

Epidemiology and Etiology of Wegener Granulomatosis, Microscopic Polyangiitis, Churg-Strauss Syndrome and Goodpasture Syndrome: Vasculitides with Frequent Lung Involvement

Aude Gibelin, M.D.,¹ Carla Maldini, M.D.,¹ and Alfred Mahr, M.D., M.P.H., Ph.D.¹

ABSTRACT

This review focuses on the epidemiological characteristics and etiologies of four primary systemic vasculitides with frequent lung involvement, namely Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and Goodpasture syndrome (GPS). Elucidation of the mechanisms underlying these vasculitides with frequent lung involvement is complicated by their rarity, which hampers the undertaking of large-scale studies; difficulties in classification; and their multifaceted clinical presentations, which infer the existence of several etiologic pathways. Notwithstanding, epidemiological research showed some evidence for international, interethnic, and temporal variations of the frequencies of these four vasculitides; led to the identification of several genetic and environmental risk factors; and provided insight on the extent to which genes and environment might contribute to their development. Available data support the concept that WG, MPA, CSS, and GPS have unique and shared risk determinants. Although the precise causes of these vasculitides are not yet fully understood and the development of prevention strategies is out of our reach at present, current knowledge enables the formulation of etiologic hypotheses to provide caregivers and their patients with valuable information on the nature of these rare entities.

KEYWORDS: Epidemiology, etiology, lung vasculitis, ANCA-associated vasculitis, Goodpasture syndrome

This review addresses the current status of our knowledge on the epidemiology and etiology of four primary systemic vasculitides with frequent lung involve-

ment: Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and Goodpasture syndrome (GPS).

¹Department of Internal Medicine, Hospital Saint-Louis, University Paris 7-Paris Diderot, Paris, France.

Address for correspondence and reprint requests: Alfred Mahr, M.D., Department of Internal Medicine, Hospital Saint-Louis, University Paris 7-Paris Diderot, Assistance Publique-Hôpitaux de Paris, 1, avenue Claude-Vellefaux, 75475 Paris Cedex 10, France (e-mail: alfred.mahr@sls.aphp.fr).

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THE CONCEPT OF "LUNG VASCULITIS": FOCUS ON WG, MPA, CSS, AND GPS

The lung is a possible target of primary systemic vasculitides and, for some of the defined entities, a commonly involved organ. Thus the term *lung vasculitis* does not pertain to a genuine disease but rather has to be understood as a clinical–pathological process involved in the genesis of pulmonary manifestations. Alveolar capillaritis is the most prominent form of lung vasculitis, presenting clinically as diffuse alveolar hemorrhage due to blood leaking into the alveoli. Herein, the term *lung vasculitis* is used in the broader sense of a systemic vasculitis known to affect the lungs.

Four systemic vasculitides are tightly associated with pulmonary involvement: WG, MPA, CSS, and GPS. All four entities are categorized among the primary systemic vasculitides predominantly affecting small-sized vessels and closely linked to particular autoantibodies, namely anti-neutrophil cytoplasmic antibodies (ANCA) or anti-glomerular basement membrane (anti-GBM) antibodies.^{1,2} ANCAs can occur in WG, MPA, and CSS, and these three diseases are commonly referred to as the ANCA-associated vasculitides (AAVs). Anti-GBM antibodies are found in GPS, which is also known as anti-GBM disease.

Although diffuse alveolar hemorrhage may be observed in all four entities, several other pulmonary features are encountered. These include parenchymal nodules and masses (in WG), asthma and eosinophilic pneumonia (in CSS), or interstitial lung disease (in MPA). With the exception of asthma, which is a key feature of CSS, the frequency of lung involvement also varies, and all patients do not have pulmonary manifestations. Importantly, not all respiratory symptoms have vasculitis as the underlying pathophysiology, and some of them are likely attributable to granulomatous inflammation (in WG), eosinophilic infiltration (in CSS), or bronchial hyperreactivity or allergy (in CSS).

