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EDITED BY
Jindong Ni,
Guangdong Medical University, China

REVIEWED BY
Mohey Eldin El Shikh,
Queen Mary University of London,
United Kingdom
Shuangxin Liu,
Guangdong Provincial People's
Hospital, China

*CORRESPONDENCE
De-Guang Wang
wangdeguang@ahmu.edu.cn

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Environmental factors influencing the risk of ANCA-associated vasculitis

Wen-Man Zhao, Zhi-Juan Wang, Rui Shi, Yu-Yu Zhu,
Sen Zhang, Rui-Feng Wang and De-Guang Wang*

Department of Nephrology, The Second Hospital of Anhui Medical University, Hefei, China

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterized by inflammation and destruction of small and medium-sized blood vessels. Clinical disease phenotypes include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The incidence of AAV has been on the rise in recent years with advances in ANCA testing. The etiology and pathogenesis of AAV are multifactorial and influenced by both genetic and environmental factors, as well as innate and adaptive immune system responses. Multiple case reports have shown that sustained exposure to silica in an occupational environment resulted in a significantly increased risk of ANCA positivity. A meta-analysis involving six case-control studies showed that silica exposure was positively associated with AAV incidence. Additionally, exposure to air pollutants, such as carbon monoxide (CO), is a risk factor for AAV. AAV has seasonal trends. Studies have shown that various environmental factors stimulate the body to activate neutrophils and expose their own antigens, resulting in the release of proteases and neutrophil extracellular traps, which damage vascular endothelial cells. Additionally, the activation of complement replacement pathways may exacerbate vascular inflammation. However, the role of environmental factors in the etiology of AAV remains unclear and has received little attention. In this review, we summarized the recent literature on the study of environmental factors, such as seasons, air pollution, latitude, silica, and microbial infection, in AAV with the aim of exploring the relationship between environmental factors and AAV and possible mechanisms of action to provide a scientific basis for the prevention and treatment of AAV.

KEYWORDS

AAV (ANCA-associated vasculitis), ANCA, air pollution, environmental risks, etiology, vasculitis

Introduction

Systemic autoimmune rheumatic diseases (SARDs) are a group of chronic autoimmune diseases that attack joints, bones, muscles, blood vessels, and related soft or connective tissues. Common SARDs include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), mixed connective tissue disease (MCTD), and systemic vasculitis. The onset of these diseases is more insidious. The course of these diseases are longer and require lifelong treatment, which severely threatens the physical and mental health of patients and has become an important public health problem (1–3). Systemic vasculitis, one of the most complex and challenging SARDs, is classified into large, medium, and small vessel vasculitis, mainly based on the size of the affected vessels (2022ACR/EULAR) (4). Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an important part of the classification of vasculitis. AAV can affect many vital organs throughout the body, including the skin, kidneys, lungs, and brain. Additionally, untreated vasculitis progresses rapidly, causing irreversible damage to vital organs in the body and even death. Therefore, exploring the etiology and pathogenesis of AAV is crucial for early diagnosis and timely treatment.

AAV is a multisystem autoimmune disease that primarily involves small blood vessels throughout the body, and it is associated with the presence of ANCA in the serum (5, 6). ANCA, which was first identified by Davies in patients with necrotizing glomerulonephritis, is divided into two main types: cytoplasmic (C-ANCA) and perinuclear (P-ANCA), whose target antigens are proteinase 3 (PR3) and myeloperoxidase (MPO), respectively. Growing evidence confirms the pathogenic role of ANCA in AAV. Transfer of splenocytes from MPO-deficient mice immunized with mouse MPO into wild-type mice resulted in hyperimmune systemic vasculitis (7). Pendergraft et al. (8) demonstrated that complementary proteinase-3 (cPR3) antibodies may induce PR3-ANCA. Additionally, a new ANCA-targeting human lysosome-associated membrane protein-2 (LAMP-2) has been described as a sensitive and specific marker for renal limited vasculitis (RLV). Rats produce LAMP-2 and induce crescentic glomerulonephritis when immunized with the adhesin FimH, which has strong homology with human LAMP-2 (9, 10).

The incidence of AAV has been increasing with the introduction of ANCA testing (11, 12). The prognosis of patients with AAV has improved since the introduction of immunosuppression in the 1960s. However, some severe cases with cumulative renal and pulmonary disease remain aggressive. The exact etiology of AAV is unknown, and a complex association exists between factors, such as polygenic genetic susceptibility (13, 14), epigenetic influences (15), and environmental factors (16), and AAV. AAV is probably not caused by any single factor, but the interaction and combination of multiple

factors ultimately lead to the occurrence of this disease (17, 18). ANCA-associated necrotizing glomerulonephritis has been reported in two sets of identical twins, suggesting that genetic factors may be involved in disease pathogenesis (19). Two genome-wide association studies (GWAS) in European and North American populations have identified disease susceptibility loci in AAV. The genetic background of different clinical subtypes of AAV is different (13). GPA, MPA, and EGPA are associated with HLA-DP1, HLA-DQ, and HLA-DRB4, respectively. Additionally, genetic variants in non-MHC regions, such as CTLA-4, FCGR2A, PTPN22, SERPINA1, and TLR9, were significantly associated with AAV. These findings help to elucidate the etiology of AAV and develop new biomarkers for diagnosis and targeted therapy.

