (10)	Vest-Agder county (Norway)	ACR	1996	53 (41-69) [*]		
Koldingsnes <i>et al.</i> (12)	Northern Norway	ACR	1998	95.1 (69-129)	1994-1998	14.4 (9.5-21.0) [†]
<i>United States of America</i>						
Cotch <i>et al.</i> (8)	Nationwide	Discharge diagnoses	1986-90	26 (17-35) ^{**}		
	New York State	Discharge diagnoses	1986-90	32 (22-45) [†]		
Zeft <i>et al.</i> (20)	Western Montana, MT	NR	2004	90 (58-122)	1993-2004	8.6 (5.7-12.5)
<i>New Zealand</i>						
Gibson <i>et al.</i> (22)	Province of Canterbury	CHCC	2003	112 (82-152)		
	Province of Canterbury	ACR	2003	93.5 (66-121)		

ACR: American College of Rheumatology classification criteria; CHCC: Chapel Hill Consensus Conference definition; NR: not reported; CI: confidence interval.

[†]Confidence interval specifically calculated based on data provided in the original article (according to an exact Poisson distribution).

Estimates for adult population aged 15 years or above[†], above 15 years[‡], 20 years and above[¶] or age cut-off not specified[§].

**99% confidence interval.

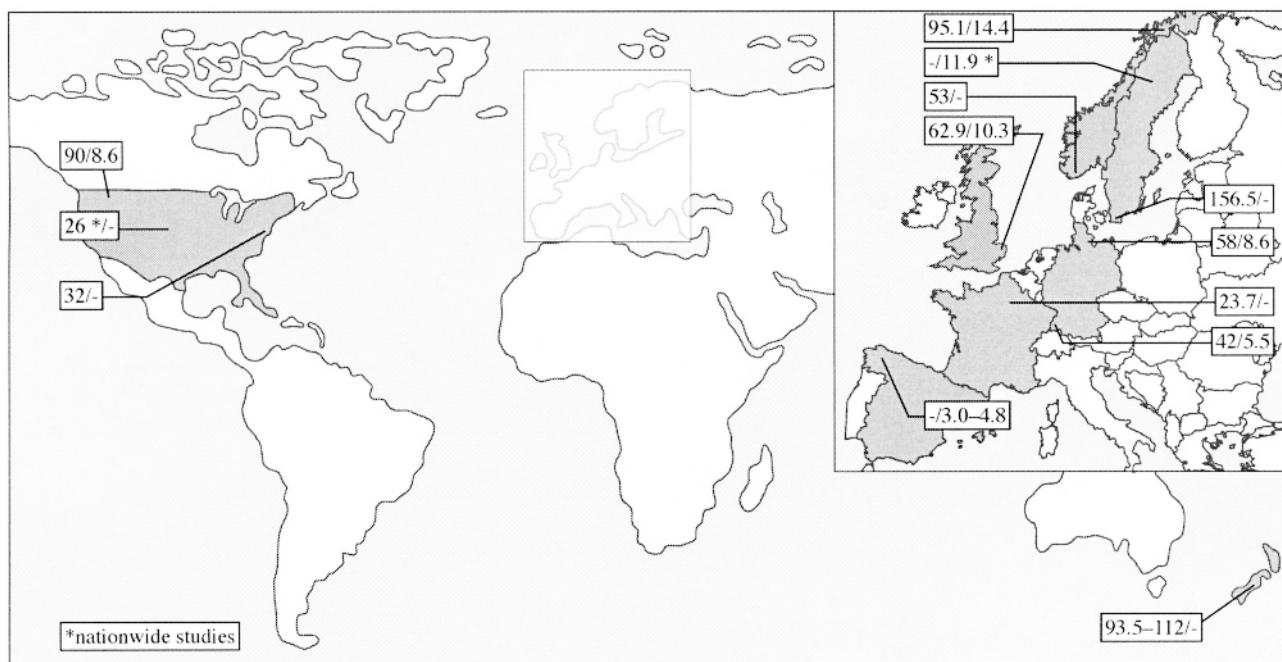


Fig. 1. Geographic distribution of WG (numbers represent prevalence/annual incidence rates per million) (data from ref. 8, 10-22).

such figures are still not directly comparable.