Pulmonary manifestations are sometimes diagnosed in other systemic vasculitides. However, they are either highly uncommon events (e.g., pulmonary artery aneurysms in Behçet syndrome) or leave unclear whether they truly reflect structural changes of the respiratory system (e.g., cough in giant cell arteritis). Similarly, lung symptoms observed in secondary, connective tissue disorder-associated vasculitis are not considered herein.

EPIDEMIOLOGICAL INVESTIGATION OF LUNG VASCULITIS

Three elements must be considered when analyzing what is currently known about the epidemiological characteristics of WG, MPA, CSS, and GPS. First, the different clinical, pulmonary and extrapulmonary, and histological attributes of these four entities make it unlikely that they have a unique common pathway. The

sometimes adopted approach of investigating AAVs as a single group is therefore not straightforward. Further complexity arises from the possibility that each disease encompasses several etiologically distinct phenotypic variants (e.g., predominantly granulomatous and predominantly vasculitic WG or ANCA-positive and ANCA-negative CSS). Second, the available classification systems for these diseases remain imperfect and do not arrive at unequivocal categorizations. This situation hampers between-study comparability, and misclassification may obfuscate the identification of entity-specific etiologic factors. Third, despite the remarkably increased number of relevant publications, the amount of available data remains limited. Moreover, owing to the rarity of the conditions considered here, the frequently small patient-sample sizes negatively affect the statistical power of studies and carry a risk of false-positive findings due to sampling errors.

Population Burden

The intensity with which the frequency of WG, MPA, CSS, and GPS has been studied varies greatly among the four vasculitides and across continents. So far, relevant studies have been performed in Europe, the United States, Australia, and New Zealand.^{3–23} For the time being, there are no data on the burden of any of these four diseases for the Asian and southern American continents or for GPS in any location.

The reported incidence and prevalence estimates are summarized in Tables 1 and 2, respectively. Hence, the respective annual incidence rates of WG, MPA, and CSS range between 2.1 and 15, 2.1 and 17.5, and 0.5 and 3.1 per million. GPS incidence is not known but is thought to be less than 1²⁴ or even lower than 0.1 per million.²⁵ Assuming a life expectancy of 75 years and an incidence of 20 per million person-years for the four vasculitides combined, the lifetime risk²⁶ of developing WG, MPA, CSS, or GPS is 1 per 670 subjects. Prevalence data provide a very similar picture regarding the comparative frequencies of WG, MPA, and CSS (Table 2). All four vasculitides satisfy the definitions for rare ("orphan") diseases used in Europe (ie, prevalence below 500 per million) and the United States (prevalence below 1 in 1500 people).

An important epidemiological characteristic of WG is its sharp rise in incidence over the last few decades (Fig. 1). Results of Swedish and Norwegian investigations suggested a gradual two to fourfold incidence rise of WG over the periods 1975 to 2001¹² and 1984 to 1998,¹³ respectively. WG prevalence in Norwich County in the United Kingdom doubled over the period 1990 to 2005,²² albeit changes in prevalence rates may also be affected by variations of survival rates. It is not known if analogous incidence changes over time exist for MPA, CSS, or GPS. Whether the increasing WG

Table 1 Annual Incidence Rates (Per Million) for Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS)