In recent years, increasing research evidence has emphasized that environmental factors are involved in the occurrence and development of AAV. Many environmental factors, including silica exposure, season, latitude, and microbial infection, have been reported to be associated with AAV. Several studies (20, 21) have shown that sustained exposure to silica in an occupational setting results in a 3.4–7-fold increased risk of positive ANCA. Additionally, season and latitude have different effects on the incidence of different subtypes of AAV. Generally, AAV tends to occur during winter (22, 23). The incidence of GPA and EGPA increased with increasing latitude and decreasing environmental ultraviolet radiation, whereas the incidence of MPA did not change significantly with changes in latitude and ultraviolet radiation (24). Kronbichler et al. (25) suggested that nasal *staphylococcus aureus* infection may be an important risk factor for the onset and recurrence of AAV. This review summarized the environmental risk factors and possible mechanisms of AAV to provide a scientific basis for the prevention and treatment of AAV.

Classification of AAV

Clinically, AAV is classified into three types: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA) (4, 26). This type of disease is characterized by necrotizing small vessel vasculitis. AAV has a predilection for the kidney, with more than 75% of patients having renal involvement. Vasculitis confined to the kidney is known as RLV, and it is characterized clinically by rapidly progressive glomerulonephritis. ANCA is an autoantibody against neutrophil granules and monocyte lysosomal components. The serological marker for AAV is ANCA positivity. All the above diseases are usually associated with circulating ANCA, and accurate ANCA testing is important for diagnosis, treatment, and prognosis. The main target antigens for C-ANCA and P-ANCA are PR3 and MPO, respectively. Additionally, due to the significant overlap in the clinical features of GPA and MPA, CHCC2012 recommended adding

a prefix to the clinical phenotype of patients with established AAV (classified as PR3-ANCA disease and MPO-ANCA disease based on ANCA specificity) (26). MPA was associated with PR3-ANCA in 26% of cases and MPO-ANCA in 58% of cases (27). Whereas GPA was characterized by PR3-ANCA in 66% of patients and MPO-ANCA in 24% of patients. Studies have shown a higher rate of disease recurrence in PR3-ANCA and a higher mortality rate in MPO-ANCA disease. As an important clue to disease diagnosis, a positive ANCA does not necessarily confirm the diagnosis of AAV, whereas a negative ANCA does not exclude the diagnosis of AAV. For example, the presence of ANCA is absent in 40%–50% of patients with EGPA (28). Therefore, clinicopathological findings are the gold standard for the diagnosis of AAV.

Epidemiology of AAV

The introduction of ANCA testing in the 1990s has led to a marked increase in the incidence of AAV in recent years (12, 29). Currently, the prevalence of AAV is approximately 300/million, with an annual incidence of 13–20/million (11, 12). In Norway, the annual incidence of AAV is as high as 24.7/million. The incidence of adult GPA, MPA, and EGPA are 15.6/million, 6.5/million, and 2.7/million, respectively (12, 29). The overall incidence of AAV is increasing in Spain, Germany, and the UK (29, 30). Compared to incidence studies, relatively few studies on AAV prevalence have been reported. The overall prevalence of AAV per million adults reported in Norway in 2013 was 351; the prevalence of GPA, MPA, and EGPA were 261, 58.2, and 32.9, respectively (29). The increased prevalence of AAV may be related to factors, such as increased incidence, improved disease definition, and improved vasculitis registry systems.

Unlike other autoimmune diseases, AAV tends to develop in older and male patients. Studies in both the UK and New Zealand have confirmed that the peak incidence of AAV is at the age of 60–79 years (31–33). The reason for the tendency of AAV to develop in patients of advanced age is unclear. This may be related to advances in ANCA testing that have led to the detection of previously unrecognized AAV. Additionally, AAV is more common in men than in women (31, 34). Studies have shown a male prevalence to female prevalence ratio between 1.07:1 and 1.48:1 (31, 35–37). In Germany and New Zealand, no significant gender differences are present in the incidence of AAV. The reasons for the above occurrence are not clear.

