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ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

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It is the mark of an educated mind to be able to entertain
a thought without accepting it.
Aristotle



Chapter 6

Hypotheses on the etiology of ANCA-associated vasculitis: the cause is hidden, but the result is known*

* Publius Ovidius Naso, *Metamorphoses*; IV: 287

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Chapter 6

Abstract

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

Introduction

ANCA-associated necrotizing vasculitis was probably first described in 1866 by Kussmaul and Maier as "polyarteritis nodosa" ¹. 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 antineutrophil cytoplasmic autoantibodies (ANCA) ⁴. WG is a systemic autoimmune disease that can cause damage in various organs. Later on, 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 etiology of ANCA production remains unresolved.

Theories have been developed to explain how ANCA could interact with neutrophils, along with monocytes and most probably T-lymphocytes, to form the lesions characteristic of ANCA-associated vasculitis, such as fibrinoid necrosis and granulomas ⁷. A recent theory of interest has been postulated by Pendergraft et al., stating that an antibody against the complementary peptide of PR-3 in an idiotypic/anti-idiotypic network is essential to the development of ANCA and to the development of clinical vasculitis ⁸. 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 *S. aureus* ¹¹, viral infection by, for instance, parvovirus B19 ¹², and thyroid drugs ¹³ have all 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, while others have been put aside. Most of the proposed mechanisms did not disappear from the spotlight because they were proven wrong, but because they could not be proven right.

In this review, a number of the most influential hypotheses about the causes of ANCA-associated vasculitis are described. We summarize research activities aimed at proving the possible mechanisms of these causes in relation to the disease. Moreover, the paper 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 epidemiological 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 epidemiological purposes has improved the situation ¹⁴. The annual incidence of the systemic vasculitides as a group is similar among regions of Norway, the UK, Germany, Spain, and Kuwait, ranging from 11 to 47 patients per million ¹⁵⁻¹⁸. From north to south, there appears 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 (CSS), a disease also within the spectrum of ANCA-associated vasculitis, was highest in the UK, compared to Norway and Spain; in the UK, incidences of WG and MPA were similar ¹⁶. Annual incidences for different geographical areas in the northern hemisphere are depicted in Table 1. These topographical incidence differences might indicate a difference in pathogenesis between WG and MPA ¹⁵.

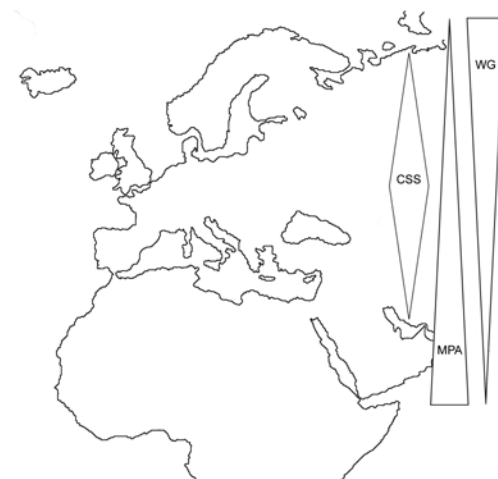


Figure 1. Image of the map of Europe, the Middle East, and North Africa in which an impression of the geographical distribution of incidence numbers of ANCA-associated vasculitis is given. CSS = Churg-Strauss syndrome, MPA = microscopic polyangiitis, WG = Wegener's granulomatosis.

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

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

Numbers are expressed as cases per million (95% CI). Columns from left to right represent regions from north to south. WG = Wegener's granulomatosis, MPA = microscopic polyangiitis, PAN = polyarteritis nodosa, CCS = Churg-Strauss syndrome, Total = annual incidences of above mentioned diseases together, NR = not reported. Patients were diagnosed according to the criteria of the Chapel Hill Consensus Conference. This table is adapted from references (16-18). Incidence numbers of Norway, the UK, and Spain are the average of the period between 1 January 1988 and 31 December 1998. Numbers from Germany are an average of the period between 1 January 1998 and 31 December 2002, while in Kuwait the period between 1 January 1993 and 31 December 1996 was analyzed.