Country of Study	Study Period	Study Population	Criteria	WG	MPA	CSS	First Author (Reference)
Spain	1988–1997	Age > 20 years	ACR	4.77		1.06	González-Gay ⁷
Spain	1998–2001	Age > 15 years	CHCC	2.95	7.91	1.31	Gonzales-Gay ⁹
Germany	1998–1999	All ages	CHCC	5–8	1–3	0–2	Reinhold-Keller ¹⁹
Germany	1998–2002	All ages	CHCC	6–12	2–3	0–2	Reinhold-Keller ¹⁸
United Kingdom	1988–1993	Adults	ACR	8.5			Carruthers ³
United Kingdom	1988–1994	Adults	ACR	8.5	2.4	2.4	Watts ⁴
United Kingdom	1988–1997	Age > 15 years	ACR/CHCC	8.7–10.3	6.8–8.9	1.5–3.7	Watts ²³
United Kingdom	1990–2005	All ages	Clinical diagnoses	8.4			Watts ²²
Sweden	1975–2001	All ages	Discharge diagnoses	3.3–11.9			Knight ¹²
Sweden	1997–2006	All ages	ECCA	9.8	10.1	0.9	Mohammad ¹⁶
Norway	1984–1998	Age ≥ 15 years	ACR	6.0–14.4			Koldingsnes ¹³
Norway	1988–1998	Age > 15 years	ACR/CHCC	10.5	2.7	0.5	Watts ³¹
Norway	1992–1996	All ages	ACR	6.6		2.7	Haugeberg ¹⁰
Lithuania	1990–1999	Age > 16 years	ACR	2.1		1.3	Dadoniene ⁶
Finland	1996–2000	All ages	Discharge diagnoses	9.3			Takala ²¹
New Zealand	1999–2003	All ages	Discharge diagnoses	5.8–15		0.8–2.8*	O'Donnell ²⁹
Australia	1995–2004	Age ≥ 15 years	ACR/CHCC	8.4–8.8	2.3–5.0	2.2–2.3	Ormerod ¹⁷
Australia	2001–2005	All ages	Discharge diagnoses	11.2*			Hissaria ¹¹

*Values derived from 5-year incidence rates.

CHCC, Chapel Hill consensus classification⁸³; ECCA, European medicines agency (EMA) consensus classification algorithm⁸⁴; ACR, American College of Rheumatology.⁸⁵

incidence reflects new environmental influences, changing classification, or heightened awareness is a matter of uncertainty. Keeping the caveat in mind that the time elapsed since the introduction of routine ANCA testing is still short, there are some indications that the rising WG incidence has not leveled off in the post-ANCA era.^{12,13,21}

Demographic Characteristics

WG, MPA, CSS, and GPS occur primarily during adulthood, but their age-specific incidence rates are not uniformly distributed across age groups. Popula-

tion-based data indicate that the WG or MPA incidence peaks for the age groups of 55 to 64 or 65 to 74 years.^{9,13,27} In contrast, the CSS incidence peak occurs slightly earlier in life, at 30 to 40¹⁷ or 55 to 64 years.²³ For GPS, a bimodal distribution was advanced with incidence peaks at 20 to 30 years and 60 to 70 years.²⁸ Despite these observations, the wide age ranges during which each of the four entities first manifests may imply that stochastic (chance) events are at work in their pathogenesis.

Sex-specific incidence rates do not provide a clear indication for uneven gender distributions for any of the four diseases. This lack of a gender effect infers that

Table 2 Prevalence Rates (Per Million) for Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), and Churg-Strauss Syndrome (CSS)

Country of Study	Study Period	Study Population	Criteria	WG	MPA	CSS	First Author (Reference)
Germany	1994	All ages	CHCC	42–58	0–9	2–7	Reinhold-Keller ²⁰
France	2000	Age ≥ 15 years	ACR/CHCC	23.7	25.1	10.7	Mahr ¹⁵
United Kingdom	1997	Age > 15 years	ACR	62.9			Watts ²³
United Kingdom	1990–2005	All ages	Clinical diagnoses	28.8–64.8			Watts ²²
Sweden	2003	All ages	ECCA	160	94	14	Mohammad ¹⁴
Norway	1996	All ages	ACR	53		13	Haugeberg ¹⁰
Norway	1998	Age ≥ 15 years	ACR	95.1			Koldingsnes ¹³
United States	1986–90	All ages	Discharge diagnoses	26–32			Cotch ⁵
New Zealand	2003	All ages	ACR/CHCC	93.5/112	NR/37		Gibson ⁸
Australia	1995–2004	Age ≥ 15 years	ACR/CHCC	64.3–95.0	17.5–39.1	11.7–22.3	Ormerod ¹⁷

CHCC, Chapel Hill consensus classification⁸³; ECCA, European medicines agency (EMA) consensus classification algorithm⁸⁴; ACR, American College of Rheumatology⁸⁵; NR, not relevant.