Immunology of AAV

The mechanisms of the AAV autoimmune response have not been fully elucidated, but molecular mimicry and dysregulation of B and T lymphocytes have dominated the disease process. Activated B lymphocytes can produce pathogenic ANCA. Regulatory B (B reg)

cells induce T cell differentiation into regulatory T (T reg) cells away from T helper 1 (TH1) and TH17 phenotypes and reduce B cell production of ANCA (38). Neutrophils are both targets of ANCA and mediators of endothelial injury. When exposed in response to infection or inflammation, the ANCA antigen-binding site can bind and activate neutrophils, leading to their degranulation and production of reactive oxygen species (ROS). It subsequently mediates vascular endothelial cell damage (18). Concurrently, intracellular signaling pathways are activated, resulting in changes in the expression and conformation of adhesion molecules, which promote the adhesion and migration of neutrophils in the vascular endothelium (39). Activated neutrophils undergo a specific form of cell death (NETosis), releasing neutrophil extracellular traps (NETs). NETs can mediate direct damage to the endothelium, transfer MPO/PR3 to the vascular endothelium and dendritic cells for antigen presentation, and activate the alternative pathway of complement. Tissue deposition of chemokines, PR3, and MPO lead to the recruitment of autoreactive T cells and monocytes, thereby aggravating vascular tissue damage. The therapeutic targets of NETs in different diseases mainly depend on the components of NETs. AAV-induced NETs were enriched in citrullinated histones, whereas SLE-induced NETs were enriched in oxidized mitochondrial DNA (40).

GPA is characterized by granuloma formation. Early granulomas are characterized by activated neutrophils forming microabscesses and scattered multinucleated macrophages. These macrophages release pro-inflammatory cytokines that promote the recruitment of neutrophils and monocytes from the blood to the lesion site. Recruited neutrophils release lytic enzymes and ROS upon encountering microorganisms and undergo lysis, leading to the formation of a necrotic core of the lesion. Advanced granulomas consist of a central area of necrosis with multinucleated giant cells at the margin, surrounded by dendritic cells, T lymphocytes, B lymphocytes, and plasma cells, forming a follicular structure of ectopic lymphoid tissue (41, 42). Lymphangiogenesis, defective transport capacity, and formation of ectopic lymph node-like structures are important mechanisms for the development of acquired immunity. Granuloma formation may be driven by B and T lymphocytes (43, 44). In patients with EGPA, elevated levels of TH2 cytokines, such as IL-4 and IL-5, are associated with eosinophilia. Eosinophils infiltrating tissues secrete eosinophilic granules, including major basic protein, eosinophilic neurotoxin, and eosinophilic cationic protein, that destroy vascular tissues.

Environmental risk factors associated with AAV

Seasons

Many studies have confirmed that the onset of AAV is strongly associated with seasonal changes, but the specific

results are inconsistent. Most studies (22, 23) report a higher number of patients with AAV hospitalized in winter, with a peak incidence during winter, and demonstrate a higher incidence of kidney damage in patients with AAV during winter. However, Mahr et al. (45) suggested that the incidence of AAV is significantly higher during summer, particularly in August. In studying the factors related to AAV relapse, Kemna et al. (46) showed that AAV is prone to relapse during autumn, accompanied by increased titers of ANCA-related immune markers. In contrast, no significant seasonal variation was found regarding the timing of symptom onset in a study of 445 patients with GPA (47). These findings cannot be merely limited to seasonal changes but also need to be extrapolated to specific causes or triggers.

The possible mechanisms that affect the incidence of AAV in different seasons may be different. Winter is a high incidence period for respiratory-related diseases, and infection may trigger the occurrence of AAV (48). Additionally, the level of vitamin D is an important factor affecting the pathogenesis of AAV. The active form of vitamin D is 1,25-dihydroxy vitamin D₃ (1,25(OH)₂D₃), which is an immunomodulator. Vitamin D and vitamin D-activating enzymes are widely present in various tissues, especially immune-related cells (Figure 1). The concentration of vitamin D in the body fluctuates with seasonal variations, and the concentration is the lowest during

winter (49, 50). Kälisch et al. (50) reported that patients with AAV had significantly lower serum vitamin D levels than healthy controls. Immune dysfunction caused by vitamin D deficiency may be involved in the development of AAV. The high incidence of AAV during summer may be caused by exposure to sunlight or air pollutants. Spring and summer are common seasons for various allergy-related diseases. Furthermore, AAV-related nasal disease may be caused by an immune response driven by Th2 cells. However, more studies are needed to confirm these speculations (30, 51, 52). Seasonal inconsistency may be due to differences in AAV disease subtypes, geographic regions, patient records, onset time deviations, and regional differences in medical levels in each study.

