Hypotheses on the Etiology of Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitis: The Cause Is Hidden, but the Result Is Known

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The first description of what is now known as antineutrophil cytoplasmic autoantibody–associated necrotizing vasculitis appeared more than 140 yr ago. Since then, many aspects of the pathogenic pathway have been elucidated, indicating the involvement of antineutrophil cytoplasmic autoantibodies, but why antineutrophil cytoplasmic autoantibodies are produced in the first place remains unknown. Over the years, many hypotheses have emerged addressing the etiology of antineutrophil cytoplasmic antibody production, but no exclusive factor or set of factors can so far be held responsible. Herein is reviewed the most influential hypotheses regarding the causes of antineutrophil cytoplasmic antibody–associated vasculitis with the aim of placing in an epidemiologic background the different hypotheses that are centered on environmental and genetic influences.

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Antineutrophil cytoplasmic autoantibody (ANCA)-associated necrotizing vasculitis was probably first described in 1866 by Kussmaul and Maier (1) as "polyarteritis nodosa." It was not until the early 1930s when the first case of what was later named Wegener's granulomatosis (WG) was described (2). The disease was named after Friedrich Wegener, who described it as an entity in 1939 (3). In 1985, antibodies associated with the disease were detected and later became known as ANCA (4). WG is a systemic autoimmune disease that can cause damage in various organs. Later, microscopic polyangiitis (MPA) was distinguished as a separate ANCA-associated vasculitis. The disease—or its immunosuppressive treatment—can cause high levels of morbidity and death, especially in patients with renal involvement. Animal experiments have shown that ANCA directed against myeloperoxidase (MPO) can cause vasculitis that resembles human vasculitic disease (5,6); however, the cause of ANCA production remains unresolved.

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[a]Publius Ovidius Naso, *Metamorphoses*; IV: 287

Theories have been developed to explain how ANCA could interact with neutrophils, along with monocytes and most probably T lymphocytes, to form the lesions that are characteristic of ANCA-associated vasculitis, such as fibrinoid necrosis and granulomas (7). A recent theory of interest has been postulated by Pendergraft *et al.* (8), stating that an antibody against the complementary peptide of proteinase-3 (PR3) in an idiotypic/anti-idiotypic network is essential to the development of ANCA and to the development of clinical vasculitis, but why and how these ANCA are produced in the first place remains unanswered. Nonetheless, many hypotheses have been developed about the initiating factor for ANCA production. Many factors, either directly or indirectly, have been considered important in the development of ANCA: Silica exposure (9); genetic predisposition (10); bacterial infection by *Staphylococcus aureus* (11); viral infection by, for instance, parvovirus B19 (12); and thyroid drugs (13) all have been correlated with and held to contribute to the incidence of ANCA-associated vasculitis. Some of these hypotheses are still the focus of ongoing research, whereas others have been put aside. Most of the proposed mechanisms did not disappear from the spotlight because they were proved wrong but because they could not be proved right.

In this review, a number of the most influential hypotheses about the causes of ANCA-associated vasculitis are described.

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We summarize research activities aimed at proving the possible mechanisms of these causes in relation to the disease. Moreover, this article focuses on the feasibility of the hypotheses and current views on their relevance to our understanding of ANCA production.

Epidemiology: Incidences with Respect to Geography and Seasons

To put the spectrum of ANCA-associated vasculitides into perspective, we first outline the epidemiologic background. Studies describing differences in incidence between the various subtypes of systemic vasculitis must be carefully interpreted with regard to the classification criteria used. Accurate and reliable classification of systemic vasculitis into WG and MPA remains difficult and controversial. The recent development of an algorithm using both the American College of Rheumatology criteria and the Chapel Hill consensus conference definitions for epidemiologic purposes has improved the situation (14).

The annual incidence of the systemic vasculitides as a group is similar among regions of Norway, the United Kingdom, Germany, Spain, and Kuwait, ranging from 11 to 47 patients per million (15–18). From north to south, there seems to be a decreasing incidence of WG, complemented by an increasing incidence of MPA, as shown in Figure 1. Remarkably, a recent study from New Zealand found a much higher incidence of WG than of MPA, suggesting a reciprocal gradient for the southern hemisphere (19). The incidence of Churg-Strauss syndrome, a disease also within the spectrum of ANCA-associated vasculitis, was highest in the United Kingdom, compared with Norway and Spain; in the United Kingdom, incidences of WG and MPA were similar (16). Annual incidences for different geographic areas in the northern hemisphere are depicted in Table 1. These topographic incidence differences might indicate a difference in pathogenesis between WG and MPA (15).