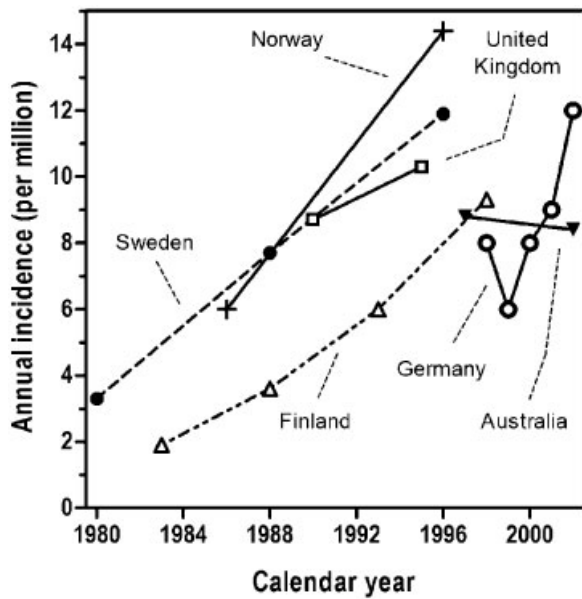


Figure 1 Temporal changes of annual incidence rates for Wegener granulomatosis reported from several population-based studies: • Knight (Sweden)¹²; + Koldingsnes (Norway)¹³; □ Watts (United Kingdom)²³; ▼ Ormerod (Australia)¹⁷; △ Takala (Finland)²¹; ○ Reinhold-Keller (Germany).¹⁸

factors closely related to sex-specific physiology are not important etiologic determinants.

Geographic and Interethnic Variations

Results from population-based surveys support the existence of differential international variations in the occurrence of WG, MPA, CSS, and GPS. It has become a well-accepted notion that the geographic distribution of WG decreases with decreasing latitude, both north and south of the equator. In Nordic countries, the incidence or prevalence of WG is roughly two- to sevenfold higher than that in southern Europe. A similar discovery was made in the southern hemisphere, with a threefold higher incidence, controlled for age, sex, and ethnicity, of WG in the southernmost compared with the northernmost part of New Zealand.²⁹ Formal quantification of this gradient indicated a significant 3% increase of WG incidence with each degree of latitude.³⁰ A similar, albeit not statistically significant, observation was made for CSS. In contrast, no clear latitude-frequency correlation was identified for MPA,³⁰ thereby challenging the hypothesis that MPA might follow an inverse, increasing north-to-south pattern for the Northern Hemisphere.³¹ The increased frequencies of WG and CSS in higher latitudes could point to a protective role of sunlight exposure, possibly via beneficial effects on vitamin D production, although they could also be explained by genetic or other environmental factors.³⁰

Ethnic origin is also thought to play a part in the development of WG, MPA, CSS, and GPS. In a

multiethnic population from France, WG, MPA, and CSS (and polyarteritis nodosa) were twice as prevalent among inhabitants of European versus non-European descent; in particular, non-European cases of WG were rare.¹⁵ In New Zealand, WG and CSS are two to four times more common in people of European ancestry than in Maoris, Asians, or Pacific Islanders.²⁹ The predilection of WG and CSS for individuals of Caucasian ethnicity is furthermore underscored by the paucity of case series reported from countries outside Europe, North America, or Oceania,³²⁻³⁶ and a population-based study on renal vasculitis in Japan that found no case of WG or CSS.³⁷ Observations from case series support that Caucasian ethnicity is also the predominant ethnic background of GPS.^{28,38} Conversely, evidence is mounting that MPA might be more common in Asians than populations of European descent. According to a study on ANCA-associated renal vasculitis in the Miyazaki Prefecture in Japan, the MPA incidence was three times higher than that in Norwich County in the United Kingdom.^{37,39}

More data are needed to obtain a more definitive assessment of the magnitude of geographic and interethnic differences in the frequencies of these diseases. Should the ethnic differences in disease risk be confirmed, clues on the etiologies of WG, MPA, CSS, or GPS could be provided by new studies focusing on the development of these vasculitides among people migrating from high-to-low-risk geographic areas or vice versa.