Air pollution

Air pollution has become a serious environmental problem, severely endangering public health (53–55). Air pollution is composed of a variety of gases and particles, including carbon monoxide (CO), sulfur dioxide (SO₂), nitrates (NOX), ozone (O₃), lead, toxic by-products of tobacco smoke, and particulate matter (PM). Fuel combustion is a major source of ambient air pollution. Combustion releases various pollutants, such as carbon oxides,

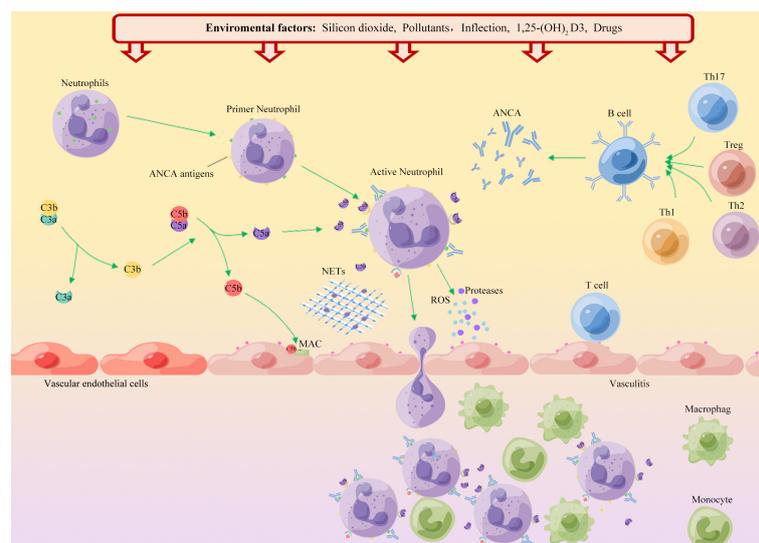


FIGURE 1

Schematic diagram of the environmental factors in the onset of AAV. ANCA autoantigens (PR3 and MPO) are usually hidden in the primitive granules of neutrophils. Environmental factors such as silica, air pollution, and infection, lead to neutrophil initiation and PR3 and MPO movement to the cell surface. Binding of ANCA to these autoantigens leads to activation of neutrophils, which adhere to the vascular endothelium. Neutrophil degranulation leads to the release of reactive oxygen species (ROS), proteases and neutrophil extracellular traps (NETs), which in turn destroy endothelial cells. Chemokines and tissue deposition of PR3 and MPO lead to increased tissue damage by recruitment of autoreactive T cells and monocytes. Additionally, ANCA binds to cell surface autoantigens, leading to neutrophil activation and release of factors that activate the complement replacement pathway. The production of the allergenic toxin C5a further attracts neutrophils and enhances neutrophil initiation and activation upon binding to cell surface C5a receptors, thereby promoting vascular inflammation.

sulfur oxides, nitrogen oxides, polycyclic aromatic hydrocarbons (PAHs), and PM, and harmful metals, such as lead and cadmium, into the atmosphere. Additionally, transportation is an important source of ambient air pollution, which can produce a large amount of pollutants, such as PM, nitrogen oxides, CO, and polycyclic aromatic hydrocarbons. Studies have shown that air pollution is associated with various rheumatic immune diseases. Air pollutants may be involved in the induction of systemic inflammation and enhancement of autoimmunity, thereby inducing or aggravating autoimmune rheumatic diseases (56–58). For example, changes in the concentrations and types of air pollutants may affect disease activity in patients with SLE. In recent years, some studies have shown that air pollution may be related to the occurrence and development of AAV. Data from a survey on the prevalence of AAV disease in China (22) showed that CO exposure was positively correlated with AAV incidence, but air pollutants (PM_{2.5}, PM₁₀, other inhalable particulate matter, NO₂, and SO₂) had no significant correlation with AAV incidence (Table 1). Previous studies have found that CO has anti-inflammatory effects; therefore, the harmful effect of CO on vasculitis needs to be further explored (77). Nuyts et al. (65) found that exposure to hydrocarbons was not a risk factor for GPA and found no significant association between lead, cadmium, and GPA. In contrast, Pai et al. (66) found significantly higher mean hydrocarbon exposure in GPA and MPA cases. Albert et al. (51) found that heavy metal exposure can significantly increase the risk of GPA; these heavy metals are mainly cadmium, lead, and mercury. Subsequently, they found that the GPA population may be exposed to high levels of industrially generated contaminants, including trichloroethylene (TCE), vinyl chloride, methyl tertiary-butyl ether (MTBE), dichloroethene (DCE), and chromic acid (67).