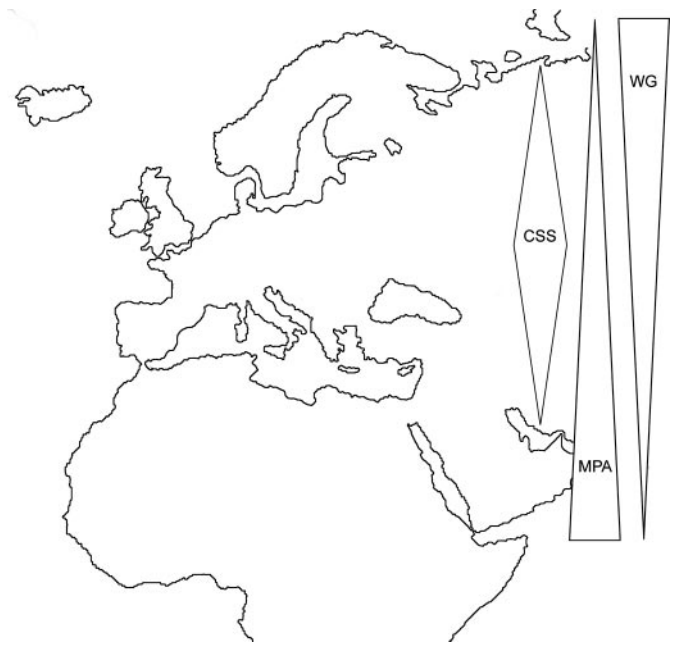

Figure 1. Map of Europe, the Middle East, and North Africa in which an impression of the geographic distribution of incidence numbers of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is given. CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis; WG, Wegener's granulomatosis.

In all areas and all disease categories, the incidence was greater in men than in women (16,18,20), except in Germany, where incidences were similar (17). The peak incidence of vasculitis was between 65 and 74 yr of age in the United Kingdom, Spain, Norway, and China, but in Sweden and the United States, these peak age ranges seemed to be somewhat lower (16,20–23).

There are few epidemiologic studies from outside Europe or North America, and data on the occurrence of vasculitis in nonwhite populations is sparse. A French study showed a risk two times greater for patients of European ancestry (24). In China, there is a striking preponderance of MPO-ANCA–associated vasculitis, and PR3-associated disease is relatively rare (22,25). A recent retrospective study from Japan has shown an incidence of renal vasculitis similar to that observed in the United Kingdom, but strikingly all of the patients from Japan were classified as having MPA and were MPO-ANCA positive. No patients with WG or PR3-ANCA were observed, whereas in the United Kingdom, there were roughly equal incidences of WG and MPA (26,27). Furthermore, it is generally believed that systemic vasculitis is rare in the Afro-Caribbean populations of the United Kingdom and North America.

Findings that point to an environmental factor inducing ANCA-associated vasculitis are supported by reports on seasonal variation, although this phenomenon is still subject to discussion. Some reports found no seasonal variability (15,21,28,29). Studies from Europe, the United States, and China that did find seasonal trends usually reported a higher incidence of vasculitis and especially WG in winter and a lower incidence in summer (20,22,30–35). Some recent reports from Italy and France, however, have identified higher incidences of WG and MPA in summer (35,36). In Australia, anti-PR3 was mostly found in April, May, and June, the fall season in the southern hemisphere (32). This apparent seasonal variability might be explained by seasonal differences in incidence of infections such as influenza or the correlation between influenza vaccinations and predominantly MPA (37,38), which might be explained by a direct effect of the vaccine or by a more general immunologic activation (39). The major confounding factor in the analyses concerning seasonal variation is the precise definition of disease onset: First symptom or clinical diagnosis.

Another remarkable finding was reported in two detailed studies from Norway and Sweden that found 3- to 5-yr trends of peak incidences, with peaks in 1985, 1989 to 1990, and 1994 (20,21) (Figure 2). It was speculated that this trend was due to environmental factors, such as infection (20,21); however, a British report found neither cyclic fluctuation of systemic vasculitis over 15 yr nor an association with peaks of influenza or other infections (34). Some evidence suggests an increase in overall incidence of ANCA-associated vasculitides (21,30,40,41), but this was most

Table 1. Annual incidence of primary systemic vasculitis in different regions in Europe and the Middle East[a]

Disease	Norway (Tromsø)	North Germany (Schleswig-Holstein)	United Kingdom (Norwich)	South Germany (Baden-Württemberg)	Spain (Lugo)	Kuwait (Kuwait City and Al-Jahra)
WG	10.5 (7.6 to 14.2)	8 (2 to 14)	10.6 (7.8 to 14.0)	6 (3 to 9)	4.9 (2.4 to 8.8)	0
MPA	2.7 (1.3 to 4.8)	3 (0 to 6)	8.4 (5.9 to 11.5)	2 (0 to 4)	11.6 (7.6 to 17.0)	25
PAN	0.5 (0.06 to 1.8)	1 (0 to 3)	0.0 (0.0 to 0.8)	2 (0 to 4)	0.9 (0.1 to 3.2)	16
CSS	0.5 (0.06 to 1.8)	0 (0 to 0)	3.1 (1.7 to 5.2)	1 (0 to 2)	0.9 (0.1 to 3.2)	NR
Total	13.7 (10.3 to 17.8)	12 (2 to 23)	18.9 (15.1 to 23.4)	11 (3 to 19)	18.3 (13.1 to 24.8)	47

[a]Adapted from references (16–18). Data are cases per million (95% confidence interval). Columns from left to right represent regions from north to south. Patients' diseases were diagnosed according to the criteria of the Chapel Hill Consensus Conference. Incidence numbers of Norway, the United Kingdom, and Spain are the average of the period between January 1, 1988, and December 31, 1998. Numbers from Germany are an average of the period between January 1, 1998, and December 32, 2002, whereas in Kuwait, the period between January 1, 1993, and December 31, 1996, was analyzed. CSS, Churg-Strauss syndrome; MPA, microscopic polyangiitis; NR, not reported; PAN, polyarteritis nodosa; WG, Wegener's granulomatosis; Total annual incidences of all diseases together.