In all areas and all disease categories, the incidence was greater in males than in females ^{16,18,20}, except in Germany where incidences were similar ¹⁷. The peak incidence of vasculitis was between 65 and 74 years of age in the UK, Spain, Norway, and China, but in Sweden and the US, these peak age ranges seemed to be somewhat lower ^{16,20-23}.

There are few epidemiological studies from outside Europe or North America, and data on the occurrence of vasculitis in non-Caucasian 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 proteinase-3 (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 UK, but strikingly all the patients from Japan were classified as MPA and were MPO-ANCA positive. No patients with WG or PR3-ANCA were observed, whereas in the UK, 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 UK 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 US, and China that do find seasonal trends usually report a higher incidence of vasculitis and especially WG in winter, and a lower incidence in summer ^{20,22,30-35}. Some recent reports have from Italy and France, however, 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 immunological activation³⁹. 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-year trends of peak incidences, with peaks in 1985, 1989-1990, 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 cyclical fluctuation of systemic vasculitis over 15 years nor an association with peaks of influenza or other infections³⁴. Some evidence suggests an increase in overall incidence of ANCA-associated vasculitides^{21,30,40,41}, but this was most likely due to increased recognition following introduction of ANCA testing^{30,40,41}.

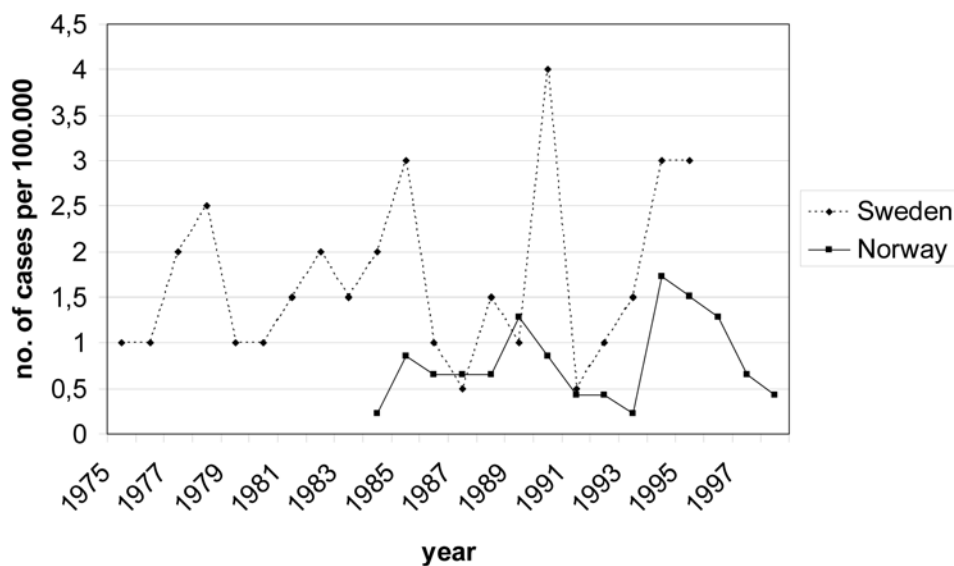


Figure 2. Incidence of Wegener's granulomatosis in northern Norway between 1984 and 1998 (straight line)²¹ and incidence of ANCA-associated vasculitis with renal involvement in Örebro, Sweden, between 1975 and 1995 (dashed line)²⁰. Of note are the concordant peaks in incidences in 1985, 1989-90, and 1994.

Although geographical 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 prior to the season of high incidence. Geographical 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 crust⁹. Silicates (SiO₄) occur in glass and cement, and silicic acid (H₄SiO₄) is one of the main constituents of soil water, soil itself, and grasses⁴². 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, biological forms of silica, such as sand, grass, grain, wood, cotton, wool, quartz, flint, and "coal" have been considered indicative of silica exposure. Jobs with high exposure to silica dust that have been associated with the occurrence of ANCA-associated vasculitis are farming, mill and textile work, sandblasting, lumber work, and drilling⁴³. Exposure to mineral silica is frequent in jobs like 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 insufficiency⁴⁵. In the 1980s, several case reports of rapidly progressive glomerulonephritis in patients previously exposed to silica appeared⁴⁶⁻⁵⁰. 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 studies⁵²⁻⁵⁷. ANCA positivity

was later confirmed in these patients ^{52,57-61}, who were diagnosed as having 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.