AAV disease is an occupational hazard of agriculture, and the reason may be related to exposure to pollutants. Lane et al. (69) found that a history of organic solvent exposure may be associated with AAV, especially GAP. The same results were obtained in two other studies (70, 71). Studies in Scotland, Germany, and Canada showed that the incidence of AAV in rural areas is higher than that in cities. This may be related to environmental pollutants and pesticide exposure in remote areas (68, 72, 78, 79). Additionally, a large Swedish case-control study (73) found no association between occupation and GPA (Table 1). Unfortunately, these studies only reported the association between pollutants and AAV disease but did not investigate the mechanisms that influence disease.

Previous studies found that tobacco smoking is associated with the development of RA and SLE (80–84). However, findings on the relationship between smoking and AAV have been inconsistent. McDermott et al. (76) proposed that smoking is a risk factor for AAV disease, especially with MPO-ANCA. Yamaguchi et al. (75) found that current smoking status was associated with recurrence (Table 1). However, Haubitz et al. (85) found that smoking may have a potential protective effect

against AAV disease. Additionally, studies have linked exposure to silica, tillage, or organic solvents to an increased risk of EGPA, whereas smoking is associated with a lower risk (74). The immunosuppressive effects of nicotine have been suggested as a potential explanation for these findings (86). A series of studies could not elucidate the effect of smoking on AAV disease (69, 70, 87). Current research on smoking and AAV risk has produced conflicting results, and further research is needed to examine the link between smoking and AAV disease progression.

Silicon dioxide

Silica is one of the most abundant minerals on earth, and exposure to silica dust has been identified as a risk factor for many SARDs, including SS, RA, SLE, and AAV (60, 88). Individuals working in agriculture, mills, drilling, painting, and textiles have been identified to have a greater risk of developing AAV disease (89). Multiple case reports (20, 21) have shown that continuous exposure to silica increases the risk of positive ANCA. Several studies have described cases of silica exposure and AAV. A 74-year-old patient with AAV developed fever and malaise after prolonged exposure to silica (90). Main and Wroe (91) described three cases of silica-exposed patients with AAV, two of whom still required dialysis after treatment. Analysis of the occupational histories of 16 patients with AAV revealed that patients with vasculitis were more likely to be exposed to silica than controls (61). Previous surveys on post-earthquake disease prevalence, such as the Kobe earthquake in Japan, the Great East Japan earthquake, and the Yunnan earthquake in China, showed that the incidence of AAV was higher than before (62–64). The change was attributed to the harmful effects of air pollution on the human body due to increased atmospheric levels of silica from the earthquake. Studies have confirmed the dose-related effects of silica exposure. A meta-analysis (60) showed that silica exposure was positively associated with AAV. A case-control study (59) suggested a 3.4-fold increased risk of ANCA serology positivity in individuals with occupational silica exposure. Only a few studies (92, 93) have proposed a relationship between sustained exposure to silica and AAV. However, research on the relationship between sustained exposure to silica and severity of AAV remains inadequate.

The mechanism by which silica causes AAV is unclear. A previous study (91) found that silica does not have a direct toxic effect on genetically susceptible individuals but rather enhances the immune response non-specifically, activates T cells and Treg cells, and leads to autoimmune dysfunction (Figure 1). With continued exposure to crystalline silica, the body produces inflammatory cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-beta (TNF- β), leading to inflammation and eventual fibrosis (60). Silica can induce apoptosis of neutrophils, macrophages, and monocytes, and damaged cells release many proteolytic enzymes, leading to chronic

TABLE 1 Study on the relationship between environmental pollutants and AAV.