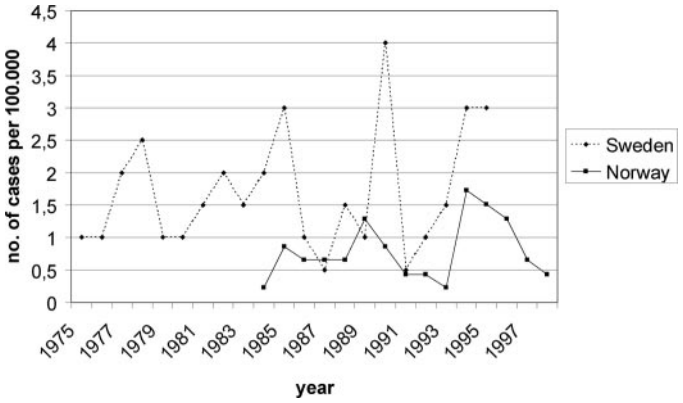

Figure 2. Incidence of WG in northern Norway between 1984 and 1998 (solid line) (21) and incidence of ANCA-associated vasculitis with renal involvement in Örebro, Sweden, between 1975 and 1995 (dashed line) (20). Of note are the concordant peaks in incidences in 1985, 1989 to 1990, and 1994.

likely due to increased recognition after introduction of ANCA testing (30,40,41).

Although geographic differences in incidence of the different vasculitides are striking, they provide only clues to the cause of the diseases. The seasonal differences in incidence might indicate an infectious agent or another environmental factor that is mainly present during or before the season of high incidence. Geographic differences may suggest that the initiating factor in vasculitis has a different temporal distribution or extent in various countries; however, the different genetic backgrounds may be as important, if not more so, in determining the response to triggering or initiating factors.

Silica

Background

Silica is probably the most extensively studied environmental factor hypothesized to play a causative role in the pathogenesis of ANCA-associated glomerulonephritis, predominantly in MPA. After oxygen, silicon (Si) is the most prominent element of the earth's crust (9). Silicates (SiO_4) occur in glass and cement, and silicic acid (H_4SiO_4) is one of the main constituents of soil water, soil itself, and grasses (42). When interpreting studies on the relationship between ANCA-associated vasculitis and silica exposure, the route of silica exposure and silica source may be relevant. In earlier studies of the relationship between silica exposure and disease, only exposure to mineral silica was evaluated. Since the 1980s, biologic forms of silica, such as sand, grass, grain, wood, cotton, wool, quartz, flint, and "coal," have been considered indicative of silica exposure. Jobs that have high exposure to silica dust and that have been associated with the occurrence of ANCA-associated vasculitis are farming, mill and textile work, sandblasting, lumber work, and drilling (43). Exposure to mineral silica is frequent in jobs such as mining and quarrying and construction work that involves cement, stone, brick, or concrete and also in pottery or china manufacturing (9,43,44).

Silica and Vasculitis

Already by the early 1950s, silica exposure was described as being associated with renal insufficiency (45). In the 1980s, several case reports of rapidly progressive glomerulonephritis in patients who were previously exposed to silica appeared (46–50). When ANCA testing became available, the first reports on silica exposure in ANCA-positive patients appeared in the early 1990s (51,52). In patients with pulmonary silicosis and renal failure, a renal biopsy revealed a pauci-immune necrotizing crescentic glomerulonephritis in a number of studies (52–57). ANCA positivity was later confirmed in these patients (52,57–61), who received a diagnosis of ANCA-associated glomerulonephritis (58,62–64). Silica-induced ANCA-positive disease is often associated with a perinuclear (P-ANCA) staining pattern under indirect immunofluorescence and with antibodies directed against MPO (52,65). Although silica-induced disease has been reported in patients with C-ANCA and anti–PR3-ANCA, as well (52,66), the clinical picture for these patients usually justifies a diagnosis of microscopic polyangiitis but very rarely of WG.

Although it has been found that silicosis is a risk factor for

developing ANCA, as determined by indirect immunofluorescence, the presence of ANCA need not necessarily be accompanied by clinical vasculitis (67–69). In fact, the titers of anti-PR3 and anti-MPO, as determined by ELISA, are usually negative or very low. The explanation for this could be that in 50% of patients with silicosis, antinuclear antibodies are present, allowing an interpretation of P-ANCA. Moreover, many of these patients have a high percentage of rheumatoid factor and high Ig levels (9).

Silica exposure is also associated with other systemic diseases, in particular Sjögren's syndrome, systemic sclerosis, and systemic lupus erythematosus (70), although for the last, the association is disputed (43). Next to silica, asbestos exposure was reported to be associated with ANCA positivity (71), but this finding was contradicted in case-control studies (72,73); however, patients who are exposed to asbestos can be exposed to silica in the same occupations (74).