While 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 enzyme-linked immunosorbent assay, 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 immunoglobulin 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 this last, the association is disputed ⁴³. Next to silica, asbestos exposure was also reported to be associated with ANCA positivity ⁷¹, but this finding was contradicted in case-control studies ^{72,73}. However, patients exposed to asbestos can be exposed to silica in the same occupations ⁷⁴.

Epidemiological Studies

To find epidemiological 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 to controls. Most of the studies defined silica exposure in terms of duration rather than intensity. Recently, this choice has been justified by the finding that duration is more important than intensity in the onset of ANCA-associated vasculitis ⁷⁷, although other reports contradict 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 while 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. However, the association between silica and ANCA-associated vasculitis is not always obvious. In a recent survey among 701 patients with ANCA-associated vasculitis, no association with environmental exposure, occupation, or hobby was found ²³. Among those who were exposed to silica, there was no increased frequency of ANCA compared to controls 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 etiology 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 exposed to silica, especially quartz, release a large amount of lysosomal enzymes, like 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 ANCAs 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 α 1-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 geographical differences in vasculitis incidence is the climate. If silica or farming are related to the development of (predominantly

MPO-associated) vasculitis, 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 9% of the population engage in agricultural employment, as opposed to 2% in the UK ⁹⁸.

These climate-based considerations could only be applied to exposure coming from silica dust, e.g. farming or air pollution, not to people exposed to occupational mineral silica. Geographical 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 have 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 are 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 (TS) has been described as successful in WG patients, 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 TS, 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 tracts, 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 relapse¹²¹, suggesting a role for *S. aureus* in the etiology 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 WG¹²². CD4-positive T cells from the peripheral blood of patients with WG show reactivity to *S. aureus*, and a substantial number also recognize PR3, suggesting a role for staphylococci-specific CD4-positive T cells in triggering the immune response¹²³. In an animal model, however, after immunization with *S. aureus*, no significant T cell proliferation in response to *S. aureus* could be observed¹²⁴.

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 vasculitis¹²⁶⁻¹²⁸.

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. First of all, 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 superantigens¹³⁶. 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 WG patients¹³⁸. Molecular mimicry could also explain the pathogenesis¹³⁹; granzyme B, a serine protease with strong similarity to PR3, is induced by *S. aureus* enterotoxin A^{140,141}. Lawyer et al. postulated that the *S. aureus* genome can also directly encode serine proteases with antigenic cross-reactivity to the C-ANCA autoantigen¹⁴⁰. Molecular mimicry of the complementary peptide to PR3 could also explain the onset of the pathogenic mechanism⁸.

On the other hand, infections cause a rise in pro-inflammatory cytokines (e.g., TNF- α and IL-1 β and 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 disease¹⁴³. 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 due to triggering of the innate immune system¹⁴⁵.

As observed, many mechanisms have been proposed for *S. aureus* to explain its role in the etiology 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 four- to five-year 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 Australia¹⁴⁶. 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 suspected to play a role, parvovirus B19 likely represents the most compelling candidate¹². B19 has been associated with a variety of autoimmune diseases¹⁴⁷ 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 serological ^{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 polyarteritis 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 3 of 15 (20%) subjects with WG as compared to 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. On the other hand, studies have suggested that viral hepatitis might induce the production of ANCA. One study found 2 P-/MPO-ANCA-positive individuals among 22 subjects 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, human immunodeficiency virus 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 WG patients with active lower airway disease failed to detect viral agents ¹⁶⁷.

Genetics

One hypothesis that has been broadly accepted is that genetic factors predispose for 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 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, both in WG and MPA. In patients with WG and MPA, Hagen et al. found a decreased frequency of HLA-DR13DR6 ¹⁷⁵, while others discovered that the frequency of HLA-DQw7 and DR1 was increased and that of HLA-DR3 was decreased ^{156,183}.