| Environmental factors | Year | Region | Study design | Participants | Main conclusions |
|---------------------------------------------------|------|-------------|---------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SiO₂ | | | | | |
| Beaudreuil et al. (59) | 2005 | France | Case-control study | Patients with AAV | Silica exposure is dose-dependently associated with ANCA positivity. |
| Gomez-Puerta et al. (60) | 2013 | USA | Systematic review and meta-analysis | Six studies | Exposure to silica increases the risk of AAV by 2.57 times. |
| Gregorini et al. (61) | 1993 | Italy | Hospital-based case-control study | Patients with AAV | Seven of the 16 cases and one of the 32 controls had positive histories of jobs with exposure to silica dust. |
| Gupta et al. (20) | 2019 | India | Case report | Patients with MPA | In a tuberculosis-endemic country, for patients presenting with diffuse alveolar hemorrhage (DAH), with history of silica exposure, differential diagnosis of ANCA-associated vasculitis must be considered. |
| Rao et al. (21) | 2020 | Australia | Case report | Patients with AAV | The relevance of occupational exposures in renal disease and the immune-stimulatory effect of silica. |
| Earthquake-related environmental exposures | | | | | |
| Yashiro et al. (62) | 1999 | Japan | Case series | Patients with AAV | The frequency of MPO-AAV cases in the Kobe area has more than doubled each year since the earthquake. |
| Takeuchi et al. (63) | 2017 | Japan | Retrospective population-based cohort study | Patients with MPO | The annual incidence of MPO-AAV doubled after the earthquake. |
| Farquhar et al. (64) | 2017 | New Zealand | Retrospective cohort study | Patients with AAV | No statistically significant difference in the incidence of AAV existed before and after the earthquake. |
| Other pollutants | | | | | |
| Li et al. (22) | 2018 | China | Retrospective cohort study | Patients with AAV | Carbon monoxide exposure was positively correlated with the frequency of AAV. |
| Nuyts et al. (65) | 1995 | Belgium | Case-control study | Patients with GPA AAV | The association between lead and cadmium and GPA was not significant. Exposure to hydrocarbons and welding fumes were not risk factors for GPA. |
| Pai et al. (66) | 1998 | UK | Case-control study. | Patients with AAV | The mean hydrocarbon exposure was significantly greater in cases than in controls. |
| Albert et al. (51) | 2004 | USA | Case-control study | Patients with GPA | Mercury was associated with GPA. The association between CO and GPA approached statistical significance. |
| Albert et al. (67) | 2005 | USA | Case series | Patients with GPA | This cluster of patients with GPA were potentially exposed to high levels of industrially generated contaminants. |
| Chung et al. (68) | 2022 | Australia | Retrospective study | Patients with AAV | No significant relationship existed between region and exposure to silica, solvents, metal, dust, farming, gardening, or sunlight. |
| Agriculture | | | | | |
| Lane et al. (69) | 2003 | UK | Case-control study | Patients with AAV | Farming exposure was associated with risk of GPA and MPA but not EGPA. High occupational silica exposure in the index year was a risk factor for AAV. The risk of MPA rises with occupations at intermediate or high silica exposure. |
| Stamp et al. (70) | 2015 | New Zealand | Case-control study | Patients with GPA | Farming was associated with an increased GPA risk. |
| Willeke et al. (71) | 2015 | Germany | Case-control study | Patients with AAV | Regular farm, cattle, and pig exposure were strongly associated with AAV. |
| Aiyegbusi et al. (72) | 2020 | UK | National cohort study | Patients with AAV | GPA (but not MPA) was positively associated with rurality. |
| Knight et al. (73) | 2010 | Sweden | Population-based case-control study. | Patients with GPA | No general association existed between 32 selected occupations and GPA. |
| Smoking | | | | | |
| Haubitz et al. (74) | 2005 | Germany | Cross-sectional cohort study | Patients with AAV | The prevalence of GPA/MPA among smokers was lower than among the general population. |

(Continued)

TABLE 1 Continued

| Environmental factors | Year | Region | Study design | Participants | Main conclusions |
|-----------------------|------|--------|----------------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yamaguchi et al. (75) | 2018 | Japan | Multicenter retrospective cohort study | Patients with AAV | Current smoking status was associated with recurrence. Smoking was significantly associated with relapse in MPA, in a dose-dependent manner. |
| McDermott et al. (76) | 2020 | USA | Case-control study | Patients with AAV | Patients with AAV were more likely to be former or current smokers; a dose-response relationship existed according to pack-years of exposure. These associations were especially strong among participants with MPO-ANCA-positive disease. |
| Maritati et al. (69) | 2021 | UK | Case-control Study | Patients with EGPA | Exposure to silica, farming, or organic solvents is associated with an increased risk of EGPA, whereas smoking is associated with a lower risk. These exposures seem to have distinct effects on different EGPA subsets. |

AAV, Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic GPA.

inflammation and tissue fibrosis (94). Another study (95) suggested that silica can induce the expression of MPO in the cell membrane of neutrophils and monocytes, causing ANCA-related autoimmune responses.

Latitude

A previous study (33) found that the incidence of AAV varies significantly with latitude, further supporting the influence of geographical region on AAV disease. Epidemiological studies (33, 34) have shown that the risk of GPA is high in the northern hemisphere of the earth, whereas the risk of MPA is high in the southern hemisphere. Quantitative changes showed marked changes, while the incidence of GPA and EGPA increased with increasing latitude and decreasing ambient UV radiation levels (24). Similarly, related studies have confirmed that the positive rate of PR3-ANCA decreases with increasing latitude and ultraviolet radiation intensity (96).