Epidemiologic Studies

To find epidemiologic evidence for a relationship between silica exposure and renal failure, several case-control studies have been performed (44,52,75,76). The results showed that among patients with ANCA-associated rapidly progressive glomerulonephritis or WG, 22 to 46% were previously exposed to silica (43,44,52,72,73). Silica exposure in each study was significantly more frequent in patients compared with control subjects. Most of the studies defined silica exposure in terms of duration rather than intensity. Recently, this choice was justified by the finding that duration was more important than intensity in the onset of ANCA-associated vasculitis (77), although other reports contradicted this finding (78,79). Of note is the difference between silica exposure and silicosis. At time of diagnosis with vasculitic disease, some patients exhibit a picture of pulmonary silicosis, whereas others do not. This difference may arise from the limitations of imaging techniques. Moreover, predisposition to vasculitis does not require the presence of severe pulmonary lesions (9,74).

Risk Factors

The finding that farming and livestock exposure are risk factors for primary systemic vasculitides (73,79) supports the causative role of silica in their pathogenesis. Other environmental risk factors are exposure to fumes or materials from construction; pesticides (29); exposure to hydrocarbons such as paint, solvent, cleaning agents, and diesel (80); and air pollution after an earthquake (81). The association between silica and ANCA-associated vasculitis is not always obvious, however. In a survey (23) among 701 patients with ANCA-associated vasculitis, no association with environmental exposure, occupation, or hobby was found. Among those who were exposed to silica, there was no increased frequency of ANCA compared with control subjects (67). The different outcomes of these studies probably arise from differences in methods of establishing silica exposure.

Hypotheses

Although silica exposure has been shown to evoke an immune response (82–85) and inflammatory reactions (86), its role in the cause of ANCA-associated glomerulonephritis is not well understood. Several hypotheses have been described. It has been suggested that at the site of pulmonary lesions, which can be caused by silica exposure, cytokines released by activated macrophages can attract polymorphonuclear cells. These cells can express the ANCA antigens PR3 and MPO and are taken up by pulmonary macrophages (87–89). Another hypothesis is that alveolar macrophages that are exposed to silica, especially quartz, release a large amount of lysosomal enzymes, such as PR3 and MPO, and reactive oxygen species (90–92). Release of these compounds is even greater when the macrophage or monocyte enters apoptosis (93). Silica can cause apoptosis of monocytes and macrophages and probably also of neutrophils by rupturing their phagolysosomal membrane (93,94). Binding of ANCA to their antigens on apoptotic cells amplifies the release of lysosomal enzymes and reactive oxygen species (95). Furthermore, silica may decrease total lymphocyte counts, which might explain the observed lymphopenia reported in some studies (96). In addition, *in vitro* silica inactivates α1-antitrypsin (97), the natural inhibitor of PR3. Although not all associations between silica exposure and vasculitis are clear-cut, these findings may suggest a causative role of silica in ANCA-associated glomerulonephritis and vasculitis.

One explanation for the geographic differences in vasculitis incidence is the climate. If silica or farming is related to the development of (predominantly MPO-associated) vasculitis, then it would be expected that in wet weather, silica particles would be scattered to a lesser extent than in dry weather. This difference could explain the relatively higher prevalence of vasculitis with MPO-ANCA in warmer countries, illustrated by a high incidence of patients with ANCA directed against MPO in Kuwait (18). The high incidence of MPO-ANCA–associated vasculitis may be explained by the amount of sand present in the air in this region. The role that farming plays in a society might also explain differences in mainly MPO-ANCA–associated vasculitis. This weather-related hypothesis is supported by the higher incidence of vasculitis with MPO-ANCA in Spain combined with the fact that 6% of the population engages in agricultural employment, as opposed to 2% in the United Kingdom (98).

These climate-based considerations could be applied only to exposure to silica dust (*e.g.*, farming, air pollution), not to people who are exposed to occupational mineral silica. Geographic differences could arise from the almost exclusive link between silica exposure and P-ANCA/anti–MPO-positive MPA that is prevalent in southern Europe and Japan.

Staphylococcus aureus

Background

Microbial infections have been associated with initiation and relapse of WG (99,100), and there are several case reports of patients with WG preceded by infections (87,101,102). In particular, *S. aureus* is often cultured in these cases (103,104). Furthermore, several patients developed ANCA-associated systemic vasculitis during subacute bacterial endocarditis (105,106). Of note, in all cocaine users with cocaine-induced midline destructive lesions, *S. aureus* nasal colonization was

present, and some of these patients were ANCA positive (107). This observation emphasizes the need for awareness regarding chronic bacterial infections in patients with ANCA-associated vasculitis, because these patients can be treated with antibiotics (105,108,109). Treatment with trimethoprim-sulfamethoxazole has been described as successful in patients with WG, even as monotherapy (103,104), helping them achieve remission (110–119) or prevent relapses (113). Although this effect could be attributed to the immunosuppressant activity of trimethoprim-sulfamethoxazole, its effects could also be ascribed to its anti-staphylococcal properties. In line with these characteristics, hypotheses have been proposed that infections, particularly in the upper or lower respiratory tract, may play a role in the pathogenesis of WG (120).

The most extensively studied bacterial association with ANCA-associated vasculitis involves *S. aureus* found in the nasal cavity, which is often affected in WG. A study of 57 patients with WG identified the chronic nasal presence of *S. aureus* as an independent risk factor for relapse (121), suggesting a role for *S. aureus* in the cause of ANCA-associated vasculitis. More recently, the presence of nasal *S. aureus* expressing the superantigen staphylococcal-toxic-shock-syndrome-toxin 1 was identified as a risk factor for relapse in WG (122). $CD4^+$ T cells from the peripheral blood of patients with WG showed reactivity to *S. aureus*, and a substantial number also recognized PR3, suggesting a role for staphylococci-specific $CD4^+$ T cells in triggering the immune response (123). In an animal model, however, after immunization with *S. aureus*, no significant T cell proliferation in response to *S. aureus* could be observed (124).