2. Demographic pattern

Although affecting individuals of virtually all ages, WG occurs primarily in middle-aged adults. According to large hospital-based series, mean or median ages at diagnoses reportedly varied between 41 and 52 years (25-30). However, population-based surveys, including 2 nationwide studies (8, 21), suggest higher mean or median ages ranging from 50 to 66 years (8-12, 18, 19, 21, 22). Similarly, age-specific incidence rates reported from population-based studies indicate the incidence of WG peaks in the age-groups of 55-64 years (16) or 65-74 years (12, 13), although in one of these studies (12) this finding was limited to male patients. Population-based data therefore provide evidence that WG might occur later in life than had been reported by hospital-based cohorts, perhaps because older patients are less prone to be referred to tertiary care centers. Likewise, a small discrepancy exists for gender distribution according to the study type. Hospital-based series quite consistently indicated a slight excess among men compared to women with male-to-female ratios ranging from

1.0-1.7 (25-30). Data from several population-based studies also suggest an increased disease risk in males with male-to-female ratios of 1.1 (19) and 1.3 (10, 18) and gender-specific annual incidence rates 1.2- (21), 1.7- (9) and 1.9-fold (12) higher in males than females. In contrast, results of other population-based investigations showed a female predominance with male-to-female ratios of 0.9 (8) or 0.6 (22) and male-to-female gender-specific annual incidence rates of 0.5 (11) or 0.8 (16). Although some of the latter findings (11, 16) were obtained from small samples, they question the classical male predominance in occurrence of WG.

3. Geographic distribution

The geographic distribution of disease occurrence suggests that WG might be more common in northern European countries compared with southern European countries (31) (Fig. 1). This hypothesis of a potential North-South decreasing gradient in the Northern Hemisphere had been addressed in greater detail in a study comparing incidences of WG in 3 different, mostly rural and Caucasian regions using homogeneous classification criteria. This study indeed revealed a 2-times

higher annual incidence in the Norwegian and English populations compared to that in Spain (31, 32). Although the characterization of this distribution of risk warrants further confirmation, it suggests the existence of a particular disease susceptibility in northern European populations on a genetic basis or as a result of exposure to putative environmental triggers. Prevalence and incidence figures are much less well documented in regions outside Europe. Data support that occurrence of WG in some North-American populations and in New Zealand might be similar to that observed in northern Europe (20, 22). Conversely, preliminary observations would indicate a low occurrence of WG in Asian countries (33).

4. Temporal changes

There is evidence suggesting an increase in the incidence of WG during the last several decades. In northern Norway, the annual incidence rates more than doubled during 3 consecutive quinquennia from 1984-1998 (12) and an almost 4-fold increase among 3 time-periods from 1975-2001 was observed in a nationwide Swedish study (21). Interestingly, both studies also suggested that this increasing trend might have extended beyond the intro-

duction of ANCA testing (12, 21). Conversely, other studies suggest the incidence has remained relatively stable, although these results were drawn from shorter observation periods (13, 19) or smaller populations (16). Even though it is highly probable that some of the temporal change in incidence simply reflects enhanced diagnostic ascertainment due to ANCA testing, the possibility remains that there has been a real increase in some areas. Future studies will help clarify whether or not the incidence of WG has reached a plateau or remains on the rise.

Results are mixed regarding the issue of the incidence of WG exhibiting temporal clustering, which, if confirmed, could support the hypothesis of an environmental component to the etiology of WG. Data from Norway indicate the occurrence of peaks in the incidence of WG every 4 to 5 years during a 15 year-period (12). Similar findings were reported for AAV – that is WG, microscopic polyangiitis and Churg-Strauss syndrome together – with apparent peaks and troughs occurring every 3 years over a 14-year period (1988-2001) in Spain (16) and every 3 to 5 years over a 21-year period (1975-1995) in an area of Central Sweden (34). However, temporal clustering was not found in the UK (13) and no major fluctuations in the annual incidence rates of WG were observed in a nationwide study in Sweden (21).