Genetic Factors

Particularly over the last decade, genetic susceptibility to WG, MPA, CSS, or GPS has been increasingly investigated. So far, all genetic studies relied on hypothesis-driven, candidate-gene approaches exploring functionally relevant gene variants inside or outside the major histocompatibility complex. While that research identified several statistically significant associations with investigated gene loci, interpretation of those findings frequently remains hampered by the lack of replication efforts or small effect sizes that could reflect linkage disequilibrium rather than an association with the true causal gene. Hypothesis-free genome-wide association studies (GWASs) are in progress for WG and MPA and may lead to the identification of yet unknown common susceptibility variants. Given that GWASs require sample sizes of 1000 case subjects or more, it is questionable whether this approach will be suitable for diseases as rare as CSS or GPS.

Another constraint to the study of genetic susceptibility to WG, MPA, CSS, or GPS comes from the difficulty of conducting studies designed to assess the degree of disease clustering among families, twins, or adopted siblings of probands with the disease. The low frequency of AAVs or GPS in the general population

hinders the application of such methodological designs because they require analyzing very high numbers of family pedigrees to be informative. Bearing this caveat in mind, published reports on familial WG, MPA, CSS, or GPS are uncommon. Two partly overlapping registry-linkage studies from Sweden estimated the familial recurrence risk of WG among first-degree relatives to be 1.6 to 3.0-fold higher than that among control relatives.^{40,41} Collectively, these observations suggest that the genetic burdens of WG, MPA, CSS, and GPS might be modest.

Nevertheless, genetic case-control studies led to the discovery of several susceptibility loci for WG, MPA, CSS, or GPS (Table 3). Particularly, histocompatibility leukocyte antigen (HLA) class II molecules that are involved in the orchestration of the secondary immune response appear to exert a genetic effect. The strongest and most consistently identified HLA association refers to *HLA-DRB1*1501*, which, according to a meta-analysis of four genetic association studies, conferred a striking ninefold risk of GPS.⁴² Because this allele was carried by up to 90% of GPS cases, it was estimated that 50 to 90% of the population risk is attributable to this factor.⁴² For WG and CSS, respective associations with *HLA-DPB1*0401* (odds ratio: 3.0 to 3.9)^{43,44} and *HLA-DRB4* (odds ratio: 1.9 to 2.5)^{45,46}

were computed. In Japan, an MPA association with *HLA-DRB1*0901* (odds ratio: 2.2) was reported⁴⁷ but awaits replication.

Apart from the HLA loci, the probably best-described genetic finding is the link between WG and α_1 -antitrypsin (α_1 AT) deficiency. An association of WG with the α_1 AT-deficiency Z allele, and possibly the S allele, was repeatedly found.^{48,49} Further evidence for a causal relationship between α_1 AT deficiency and WG comes from the observation that homozygous (ZZ, SS) or composite heterozygous (SZ) deficiency-allele carriers were at substantially increased risk for WG compared with subjects carrying the deficiency alleles in a heterozygous state (odds ratio: 15 vs 1.5).⁵⁰ Because α_1 AT-deficiency alleles were found only in a minority of patients, their effect might at best explain 8% of WG cases.⁵⁰ The pathway by which deficiency in the anti-protease α_1 -AT predisposes to WG remains enigmatic, and it is unknown whether α_1 AT also confers risk for MPA, CSS, or GPS. There is evidence that WG with positive perinuclear-anti-myeloperoxidase-ANCA serology, which is the predominant ANCA pattern in MPA and CSS, is not linked to α_1 AT deficiency.⁵⁰

While the former findings suggest that WG, MPA, CSS, and GPS harbor distinct susceptibility loci, they also appear to share some genetic determinants. The

Table 3 Selected Genetic Factors Associated with Wegener Granulomatosis (WG), Microscopic Polyangiitis (MPA), Churg-Strauss Syndrome (CSS), or Goodpasture Syndrome (GPS)