UV radiation is a sensitive factor that varies with latitude, and related studies have found a close relationship between UV radiation and immune diseases (46). UV radiation, which changes with latitude, is considered to be the actual cause of AAV. UV radiation is necessary for the skin's synthesis of 1,25(OH)₂D₃, which regulates immune system homeostasis. UV irradiation of the skin induces vitamin D synthesis, which in turn inhibits the proliferation of Th1 and Th17 cells and the production of cytokines. These changes cause the immune system to differentiate into Th2 cells, thereby enhancing the activity of CD24+, CD25+, and CD8+ cells. This is consistent with a mechanism mediated by Th1 and/or Th17 cells in the pathogenesis of GPA (97–99). This may explain why the association between MPA and UV light is not strong, since granulomas are not present in MPA. However, accurate estimation of the average amount of UV radiation in a region is challenging. The influence of immigration, clothing characteristics, skin color preferences, religious and cultural

beliefs, and other factors need to be excluded, as well as the influence of dietary intake of vitamin D, related drugs, and other environmental factors on the final serum vitamin D level in each region. These challenges should be addressed in future studies.

Microbial infections

Staphylococcus aureus

Microbial infection is considered to be an important risk factor for the development of AAV. Intranasal *staphylococcus aureus* (*S. aureus*) infection is most closely associated with AAV (25). The early symptoms of patients with GPA are mainly runny nose, nosebleeds, and other symptoms, because the most prominent feature of the disease is the granulomatous inflammation of the respiratory tract. *S. aureus* infection that colonizes the respiratory tract may trigger GPA disease activity (100). Previous studies (101) have found that the detection rate of *S. aureus* in patients with GPA is significantly higher than that in healthy individuals, and patients with GPA with chronic *S. aureus* infection have a significantly increased risk of recurrence. A randomized controlled trial (102) in the Netherlands showed that patients treated with trimethoprim/sulfamethoxazole (T/S, 960 mg three times a week) had a decreased recurrence rate by 66%. In contrast, prophylactic treatment of chronic *S. aureus* carriers with T/S did not reduce the risk of relapse (101). This may be related to factors, such as drug dosage and different bacterial detection methods (102). Further studies found that the imbalance in the proportion of various bacteria colonized in respiratory tract may contribute to the incidence of AAV. The proportion of *S. aureus* colonization in nasal samples of patients with GPA increased, but the diversity of the microbiome decreased (103–105). Current studies indicate that *S. aureus* is only related to the pathogenesis of GPA, but no obvious relationship seems to exist between *S. aureus* and the pathogenesis of MPA and EGPA.

The role of *S. aureus* in the pathogenesis of AAV may be as follows: (1) Superantigens of *S. aureus* directly stimulate B cells and T cells. Among them is the polyclonal activation of B cells by *S. aureus* cell wall components. Additionally, *S. aureus* may directly initiate neutrophils, leading to surface expression of PR3 (106). (2) *S. aureus* contains a highly homologous complementary form of the protein in humans. cPR-3 (105–201) acts as a protein complementary to the human autoantigen PR3 and elicits an autoimmune response (8). (3) The CpG motif of *S. aureus* may trigger B lymphocytes in the peripheral blood of patients in remission, leading to the production of ANCA and relapse of AAV (107). (4) The polypeptide 6-phosphogluconate dehydrogenase (6PGD) 391–410 encoded by the *S. aureus* plasmid is homologous to the previously determined immunodominant MPO-T cell epitope, and it is immunogenic in humans. Studies have shown that 6PGD induces MPO-related nephritis (108). (5) *S. aureus*-derived extracellular adhesion protein (EAP) and Staphylococcus peroxidase inhibitor (SPIN) can induce the body to produce ANCA (109). (6) *S. aureus* is an effective inducer of NETs, DNA extracellular complex, and antibacterial factors secreted by neutrophils. Exposure of ANCA antigens to the immune system can initiate an autoimmune response to AAV (110, 111).

Viruses

Epstein-Barr virus (EBV) infection is most closely related to various SARDs (112–116). Multiple case reports found that patients with AAV may develop anti-MPO antibodies following EBV infection. Treatment with glucocorticoids combined with ganciclovir can significantly relieve clinical symptoms and reduce viral load (117–119). Lidar et al. (120) found that anti-EBV capsid antigen antibodies and anti-EBV early antigen antibodies were significantly higher in the sera of patients with AAV than in healthy individuals. Treatment with glucocorticoids in combination with ganciclovir significantly relieved clinical symptoms and reduced viral load. Hepatitis B virus (HBV) and hepatitis C virus (HCV) may be triggers for SARDs. An Egyptian study (121) found 62.7% hepatitis C virus infection in 42 patients with AAV, and C-ANCA levels were significantly correlated with hepatitis C virus antibody levels. Lee et al. (122) found a significantly higher risk of relapse in anti-HBc-positive patients with EGPA. Resolved HBV infection may have an important impact on vasculitis activity at diagnosis and subsequent relapse after remission in patients with EGPA. Recently, ANCA has been identified in patients with coronavirus disease 2019 (COVID-19) infections, but relatively few cases have been reported (123, 124). Studies have proposed the involvement of the parvovirus B19, human herpesvirus, and hantavirus in the occurrence of AAV (122, 125, 126). However, these studies are few and have not found a significant correlation between these viruses and the development of AAV.