Other bacterial infections, such as *Stenotrophomonas* (*Pseudomonas*) *maltophilia*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*, have also been associated with crescentic glomerulonephritis (102,125). In these cases, vasculitis was noticed after chronic bronchial suppuration, which is hypothesized to be responsible for MPO-ANCA formation and subsequently causing vasculitis (126–128).

Hypotheses

Different hypotheses have been postulated in extensive reviews on the etiology behind infections that lead to vasculitis (11,119,129–131), most of which could act in proximity with each other. Bacterial toxins, such as those produced by *S. aureus*, may function as superantigens that may unrestrictedly stimulate B and T cells, resulting in ANCA production (130,132–135); however, part of this hypothesis was more or less debunked by the fact that no relationship could be demonstrated between T cell expansion and *S. aureus* or its superantigens (136). Otherwise, a staphylococcal acid phosphatase may be nephritogenic (137,138) and, bound to endothelial cells, can act as a planted antigen and be recognized by sera of patients with WG (138). Molecular mimicry could also explain the pathogenesis (139); granzyme B, a serine protease with strong similarity to PR3, is induced by *S. aureus* enterotoxin A (140,141). Lawyer *et al.* (140) postulated that the *S. aureus* genome can also directly encode serine proteases with antigenic cross-reactivity to the C-ANCA autoantigen. Molecular mimicry of the complementary peptide to PR3 could also explain the onset of the pathogenic mechanism (8).

Infections cause a rise in proinflammatory cytokines (*e.g.*, TNF-α, IL-1β, IFN-γ), leading to the production of PR3 and bringing it to the cell surface, thereby exposing it to ANCA (119,142). Although this mechanism cannot be responsible for ANCA induction, it can play a role in relapse of disease (143). Finally, infections promote interaction between B and T cells, supposedly by molecular mimicry, mediated in an HLA-II–dependent manner and resulting in differentiation of ANCA-producing plasma cells (119,139,144). In summary, infections can induce autoimmune responses by antigenic mimicry and by enhancing immunogenicity of host antigens as a result of triggering of the innate immune system (145).

As observed, many mechanisms have been proposed for *S. aureus* to explain its role in the cause of ANCA-associated vasculitis. Despite numerous indications for an association between ANCA-associated vasculitis and infections in general—and *S. aureus* infection in particular—no attempt has been successful in fully explaining their cause-and-effect relationship, and their connection remains poorly understood.

Epidemiology

With regard to incidence, both the 4- to 5-yr cyclic pattern and the seasonal fluctuations are hypothesized to be associated with infections of bacterial or viral origin (20,21). Underlining this hypothesis, the peak incidences of *S. aureus* infection have been reported in the wet season in Australia (146). This relationship may possibly explain the higher incidence of vasculitis directly after the wet season, in winter, but also the higher incidence of vasculitis with ANCA directed to PR3 in countries with more rainy days, such as those in Northern Europe. Another explanation for a higher incidence of ANCA-associated vasculitis in winter is the higher incidence of respiratory illness, such as that arising from influenza infection, when *S. aureus* residing in the nose can cross the damaged nasal epithelium.

Viral Infections

There is not much supportive evidence for the hypothesis that ANCA-associated vasculitides are caused or triggered by a virus. Among the few viruses that are suspected to play a role, parvovirus B19 likely represents the most compelling candidate (12). B19 has been associated with a variety of autoimmune diseases (147), and several publications have reported the co-occurrence of acute B19 infection and WG (12,148,149). Moreover, acute B19 infection may trigger production of C- or P-ANCA and PR3- or MPO-ANCA, and these autoantibodies disappear, at least in some instances, once the infection has subsided (147,150,151); however, none of these cases of ANCA-positive B19 infection presented with clinical signs suggestive of systemic vasculitis (147,150,151), and larger serologic (152,153) or molecular investigations (153,154) have not supported the relationship between B19 infection and ANCA-associated vasculitis. Taken together, B19 might constitute a possible but not a predominant cause or trigger of ANCA-associated vasculitis.

Hepatitis B virus infection has been closely linked to polyar-

teritis nodosa (155), but the data to support that this or other hepatotropic viruses might be involved in ANCA-associated vasculitis are not convincing. The presence of anti–hepatitis B antibodies has been occasionally observed in WG (156), including a study that detected hepatitis B antigen in three (20%) of 15 patients with WG as compared with 3% of the healthy population (156). This finding might point to a pathogenic role of hepatitis B virus, but it could also arise from an increased susceptibility to hepatitis B infection as a consequence of immunosuppressive therapy (156). Conversely, studies have suggested that viral hepatitis might induce the production of ANCA. One study found two P-/MPO-ANCA–positive individuals among 22 individuals who were infected with hepatitis B virus (157). Similar reports have emerged regarding the presence of ANCA in patients with hepatitis C infection (158,159), including one study that found ANCA in as many as 56% of patients with a predominant anti-PR3 specificity (158). Although the high prevalence of ANCA in the setting of hepatitis is intriguing, evidence for a causal association between these viruses and ANCA-associated vasculitis remains poor.