ANCA can activate neutrophils by binding to their Fc γ -receptors (Fc γ -R). The co-occurrence of the homozygous polymorphisms Fc γ RIIa-H/H¹³¹ and Fc γ RIIIa-V/V¹⁵⁸ has been identified as a risk factor for developing 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, while 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 females, a polymorphism of IL-10, was more frequent compared to healthy controls ¹⁹³. Differences in frequencies of polymorphisms in other genes encoding for proinflammatory cytokines, such as TNF- α , IL-1, IL-1 β , IL-2, IL-5R α , 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- β 1 genes ¹⁹⁴⁻¹⁹⁶. IL-1 and IL-1R antagonist genotypes ¹⁹⁷ and polymorphisms of the IFN- γ and CTLA-4 genes were associated with end-stage renal disease in PR3-ANCA-positive vasculitis ¹⁹⁴.

Hypotheses on the etiology of ANCA-vasculitis

Table 2. Genetic alterations and their possible clinical implication

Reference	Gene encoding for	Gen
EC Hagen (175)	HLA	HLA-DR13DR6
SJ Spencer (183)		HLA-DR3 decr
SJ Spencer (183)		HLA-DQw7 inc
M Gencik (176)		HLA-DRB1*04
KA Boki (156)		HLA-DR1 antiq
SS Papthia (177)		HLA-DR1-DQw
P Katz (178)		HLA-B8 increa
MF Cotch (179)		HLA-B50 incre
MF Cotch (179)		HLA-DR9 incre
KB Elkon (180)		HLA-DR2 incre
SJ Spencer (183)		HLA-DR4DQ7
P Jagiello (181)		HLA-DPB1*04
P Jagiello (181)		HLA-DPB1*03
N Tsuchiya (182)	Apoptosis	HLA-DPB1*09
M Gencik (176)		HLA-DRB1*13
M Gencik (176)		HLA-DQB1*06
P Jagiello (181)		Casp14

A homozygous phenotype of deficient α 1-AT and a heterozygous deficient/normal phenotype were associated with PR3-ANCA-positive vasculitis¹⁷⁴ and may contribute to disease induction. Moreover, heterozygote α 1-AT deficiency—as compared to homozygote non-deficiency—in PR3-ANCA-associated vasculitis increases the risk of dissemination of the vasculitic process and the risk of fatal outcome¹⁹⁸.

As for the PR3 gene itself, the promoter region seemed to be overexpressed in WG¹⁹⁹. Polymorphisms in the promoter region of the MPO gene have been associated with an increased risk for developing MPO-ANCA-associated vasculitis, but also with increased relapse and earlier age of diagnosis²⁰⁰. Moreover, an increase in PR3 and MPO mRNA expression in circulating leukocytes was associated with ANCA-associated glomerulonephritis²⁰¹. PR3 membrane expression was significantly increased in patients with ANCA-associated vasculitis as compared to 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 twins²⁰⁴. Anti-PR3 antibody was shown to induce activation of neutrophils with high PR3 membrane expression in a dose-dependent manner, while high PR3 membrane expression appeared to be associated with relapse, possibly mimicking the initial activation step of induction of PR3-ANCA-positive vasculitis^{205,206}.

Pharmacological induction

Numerous articles have appeared on ANCA-positivity arising from administration of propylthiouracil (PTU) for anti-thyroid treatment in patients with Graves' disease, hyperthyroidism, and thyrotoxicosis^{13,207-209}. The majority of these patients have ANCA directed against MPO, though 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 titers²¹¹. In 4.1-64.0% of patients treated with PTU, MPO-ANCA levels could be detected but were only detectable in 0-3.4% of patients treated with methimazole and in 0-5.9% 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, MPO levels decreased significantly and sometimes even vanished^{207,217}. One case report even describes a change in ANCA type in a WG patient from PR3-ANCA to MPO-ANCA after PTU therapy and a switch back upon cessation of the therapy²¹⁸. In most patients with vasculitis, these symptoms disappeared when PTU therapy was stopped²¹⁸, 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-positive lymphocytes, whereas CD8-positive T cells were increased²¹⁹. While some reports claim that PTU induces polyclonal activation of B cells, thereby causing vasculitis^{220,221}, in other studies, no difference in early T and B cell activation after PTU treatment was demonstrated^{222,223}. MPO is necessary to transform PTU into its reactive product, which induces neutrophil-dependent cytotoxicity²²⁴. In animal models, an induction of T cell sensitization²²⁵ and a decrease in T cell proliferation appeared in PTU-treated mice, but no differences in B cell response were apparent²²⁶. Thus, the link between PTU and vasculitis remains unclear.