Gene/Polymorphism	Disease	Allele (A) or Gene (G) Frequencies for Cases	Odds Ratio*	First Author (Reference)
<i>HLA-DR2/HLA-DRB1*1501</i>	GPS	64–79% (G)	8.5	Phelps ⁴²
<i>HLA-DR4</i>	GPS	Not reported	1.4	Phelps ⁴²
<i>HLA-DPB1*0401</i>	WG	70–77% (A)	3.01–3.91	Heckmann, ⁴³ Jagiello ⁴⁴
<i>HLA-DRB1*04</i>	CSS	20–39% (A)	1.86–2.49	Vaglio, ⁴⁵ Wiczorek ⁴⁶
<i>HLA-DRB1*07</i>	CSS	16–27% (A)	1.57–2.42	Vaglio, ⁴⁵ Wiczorek ⁴⁶
<i>HLA-DRB3</i>	CSS	35–41% (A)	0.54–0.61	Vaglio, ⁴⁵ Wiczorek ⁴⁶
<i>HLA-DRB1*0901</i>	MPA	50% (G)	2.2	Tsuchiya ⁴⁷
Alpha ₁ -antitrypsin deficiency (Z/S alleles)	WG	2.3% (G)	14.58	Mahr ⁵⁰
<i>PTPN22*620W</i>	WG	16% (A)	1.75–2.01	Carr, ⁵¹ Jagiello ⁵²
<i>PTPN22*620W</i>	MPA	Not reported	2.55	Carr ⁵¹
<i>CD226 Gly307Ser</i>	WG	50% (A)	1.23	Wiczorek ⁵⁴
<i>CTLA-4 rs3087243 G>A</i>	AAV	41% (A)	0.84	Carr ⁵¹
<i>CTLA-4 -318T</i>	WG	31% (G)	0.36	Giscombe ⁵⁵
<i>CTLA-4 +49G</i>	AAV	70% (G)	1.92	Slot ⁵⁶
<i>CTLA-4 AT repeat</i>	WG	47% (G)	0.38	Zhou ⁵⁸
<i>CTLA-4 AT repeat</i>	WG	22% (G)	0.4	Spriewald ⁵⁷
<i>IL-10.G allele 134</i>	WG	21% (A)	3.11	Zhou ⁸⁶
<i>IL-10 -1082AA</i>	WG	25% (G)	2.82	Bártfai ⁸⁷
<i>IL-10 -1082AA</i>	MPA	39% (G)	5.43	Bártfai ⁸⁷
<i>IL-10 -3575/-1082/-592 TAC haplotype</i>	CSS	39% (G)	1.73	Wiczorek ⁸⁸

*Values refer either to allelic or genotypic odds ratios.

The Table includes only findings that were either replicated or with other evidence for a causal role. AAV, ANCA-associated vasculitides.

620W polymorphism of the protein tyrosine phosphatase nonreceptor (*PTPN22*) gene, which encodes a lymphoid tyrosine phosphatase that acts as a negative regulator of signaling through the T cell receptor, was found to be associated with WG and MPA.^{51,52} This finding is pertinent because *PTPN22*620W* has emerged as an important risk locus for human autoimmunity. A meta-analysis combining two studies gave a pooled odds ratio of 1.40 for the risk of developing WG or MPA associated with this genetic polymorphism.⁵¹ In contrast, *PTPN22*620W* may not be associated with CSS.⁵³ Genetic studies also uncovered associations with other autoimmune disease-associated gene variants, such as the *CD226* Gly307Ser gene polymorphism⁵⁴ or various distinct polymorphisms in the cytotoxic T-lymphocyte antigen-4 (*CTLA-4*) gene exerting either deleterious or protective effects.^{51,55–58} In line with those findings, familial clustering of WG with rheumatoid arthritis⁵⁹ or autoimmune diseases at large⁴¹ has been shown, although with only a relatively modest risk increase of ~1.3.

Additional genetic associations with one of the considered vasculitis entities are summarized in Table 3.