5. Seasonality of disease onset

Several hospital- (34-37) and population-based studies (9) have suggested that the onset of WG peaks predominantly during the winter, a finding that is often cited to support an environmental factor and, particularly, an infectious cause in the etiology of WG. These studies observed that 30-43% of patients' first symptoms attributable to WG occurred during December-February as compared to an expected random distribution of 25% (9, 34-36). However, the issue of seasonality in the onset of WG remains controversial. Most of these studies (9, 34, 35, 37) were not specifically designed to investigate this complicated question, and one of them evaluated seasonality in a

mixed population of patients with WG and microscopic polyangiitis (35). Most importantly, two other studies did not demonstrate evidence of a consistent seasonal pattern in the onset of WG (12, 38) including an evaluation that suggested a non-significant increase in the summer season (12).

6. Urban-rural differences

Examining differences in disease frequency between urban and rural populations provides opportunities to assess the effects of a variety of specific environmental exposures, including air pollution, occupational factors, or lifestyle. In an attempt to explain the higher occurrence of WG in their population compared to previous surveys from the UK, Carruthers *et al.* were the first to hypothesize that WG might occur more frequently in the countryside than in cities (9). A similar suggestion was made by Cotch *et al.* who mapped the prevalence of WG in New York State, USA and found that the highest figures were observed not only in New York City but also in a number of rural areas (8). The only population-based frequency estimate that was derived from an almost exclusively urbanized area, the greater Parisian metropolitan area in France, indeed yielded the lowest prevalence rate for WG reported to date, although this difference might also be explained by several other variables (18). However, studies that directly compared the frequency of WG among rural and urban areas within the same region did not find any significant differences (14, 16). Although it is not entirely clear what methods were used to define the urban-rural status in these studies, the possibility of the frequency of WG varying between cities and the countryside seems rather unlikely in light of the currently available data.

7. Migration studies

An interesting approach to discern the respective inputs of environmental and genetic factors in the development of a condition is to study the disease risk in migrant populations. The impact of migration from one country to another has not yet been assessed with respect

to WG, but several observations suggest that disease risk among non-Caucasian migrants residing in North America or Europe is lower than that among the non-migrants of these areas. Assessment of disease by ethnic distributions in US hospital-based (25, 27, 29) or population-based (8) cohorts demonstrated that 83-97% of patients with WG are Caucasian Americans and 2-8% are African Americans with this excess among Caucasians being greater than expected from the background populations. Additional support for the decreased occurrence of WG in non-Caucasian migrants comes from a prevalence study within a French multi-ethnic population that included many residents of African, Asian and Caribbean ancestries. Among 21 patients with WG identified in that area, 14% were of non-European background as compared to an expected rate of 26%. The overall prevalence of AAV combined with another vasculitic disorder, polyarteritis nodosa, was significantly lower – by a factor of 2 – in the non-European than in the European populations (18). Although one might postulate that ethnic disparities in risk of WG reflects underascertainment or reduced access to medical care facilities within immigrant populations, these figures strongly suggest that non-Caucasian migrants may have a lower risk of WG even though they are exposed to similar environments. This finding supports the contribution of genetic factors for susceptibility to WG although culturally-based differences in behavior or socio-economic status might also play important roles.

Analytic epidemiology

Analytic epidemiology aims to identify the determinants of disease occurrence with putative risk factors commonly falling into 2 major categories: genetics and environment. In that context, the term 'environment' is generally used to designate all non-genetic variables regardless whether they are truly external to the host, e.g. infection, occupation, or diet, or endogenous, e.g. hormonal influences. Concerning WG, while considerable effort has been directed at studying genetic factors,

less attention has been given to the examination of environmental risk factors. In particular, the theoretical roles of hormonal, dietary or socioeconomic factors have not yet been assessed. Because WG is rare, almost all available data on analytic epidemiology were derived from case-control studies. However, all these studies included prevalent cases which, compared to enrollment of incident cases, increases the risk of selection and recall biases and renders reliable establishment of temporality between exposures and the onset of WG more difficult.