A number of other viral illnesses, including Epstein-Barr virus (151), arbovirus (160), HIV (161–165), and influenza virus (166), may give rise to ANCA of various types, but these observations do not provide strong support to implicate those viruses in ANCA-associated vasculitis. Results of a study examining bronchoalveolar lavage fluids and lung biopsies of patients WG and active lower airway disease failed to detect viral agents (167).

Genetics

One hypothesis that has been broadly accepted is that genetic factors predispose to the induction of ANCA-associated vasculitis. Several reports have described familial cases of ANCA-associated vasculitis (168–173), but such cases are unusual. Numerous studies have been conducted on the genetic susceptibility of both development and relapse of the disease (reviewed in reference [10]). Efforts target gaining insight into the genes involved in immune responses in patients and into factors that determine the expression of target antigens, PR3 and MPO, in and on cells. Polymorphisms of the main inhibitor of PR3, α-1-AT, and of HLA genes have been described as well (174–182).

An overview of genetic alterations and their possible clinical implications is given in Table 2. Polymorphisms of HLA genes, predominantly of HLA-DR, have been held responsible for a longer duration of the immune response, in both WG and MPA. In patients with WG and MPA, Hagen *et al.* (175) found a decreased frequency of HLA-DR13DR6, whereas others (156,183) discovered that the frequency of HLA-DQw7 and DR1 was increased and that of HLA-DR3 was decreased.

ANCA can activate neutrophils by binding to their Fcγ receptors (FcγR). The co-occurrence of the homozygous polymorphisms FcγRIIa-H/H131 and FcγRIIIa-V/V158 has been identified as a risk factor for development of WG (184). These polymorphisms result in a decrease of Fc receptor–mediated clearance, promoting a chronic nasal presence of *S. aureus*. Moreover, these polymorphisms could bind more IgG1 and IgG3, suggesting a stronger interaction with ANCA (184). As for complement, the C4A3 and C3F were increased in ANCA-positive vasculitis, whereas the C4B allele seemed to be increased in PR3-ANCA–positive patients, possibly modulating the immune response and influencing antibody production (185).

Other polymorphisms in relation to immune responses were also studied. CD18 gene polymorphisms were found to be associated with MPO-ANCA–positive vasculitis (186), indicating a facilitated degranulation and respiratory burst by an increase in adhesion of polymorphonuclear neutrophils to endothelial cells (187). Furthermore, regarding genes that encode inhibitory molecules of T cell activation, a microsatellite of CTLA-4 has been associated with WG (188–190) and may account for increased T cell activation (190–192).

In WG and MPA, especially in women, a polymorphism of IL-10, was more frequent compared with healthy control subjects (193). Differences in frequencies of polymorphisms in other genes encoding for proinflammatory cytokines, such as TNF-α, IL-1, IL-1β, IL-2, IL-5Rα, and IL-6, could not be found (187,188,191), although others found increased polymorphisms of the TNF-α, the IFN-γ, and the TGF-β1 genes (194–196). IL-1 and IL-1R antagonist genotypes (197) and polymorphisms of the IFN-γ and CTLA-4 genes were associated with ESRD in PR3-ANCA–positive vasculitis (194).

A homozygous phenotype of deficient α1-AT and a heterozygous deficient/normal phenotype were associated with PR3-ANCA–positive vasculitis (174) and may contribute to disease induction. Moreover, heterozygote α1-AT deficiency—as compared with homozygote nondeficiency—in PR3-ANCA–associated vasculitis increases the risk for dissemination of the vasculitic process and the risk for fatal outcome (198).

As for the PR3 gene itself, the promoter region seemed to be overexpressed in WG (199). Polymorphisms in the promoter region of the MPO gene have been associated with an increased risk for development of MPO-ANCA–associated vasculitis but also with increased relapse and earlier age of diagnosis (200). Moreover, an increase in PR3 and MPO mRNA expression in circulating leukocytes was associated with ANCA-associated glomerulonephritis (201). PR3 membrane expression was significantly increased in patients with ANCA-associated vasculitis as compared with healthy subjects, suggesting a genetic susceptibility (202,203). More evidence for genetically controlled PR3 membrane expression came from a study that found a strong correlation between the percentage of PR3-positive polymorphonuclear neutrophils in identical twins (204). Anti-PR3 antibody was shown to induce activation of neutrophils with high PR3 membrane expression in a dosage-dependent manner, whereas high PR3 membrane expression seemed to be associated with relapse, possibly mimicking the initial activation step of induction of PR3-ANCA–positive vasculitis (205,206).