Environmental Factors

Despite offering the theoretical possibility of disease prevention, the study of environmental risk factors has so far been accorded inadequate attention in the context of WG, MPA, CSS, and GPS. A possible explanation for the scarcity of that research is that environmental etiologies are even less tractable than genetic influences. Compared with genetic research, the study of environmental determinants is methodologically complicated by the vagaries of recall bias, the need for establishing the temporal sequence between exposure and event, and the more complex assessment of dose–effect relationships.

INFECTION

It is a long-held belief that the etiology of systemic vasculitides could be infectious. For vasculitides with frequent pulmonary involvement, this hypothesis is all the more relevant because lung disease could be explained by airborne infections. The most compelling observation to support an infectious cause comes from circumstantial evidence that the onset of these diseases is preceded by infectious events, and studies supporting that WG and MPA first become evident during the fall and winter months, a season with very frequent respiratory infection epidemics. However, controversy exists regarding this concept of seasonality in disease onset, with other studies suggesting either no WG seasonality⁴⁹ or its increased occurrence in summer.⁶⁰

For the time being, direct support for an infectious cause of any of the four diseases under consideration is lacking. It was recently discovered that most

patients with renal AAVs had antibodies directed against the lysosome-associated membrane protein 2 (LAMP2), and the molecular mimicry between LAMP2 and the adhesion protein FimH expressed by gram-negative bacteria.⁶¹ Based on those observations, as yet unconfirmed, the implication of infection with gram-negative bacteria in the pathogenesis of WG and MPA was hypothesized. The link between nasal carriage of *Staphylococcus aureus* and WG generated a lot of interest in the past, even though the role of this pathogen, if any, can at best be regarded as relapse-initiating rather than as being a true causative agent. Attempts at identifying the responsible microorganisms might also be hindered by the possibility that numerous infectious agents might be able to precipitate WG, MPA, CSS, or GPS onset.

OCCUPATIONAL AND LIFESTYLE FACTORS

Exposure to crystalline silica stands out as the most convincing environmental risk factor, conferring a risk two to 14 times higher for WG, MPA, or CSS.^{27,62–64} One study also detected a dose–effect relationship, with higher exposure conferring higher risk for ANCA-associated diseases.⁶⁵ Analogous observations were made for rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus,⁶⁶ and the hypothesis was put forth that exposure to silica or silica compounds acts as an adjuvant for autoantibody production. Various other positive relationships were suggested for WG, MPA, and CSS, including farming (particularly by contact with livestock),²⁷ organic solvents,²⁷ inhalation of particulate material and fumes,⁶⁷ and exposures to lead, cadmium,⁶² or mercury.⁶⁸ Thus the role of occupational exposures as determinants of WG risk conflicts with a recent study that found no relationship between professional occupation and WG.⁶⁹

The idea that the “hygiene hypothesis,” which is based on the theory that the lack of early childhood infections augments the susceptibility to allergic and autoimmune diseases, may play a part in WG etiology could be supported by case–control studies, indicating a link with a prior history of allergy,^{27,68,70} and the observation that WG predominates in people of higher socioeconomic status.²⁹ Studies assessing the risk between AAVs and smoking found that tobacco smoking decreased the risk,⁷¹ whereas another study identified smoking as perhaps having a disease-modifying effect on WG.⁷² Concerning GPS, there is an indication that smoking might enhance risk of developing GPS overall or for alveolar hemorrhage.²⁸

DRUGS

The role of drugs or other therapies in inducing or causing WG, MPA, CSS, or GPS has given rise to numerous speculations. Most of the suggested links with drugs relied on case reports and provided only minimal

scientific evidence. Two types of medications (ie, antithyroid drugs and anti-leukotriene-receptor antagonists) were more intensively studied as possible triggers for AAV, but their causative roles remain disputed. Both examples illustrate the complexity in disentangling association from causation in pharmacoepidemiological research.