1. Genetic factors

Genetic predisposition to WG is suggested by ethnic variation (see above) and by reports of familial aggregation (39-45). Increased recurrence risk for relatives of affected individuals is generally considered an important indication of a genetic component to the etiology of diseases, although not definitive support because familial aggregation can also result from shared environmental exposures. Several case reports describe familial clustering of WG among siblings (39-42), parents and children (43, 44) or second and higher-degree relatives (45). Additional reports of the occurrence of polyarteritis nodosa (44) or Churg-Strauss syndrome (46) among relatives of WG patients may further suggest the existence of a common genetic risk factor across vasculitides. Conversely, occurrence of WG has also been reported in

unrelated family members (47, 48) and other data suggests that the familial recurrence of WG is rather modest. A survey of 701 people with self-reported WG did not detect a single familial case (49). In addition, 12 of the 701 individuals reported having a twin (49), a finding consistent with previous case reports on discordance for WG among twins (50, 51). Taken together, these observations provide indirect evidence of a genetic effect, but they also indicate that development of WG can not be explained by genetics alone.

More direct evidence of genetic risk for WG stems from identification of several candidate genes by gene association studies (reviewed in 52, 53). Human leucocyte antigen (HLA) typing studies yielded divergent results detecting either no particular WG-related pattern (54-56) or various associations with HLA-B8 (57, 58), -B50 (59), -DQw7 (60), -DR1 (61), -DR2 (62), -DR9 (59) genes, or the DR4DQ7 haplotype (59, 60). Other investigations suggested a protective effect of HLA-DR3 (60) or -DR13DR6 (63). Many studies focused on other potentially important genetic markers, e.g. cytokines, chemokines, adhesion molecules or proteinase 3. A number of these studies were consistent in showing a link with the Z deficiency allele of α 1-antitrypsin (64-72) with some of these demonstrations not directly referring to WG but to C-ANCA- (66, 69, 71), anti-PR3-positive vasculitis (67, 71) or AAV (70) (Table II). The significance of the 3-7-fold

overrepresentation of Z phenotypes in WG is not well understood but a plausible theory is that since α 1-antitrypsin has a major role in inactivating neutrophil enzymes proteinase 3 and elastase, individuals deficient in α 1-antitrypsin suffer from an increased proteolytic activity with resultant tissue injury (64). However, the frequency of Z phenotypes among patients with WG (or C-ANCA/anti-PR3-positive vasculitis) did not exceed 7-27% (Table II), suggesting that this susceptibility gene could explain disease development for only a subset of cases. Other potentially relevant polymorphisms have been found for the genes encoding cytotoxic T lymphocyte associated antigen-4 (CTLA-4) (73-75), interleukin-10 (76-78), proteinase 3 (79), the complement component 4B (61) and the intracellular tyrosine phosphatase protein PTPN22 (80). Another study reported an association between the absence of the Δ 32 allele of CCR5 and ANCA-negative WG (81). Thus, for many of these polymorphisms, it is not clear whether they are functionally relevant and some associations with WG were weak, suggesting that they may not be key determinants in the development of the disease.

In the future, screening of the entire genome using microarray techniques might identify chromosomal areas that include genes predisposing to WG (53). To date, the only genetic study that had used such a reverse approach was based on an extended association

Table II. Genetic α 1-antitrypsin polymorphism (expressed as frequency of phenotypes with the Z allele) and WG or C-ANCA/anti-PR3-positive vasculitis.

References	Year of publication	Diagnosis	No. of patients/controls	Z phenotype		P
				Cases, %	Controls, %	
Elzouki <i>et al.</i> (65)	1994	WG	66/NR [†]	22.7	4.7	< 0.0001*
Lhotta <i>et al.</i> (66)	1994	C-ANCA-positive vasculitis	32/868	15.6	2.8	0.003*
Savige <i>et al.</i> (67)	1995	Anti-PR3-positive vasculitis	31/NR [‡]	9.7	1.5	< 0.05
Baslund <i>et al.</i> (68)	1996	WG	44/NR [†]	18.2	4.7	< 0.001
Griffith <i>et al.</i> (69)	1996	C-ANCA-positive vasculitis	99/2310	10.1	3.6	0.004*
Callea <i>et al.</i> (70)	1997	C- or P-ANCA-positive vasculitis	84/200	7.1*	1.5	0.022
Esnault <i>et al.</i> (71) [§]	1997	C-ANCA/anti-PR3-positive vasculitis	37/1310	27.0	3.8	< 0.0001*
Borgmann <i>et al.</i> (72)	2001	WG	79/752	8.9	2.5	< 0.0001

NR: not reported.