The occurrence of ANCA-associated vasculitis and glomerulonephritis has also been associated with hydralazine treatment²²⁷⁻²²⁹, administered for hypertension. Again, MPO is the most important antigen that ANCA target in these patients^{230,231}. Some case reports implied 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 vasculitis²³²⁻²³⁶; however, in larger studies, these hypotheses could not be confirmed²³⁷. The patient's condition usually improves with withdrawal of the drug²³²⁻²³⁴.

It is possible that drug allergies are responsible for the association between these drug treatments and the development of ANCA-associated vasculitis⁷⁹. Allergies in general have a relatively high prevalence among vasculitis patients and their families²³⁸. 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. On the other hand, drug allergies can be evoked by antibiotics and therefore be a surrogate marker for previous infection⁷⁹, which has been correlated with the occurrence of vasculitis, as described above.

Conclusion

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 etiology (Figure 3). Environmental factors, such as silica, bacterial or viral infectious agents, medication, and genetic susceptibility have all been described as being involved in either creating the environment for inducing ANCA production or inducing ANCA themselves.

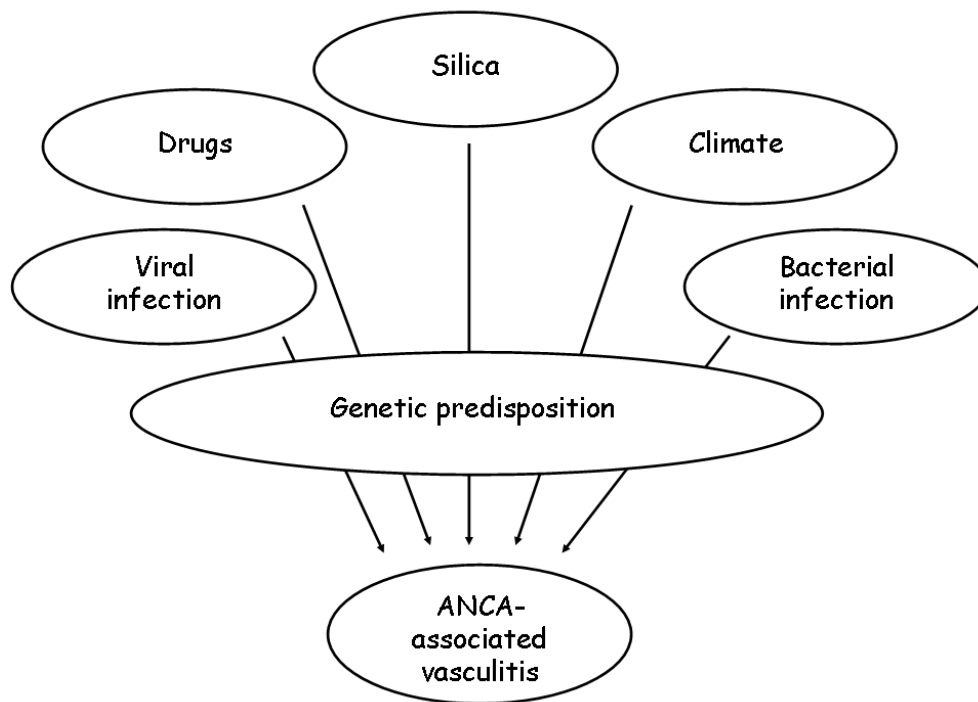


Figure 3. In people with a genetic predisposition, the interplay of different environmental factors can eventually lead to ANCA-associated vasculitis.

Although the typically advanced age at disease onset suggests an environmental cause rather than genetic factors, genetic differences have been identified between patients and controls. Differences in incidence by season and by geographical 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 etiological 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 vasculitis patients. Although it is important to identify etiological 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 appears multifactorial, with an interplay of environmental factors and genetic predisposition creating the environment for developing disease.

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