Other microorganisms

Few studies have been conducted on other microorganisms in AAV. A Japanese study (127) reported that *Aspergillus* infections, including *Candida*, *Candida*, and *Fusarium*, were found in patients with both allergic bronchopulmonary mycosis (ABPM) and EGPA. Kuwabara et al. (128) found that *Mycobacterium tuberculosis* infection and anti-tuberculosis drugs may be related to AAV. Fujita et al. (129) found that the positive rate of *Chlamydia pneumoniae* in patients with MPO-AAV was 33%. A Japanese report (130) described a woman who underwent total thyroidectomy, developed PR3-ANCA 3 months after surgery, and had a chronic infection with *Tsukamurella pulmonis*. GPA often occurs in gastrointestinal mucosal lesions, and the study detected 25 cases of *Helicobacter pylori* infection among 36 patients with GPA (131). Currently, the effect of these microorganisms on AAV is only speculative, and further large-scale studies are needed to verify.

Other environmental risk factors

Drugs

Drug-induced small vessel vasculitis is a small group of AAV disorders that still do not have a precise definition. Drugs that may be associated include hydralazine, allopurinol, propylthiouracil, phenothiazine, nitrofurantoin, methimazole, minocycline, phenytoin sodium, penicillamine, lorazepam, levamisole, cocaine, isoniazid, montelukast, erlotinib, and tofacitinib (86, 89, 128, 132–134). Among them, the incidence of AAV caused by antithyroid drugs is higher, especially propylthiouracil. The clinical manifestations of propylthiouracil-induced AAV disease are similar to those of primary AAV, whereas the disease severity is less severe and prognosis is better. After cessation of antithyroid drug use, symptoms of patients with AAV gradually resolve and ANCA titers decrease significantly (135). Treatment strategies for drug-induced AAV differ from those for primary AAV (136). In patients with mild symptoms, immediate discontinuation of the relevant drug can lead to disease remission. Patients with severe diseases should be treated aggressively. However, immunosuppressive maintenance therapy is often unnecessary (137). The mechanism of drug-induced AAV disease may be related to NETs (138). However, further studies are needed to verify the exact mechanism (132). NETs are associated with inflammation in various ways. NETs can directly induce endothelial damage and activate alternative complement pathways (139). Additionally, they are a major component of thrombosis. The relationship between NETs and ANCAs seems to be bidirectional, a vicious circle (111, 140, 141).

Vaccines

The efficacy of vaccines is based on the ability of the host immune response to the antigen to elicit a memory T-cell response over a period of time. The influenza vaccine is

generally considered safe and effective. However, in recent years, the population after influenza vaccination has developed various autoimmune phenomena, such as Guillain-Barré syndrome, RA, pemphigus vulgaris, psoriasis, giant cell arteritis, and AAV (142, 143). Several AAV cases associated with influenza vaccination have been reported (144, 145), but influenza vaccination does not increase the recurrence rate of AAV disease. The exact etiology of AAV induced by influenza vaccination is unclear and may be related to molecular mimicry and autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) (146–148). Recent studies (149, 150) have found that AAV may occur after receiving the COVID-19 mRNA vaccine, and patients with existing AAV may experience recurrence after receiving the COVID-19 mRNA vaccine. The mechanism of new or recurrent AAV after vaccination is still a mystery and may be similar to the mechanism of AAV caused by influenza vaccine. Additionally, the enhanced immune response and presence of monocytes after vaccination may cause MPO-ANCA and PR3-ANCA (151). However, this evidence originates from individual case reports, and no specific mechanism has been explored.

Conclusion

Studies to identify modifiable environmental risk factors for AAV can provide insights into disease pathogenesis and can facilitate the development of preventive strategies, especially in those individuals at high risk. The current consensus is that multiple environmental and epigenetic factors interact in a complex manner. Different triggers and extent of their roles in disease activity may vary by subgroups (e.g., ANCA subtype, geographic region). Numerous epidemiological studies support the relationship between exposure to various environmental pollutants, UV radiation deficiency, and microbial infections and the risk of developing AAV. Other environmental factors, including seasonal changes, latitudinal changes, medications, and vaccinations may be associated with an increased risk of AAV. Further studies are needed to confirm these findings. Additionally,

future studies on environmental factors and AAV susceptibility subgroups need to be advanced, and exposures throughout the life course should be considered comprehensively.

Author contributions

W-MZ, Z-J W and D-GW were part of the organizing committee of the workshop. W-MZ wrote the manuscript. Z-JW, RS, Y-YZ, SZ, and R-FW contributed to the revision of the initial draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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