*Calculations specifically performed based on data provided in the original article (comparisons used 2-sided Fisher's exact tests).

†Population-based estimates from Sweden[†] and Australia[‡] used as controls.

§Include patients from reference (64).

screen of functionally relevant genes using microsatellite markers (82). Results of this study suggest a linkage with the genomic region 6p21.3 within the human major histocompatibility complex and identifies an association with the HLA DPB1*0401 allele and the extended DPB1*0401/RXRBO3 haplotype (82).

2. Environmental factors:

a. Infection

Although it has long been suggested that exposure to an infectious agent might be the trigger for WG (83), to date there is little evidence for this hypothesis. Most of the support for a relationship between infection and WG remains indirect and refers to: i) data demonstrating seasonal variations or temporal clustering in occurrence of WG (see above); ii) findings that disease onset is often preceded by flu-like symptoms (35) and disease relapse may coincide with infectious episodes (84); and iii) the seminal observation (85) and numerous confirmatory reports of a beneficial effect of trimethoprim-sulfamethoxazole on WG and a therapeutic trial demonstrating that this antibiotic reduced the relapse rate in WG (86). Interpretation of the studies involving trimethoprim-sulfamethoxazole is not straightforward. Although it is tempting to consider that trimethoprim-sulfamethoxazole exerts its effects via its anti-microbial, and perhaps more specifically anti-staphylococcal, properties, it can not be ruled

out that this anti-folate agent also has a separate immunosuppressive activity (85). There have been only a few investigations evaluating the role of specific infectious agents in the occurrence of WG. Particular interest has focused on *Staphylococcus aureus* since this agent has been held responsible for most of the secondary infections of the upper airways (87) and can be cultured from bronchoalveolar lavages (88) in patients with WG. The most striking evidence for a role of this microorganism in disease pathogenesis came from a study showing that chronic nasal carriage of *S. aureus* has been associated with disease relapses (89). Thus, even though *S. aureus* could influence the course of WG, there is little support to date that this agent induces the disease *per se*. Several other microorganisms have been invoked as possible causes of WG, including *Mycobacterium tuberculosis* (90-92), *Mycobacterium avium intracellulare* (93), or Parvovirus B19 (94, 95), but these are often case reports and the data conflict with the negative results of larger studies (93, 96).

b. Occupational exposures

The commonly prominent airway disease seen in WG has also raised the hypothesis that occupational exposure, especially to an inhalant, may be the causative agent of the disease. The association between potential occupational risk factors and WG has been assessed by several case-control stud-

ies (38, 97-101). These studies are consistent in finding positive associations between crystalline silica exposure and risk of WG with odds ratios of 2.5-5 (97, 98, 100) and exposure to silica among patients of 31-50% (97-99) (Table III). Importantly, these results are in line with other studies suggesting an analogous association between crystalline silica exposure and AAV (99, 102, 103) (Table III) or other autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis) (104). Although controversial (99), studies of AAV demonstrated a dose-response relationship between different levels of silica exposure and the disease with the intensity more so than the duration of exposure being of importance (100, 103).

Additional occupational risk factors for WG have been reported with fewer consistencies. Lane *et al.* (100) suggested an association between the risk of WG and high exposure to organic solvents; the same survey also linked farming to WG (100) but this finding was in contrast with that of a previous study (38). Exposure to industrial pollutants such as mercury (101), lead, and cadmium (97) had been found among patients with WG but these associations were weak (101) or statistically non-significant (97). Another study revealed exposure to pesticides, particulate matter, or fumes as potential risk factors for WG (38). Interpretation of these investigations of occupational risk has to be done with recognition of

Table III. Occupational exposure to crystalline silica exposure and WG or ANCA-associated vasculitis.