Pharmacologic Induction

Numerous articles have appeared on ANCA positivity arising from administration of propylthiouracil (PTU) for anti-thyroid treatment in patients with Graves disease, hyperthyroidism,

Table 2. Genetic alterations and their possible clinical implications in patients with ANCA-associated vasculitis[a]

Reference	Gene Encoding for	Genetic Alteration	Diagnosis	Clinical Implication of Alteration
Hagen *et al.* (175)	HLA	HLA-DR13DR6 antigen decrease	WG and MPA	Unknown
Spencer *et al.* (183)		HLA-DR3 decrease	WG and MPA	Inhibits autoreactive T cell elimination and inhibition of induction of antigen-specific T suppressor cells
Spencer *et al.* (183)		HLA-DQw7 increase	WG and MPA	Influences duration of immune response
Gencik *et al.* (176)		HLA-DRB1*04 increase	WG with ESRD	Contributes to severe courses of WG
Boki *et al.* (156)		HLA-DR1 antigen increase	WG	Unknown
Papiha *et al.* (177)		HLA-DR1-DQw1 increase	WG	Unknown
Katz *et al.* (178)		HLA-B8 increase	WG	Predisposes to abnormal hypersensitivity reaction
Cotch *et al.* (179)		HLA-B50 increase	WG	Unknown
Cotch *et al.* (179)		HLA-DR9 increase	WG	Increases susceptibility to allergy
Elkon *et al.* (180)		HLA-DR2 increase	WG	Predisposes to abnormal hypersensitivity reaction
Spencer *et al.* (183)		HLA-DR4DQ7 increase	WG and MPA	Results in transient positive ANCA and high TNF-α synthesis
Jagiello *et al.* (181)		HLA-DPB1*0401 increase	WG	Stimulates development of granulomatous inflammation
Jagiello *et al.* (181)		HLA-DPB1*0301 decrease	WG	Stimulates development of granulomatous inflammation
Tsuchiya *et al.* (182)		HLA-DPB1*0901 increase	MPA	Unknown
Gencik *et al.* (176)		HLA-DRB1*13 decrease	WG and MPA	May modulate the response of autoreactive T cells
Gencik *et al.* (176)		HLA-DQB1*0603 decrease	WG and MPA	
Jagiello *et al.* (181)	Apoptosis	Casp14	WG	Shifts the balance of apoptosis, resulting in loss of self-tolerance or persistent inflammation
Jagiello *et al.* (181)		Ripk1	WG	Shifts the balance of apoptosis, resulting in loss of self-tolerance or persistent inflammation
Dijstelbloem *et al.* (184)	Fcγ receptor	Polymorphism of FcγRIIa: Homozygosity for R131 form	WG	Decreases FcR-mediated clearance, promoting chronic nasal carriage of *S. aureus* and stronger interaction with ANCA, increasing relapse risk
Dijstelbloem *et al.* (184)		Polymorphism of FcγRIIIa: Homozygosity for R158 form	WG	Decreases FcR-mediated clearance, promoting chronic nasal carriage of *S. aureus* and stronger interaction with ANCA, increasing relapse risk
Persson *et al.* (185)	Complement	C3F increase	WG and MPA	Influences antibody production
Persson *et al.* (185)		C4A3 increase	WG and MPA	Modulates immune response
Papiha *et al.* (177)		C4B increase	WG	Modulates immune response
Gencik *et al.* (186)	Adhesion of PMN	Polymorphism of CD18, AvaII + allele overexpression	MPO-ANCA	Increases adhesion, facilitating degranulation and respiratory burst
Huang *et al.* (188)	T cell gene	Microsatellite of CTLA-4: Shortest allele decrease	WG	Increases T cell activation
Zhou *et al.* (191)		Microsatellite of CTLA-4: Shortest allele decrease	WG	Increases T cell activation and clonal expansion
Giscombe *et al.* (192)		CTLA-4 SNP in the promoter region	PR3-ANCA	Results in persistence of T cell activation
Spriewald *et al.* (194)		Polymorphism of CTLA-4	WG with ESRD	Increases T cell activation
Bartfai *et al.* (193)	Cytokine genes	Polymorphism in IL-10 increase	WG and MPA	This Th2-type cytokine is important in B cell proliferation and differentiation but can also exert anti-inflammatory activity
Murakozy *et al.* (195)		Polymorphism in IL-10 increase	WG	Decreases IL-10 level with loss of inhibition of Th1 responses and monocyte function
Borgmann *et al.* (197)		IL-1β increase and IL-1R antagonist decrease	PR3-ANCA with ESRD	Proinflammatory genotype causes proinflammatory responses
Spriewald *et al.* (194)		IFN-γ polymorphism increase	WG	Increases IFN-γ production and modulates proinflammatory responses
Spriewald *et al.* (194)		IFN-γ polymorphism increase	WG with ESRD	Modulates disease susceptibility
Spriewald *et al.* (194)		TNF-α polymorphism increase	WG	Increases TNF-α production and modulates proinflammatory responses
Murakozy *et al.* (195)		TGF-β1 increase	WG	Proinflammatory genotype causes proinflammatory responses
Csernok *et al.* (196)		TGF-β1 increase	WG and MPA	Inducing angiogenesis and being strongly chemotactic, TGF-β1 serves as a proinflammatory factor
Esnault *et al.* (174)	PR3 inhibitor	Homozygous and heterozygous α1-AT deficiency	PR3-ANCA	Contributes to disease induction
Gencik *et al.* (199)	PR3	Overexpression of the promoter region	WG	Probably increases PR3 protein expression
Reynolds *et al.* (200)	MPO	Polymorphism in the promoter region	MPO-ANCA	Probably increases MPO protein expression

[a]ANCA, antineutrophil cytoplasmic autoantibody; PMN, polymorphonuclear cells; SNP, single-nucleotide polymorphism.