The observation was recurrently made that ANCAs are detectable in subjects exposed to antithyroid agents, mainly propylthiouracil,⁷³⁻⁷⁸ but also carbimazole and methimazole.^{75,77} Results suggested that intake of an antithyroid agent conferred a significant 2.2- to 11-fold higher risk of testing ANCA-positive for various immunological specificities.^{75,77} The fundamental question persists as to whether ANCA production coincides with vasculitis, and data from Asia suggest that as many as one out of four ANCA-positive propylthiouracil users develop a true vasculitis.⁷⁹ In contrast, data from the United States indicated that only 1.5% of 129 subjects with renal AAVs had a history of antithyroid treatment, whereas 20% of them had a prior history of thyroid disease (compared with 7% of control subjects, odds ratio: 3.7).⁸⁰ The latter study raised the question of whether the link between exposure to antithyroid drugs and AAVs might be confounded by the clustering of AAVs with autoimmune thyroiditis, and that, even if a true causal relationship exists, the use of antithyroid medications could only explain a minor fraction of AAV cases.⁸⁰ The mechanism by which antithyroid compounds might operate in ANCA synthesis remains elusive.

A similar question has been raised with respect to the leukotriene-receptor antagonists used to treat asthma. Numerous case reports have described asthmatics exposed to these medications who subsequently developed CSS. Findings from case-control studies confirmed an association between antileukotriene use and CSS development, but comparable relationships exist for other medications used to treat asthma (e.g., inhaled long-acting β -agonists or oral corticosteroids).^{81,82} Those findings support that antileukotrienes are merely a marker of the severity and gradual worsening of the asthma preceding CSS onset, rather than a real culprit in CSS.

EPIDEMIOLOGY AND ETIOLOGY OF WG, MPA, CSS, AND GPS: CURRENT STATE AND FUTURE PERSPECTIVES

A significant body of data has accumulated from descriptive and etiologic epidemiological research on WG, MPA, CSS, and, to a lesser extent, GPS. A progressive shift has occurred from the paradigm of diseases of unknown etiology toward the concept that these four entities represent, like most chronic diseases, etiologically complex conditions caused by a combination of

environmental and genetic factors. Results of this research suggest that these four vasculitides are the consequence of entity-specific etiologic factors (e.g., specific HLA associations) but also partly overlapping risk determinants, as illustrated by the link with the *PTPN22*620W* gene locus or silica exposure. Importantly, all of the identified etiologic factors common to WG, MPA, CSS, or GPS were also recognized as risk factors for other autoimmune diseases. Thus the etiologic link predisposing specifically to any combination of the four entities remains unclear.

While case-control studies support that both genes and the environment are implicated in the pathogenesis of WG, MPA, CSS, and GPS, the lingering question is to what extent do both factors weigh on disease occurrence. Data suggest that the degree of familial clustering is modest and, thus, imply a polygenic inheritance pattern and perhaps also low heritability. The possible incidence rise and substantial geographic variations of the frequencies of these vasculitides, which cannot be explained by genetic factors alone, also point toward a predominant role of the environment. However, the responsible environmental factors are not yet well known.

Much more research is needed to expand our understanding of the etiopathogenesis of WG, MPA, CSS, and GPS. The study of gene-gene and gene-environment interactions is a possible direction for future research. Each of the four conditions will have to be explored individually and also within specific subgroups; however, investigators' increasing attempts to analyze subgroups will be at the expense of generating spurious findings due to multiple statistical testing. Better international consensus on disease classification and collaborative networks will facilitate analyses of homogeneous patient groups with appropriate sample sizes to achieve sufficient statistical power. In addition to case-control association studies, the input of new population-based studies, ideally including as yet uninvestigated geographic areas, should not be dismissed. Such research will help further describe the racial, temporal, and latitudinal occurrence patterns of these vasculitides, and confirm or refute the current hypotheses.

Unraveling the causes of WG, MPA, CSS, and GPS may turn out to be a thorny undertaking fraught with various obstacles. The lack of clear gender predominance, the wide age ranges at disease onset, and the variability of clinical presentations suggest etiologic heterogeneity involving multiple causal models, and the interference of stochastic (chance) events. Even though these efforts might ultimately not be rewarded by discovering the exact etiologies, the ensuing insights could be useful for diagnostic, prognostic, or therapeutic purposes and enable caregivers and their patients to understand better the nature of these rare diseases.

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