References	Year of publication	Diagnosis	No. of patients/controls	Exposure to silica		Odds ratio (95% CI)
				Cases, %	Controls, %	
Gregorini <i>et al.</i> (102)	1993	ANCA-associated vasculitis†	16/32	44	3	14.0 (1.7-113.8)
Nuyts <i>et al.</i> (97)	1995	WG	16/32	31	3	5 (1.4-11.6)
Hogan <i>et al.</i> (98)	2001	ANCA-associated vasculitis	65/65	46	20	4.4 (1.4-14.4)
		WG	21/65	NR	20	2.5 (0.8-8.5)
Stratta <i>et al.</i> (99)	2001	ANCA-associated vasculitis	31/58	45	24	2.6 (1.02-6.5)§
		WG	6/58	50	24	3.1 (0.6-17.4)§
Lane <i>et al.</i> (100)	2003	ANCA-associated vasculitis	75/273	14	4	3.0 (1.0-8.4)
		WG	47/273	48	24	3.5 (0.7-16.8)
Beaudreuil <i>et al.</i> (103)	2005	ANCA-positive disease‡	60/120	21	11	3.4 (1.1-9.9)

NR: not reported, CI: confidence interval.

†Calculations specifically performed based on data provided in the original article (comparisons used 2-sided Fisher's exact tests).

‡P-ANCA/anti-myeloperoxidase-positive rapidly progressive glomerulonephritis.

§Including 42 patients with ANCA-associated vasculitis (among which 20 cases of WG) and 18 patients with other diseases and positive ANCA serology.

potential methodological flaws: apart from single studies (97, 99), most of these investigations did not include controls matched for the area of residence and, as discussed above, results had been obtained on prevalent cases.

c. Miscellaneous factors

A number of other factors have been associated with WG. Investigations indicated that patients with WG more frequently had a history of allergy than controls (100, 105). In particular, these studies suggested a link with prior drug allergy (100, 105) although that result could not be replicated by another study (101). Studies assessing the relation between smoking and the development of WG or AAV found either no association (98, 100) or a protective effect (106). The simultaneous occurrence of WG and renal cell carcinomas (107) or various malignancies (108) and increased occurrence of other autoimmune diseases in patients with WG (45) or their families (45, 49) have been reported, but the significance of these findings is uncertain. Finally, a variety of drugs have been described as putative initiators of AAV, including cases of WG (109, 110), with the best evidence for a causal relationship existing for propylthiouracil and hydralazine (111). However, the precise risk of developing WG in association with any therapeutic agent remains unknown yet.

Conclusion

A substantial body of literature has now provided insights into the epidemiology of WG. Descriptive studies show evidence that the disease might not be evenly distributed among geographic areas, time intervals, and ethnic populations. Analytic investigations suggest several potential contributors to the development of WG, including various genetic polymorphisms, a possible association with crystalline silica exposure and more preliminary links with other environmental factors. Thus, for any of the observed associations, it is presently unclear whether they reflect causality or whether they are modifiers of disease expression or merely confounders.

In light of the variety of potential risk factors identified to date and the fact that none of these associations is either sufficient or necessary to explain all cases, there is a general consensus that WG is a multifactorial disease resulting from the interaction of both genetic and environmental determinants. However, the respective degrees to which genetic and environmental factors might influence the susceptibility to WG remain critical and unanswered questions. Formal assessment of the familial recurrence risk and migration studies might help to better dissect the gene-environment interaction and thereby guide more targeted etiologic research. In addition, the possibility that different disease patterns of WG, such as various clinical profiles or ANCA status, might reflect etiologic heterogeneity should not be dismissed.

Epidemiological research in WG faces interesting challenges in the future. Further structured investigation is warranted to strengthen previously established hypotheses of distribution and determinants of WG and to seek unknown risk factors. Innovative technologies such as genetic molecular techniques may provide significant progress but increases in the yields of epidemiological research might also be achieved by improved study designs. In particular for descriptive studies, there is an unmet need to harmonize the use of classification criteria (112). Moreover, investigations should be disease-specific and will require collaborative efforts to assemble sufficiently large number of patients for properly powered studies. There is much hope that, in time, continued study of the epidemiology will provide further contributions in deciphering the enigmatic etiology of WG.

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