and thyrotoxicosis (13,207–209). The majority of these patients had ANCA directed against MPO, although ANCA that were simultaneously directed against other antigens such as human leukocyte elastase, lactoferrin, and even PR3 were also described (210,211). Even cases of classical WG induced by PTU have been reported (212,213); however, a number of patients showed no clinical signs of vasculitis, despite persistent positive PR3-ANCA titers (211). In 4.1 to 64.0% of patients who were treated with PTU, MPO-ANCA levels could be detected but were detectable in only 0 to 3.4% of patients who were treated with methimazole and in 0 to 5.9% of untreated patients (207,211,212,214–217). Although in some cases, the development of anti–MPO-ANCA seems to be related to PTU treatment, only a minority of patients with thyroid disease, PTU treatment, and anti-MPO antibodies developed clinical vasculitis (211,216,217). Usually, with cessation of PTU treatment,

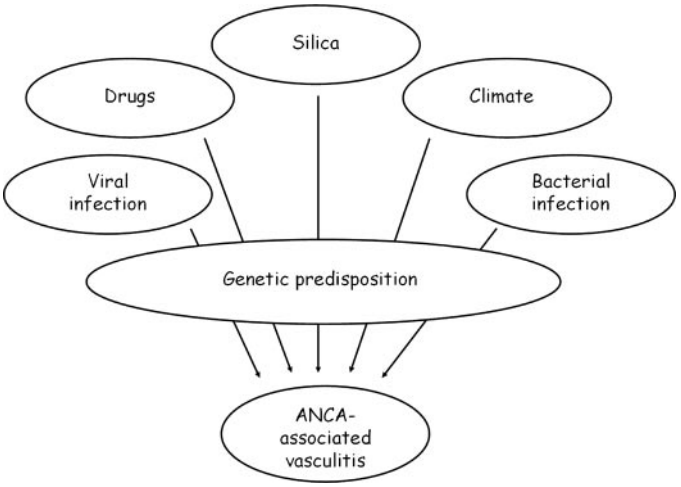

Figure 3. In people with a genetic predisposition, the interplay of various environmental factors can eventually lead to ANCA-associated vasculitis.

MPO levels decreased significantly and sometimes even vanished (207,217). One case report even described a change in ANCA type in a patient with WG from PR3-ANCA to MPO-ANCA after PTU therapy and a switch back upon cessation of the therapy (218). In most patients with vasculitis, these symptoms disappeared when PTU therapy was stopped (218), although additional immunosuppressive therapy may still be needed; therefore, PTU may be regarded as a factor inducing ANCA and (transient) vasculitis in a specific group of patients under specific circumstances.

Hypotheses for how PTU can induce vasculitis or modulate the immune system remain controversial. PTU therapy has been shown to reduce intrathyroidal $CD4^+$ lymphocytes, whereas $CD8^+$ T cells were increased (219). Whereas some reports (220,221) claimed that PTU induced polyclonal activation of B cells, thereby causing vasculitis, in other studies (222,223), no difference in early T and B cell activation after PTU treatment was demonstrated. MPO is necessary to transform PTU into its reactive product, which induces neutrophil-dependent cytotoxicity (224). In animal models, an induction of T cell sensitization (225) and a decrease in T cell proliferation appeared in PTU-treated mice, but no differences in B cell response were apparent (226). Thus, the link between PTU and vasculitis remains unclear.

The occurrence of ANCA-associated vasculitis and glomerulonephritis has also been associated with hydralazine treatment (227–229), administered for hypertension. Again, MPO is the most important antigen that ANCA target in these patients (230,231). Some case reports suggested that, next to PTU and hydralazine, a variety of other medications, such as penicillamine, minocycline, allopurinol, sulfasalazine, levamisole, and thioridazine, were associated with ANCA-associated vasculitis (232–236); however, in larger studies, these hypotheses could not be confirmed (237). The patient's condition usually improved with withdrawal of the drug (232–234).

It is possible that drug allergies are responsible for the association between these drug treatments and the development of ANCA-associated vasculitis (79). Allergies in general have a relatively high prevalence among patients with vasculitis and their families (238). Theories have been postulated about the role for a Th2 (atopic) cytokine environment, and these ideas find support in the association of allergies with vasculitis; however, drug allergies can be evoked by antibiotics and therefore be a surrogate marker for previous infection (79), which has been correlated with the occurrence of vasculitis, as described.

Conclusions

Evidence accumulates supporting a pathogenetic role for ANCA in ANCA-associated vasculitides, and many factors of various origins have been assigned a part in its cause (Figure 3). Environmental factors, such as silica, bacterial or viral infectious agents, medication, and genetic susceptibility, all have been described as being involved in either creating the environment for inducing ANCA production or inducing ANCA themselves. Although the typically advanced age at disease onset suggests an environmental cause rather than genetic factors, genetic differences have been identified between patients and control subjects. Differences in incidence by season and by geographic region could point to an environmental agent, such as *S. aureus*, as triggering predominantly PR3-ANCA–associated disease or to silica as triggering predominantly MPO-ANCA–associated disease; however, these factors cannot explain the etiologic role of medication. For each environmental factor, exposure does not in all cases result in ANCA-associated vasculitis, and these factors are not necessarily associated with all patients with vasculitis. Although it is important to identify etiologic and risk factors for disease, not much is known about how these factors contribute to or are necessary for disease onset. The induction of ANCA-associated vasculitis seems multifactorial, with an interplay of environmental factors and genetic predisposition creating the environment for development of disease.

Disclosures

None.

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