Infection is associated with increased risk of MPO- but not PR3-ANCA-associated vasculitis

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Abstract

Objectives. To determine whether development of ANCA-associated vasculitis (AAV) shows a relationship with a prior infection and if prior infection affects disease characteristics and outcome.

Methods. All incident cases of AAV diagnosed in a defined region of Sweden from 2000 through 2016 were identified. For each case, 10 individuals from the general population, matched for age, sex and area of residence, were selected. Infections occurring in AAV patients and controls prior to the date of AAV diagnosis (index date for respective controls) were identified using an administrative database. Conditional logistic regression models were used to calculate odds ratios (OR) of developing AAV. Occurrence, clinical characteristics and outcome of AAV were analysed with respect to prior infection.

Results. Two-hundred and seventy patients with AAV (48% female) and 2687 controls were included. Prior to diagnosis/index date, 146 (54%) AAV patients had been diagnosed with infection vs 1282 (48%) controls, with OR for AAV 1.57 (95% CI 1.18, 2.19) in those with infections of the upper respiratory tract and 1.68 (1.02, 2.77) in those with pneumonia. Difference from controls was significant in patients with MPO-ANCA 1.99 (95% CI 1.25, 3.1) but not in those with PR3-ANCA 1.0 (0.61, 1.52). Patients with prior infection showed higher disease activity at AAV diagnosis. No differences in disease characteristics, comorbidities or outcome in those with and without prior infections were observed.

Conclusions. Respiratory tract infections are positively associated with development of MPO- but not PR3-ANCA vasculitis. Prior infection is associated with higher disease activity at AAV diagnosis.

Key words: epidemiology, systemic vasculitis, autoimmune disease, autoantibodies, granulomatosis with polyangiitis

Introduction

ANCA-associated vasculitides (AAV) are rare diseases involving inflammation of small blood vessels, resulting in necrotizing or granulomatous vasculitis in the affected organ system. AAV can be organ-limited or systemic and is categorized as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis according to clinicopathologic characteristics [1]. ANCAs are IgG antibodies
which can be detected in most cases of AAV [2] and target antigens in neutrophil granules and monocytes, predominantly MPO or PR3 [3], but other target molecules have been described [4]. Binding of ANCA to their target antigens on innate immune cells (neutrophils and monocytes) can lead to activation of inflammatory processes resulting in vessel wall injury [5]. The aetiology of AAV is unknown, but complex mechanisms involving drugs, genetic [6] and environmental factors including airborne particles, especially silica dust, and infectious agents have been suggested [7]. Several infectious agents have been studied and implicated in the pathogenesis of small and medium vessel vasculitis [8], however the evidence for such association is scarce for AAV.

The pathogenic mechanism underlying vasculitis following exposure to infection is not well known. Vessel wall injury could be triggered by deposition of immune complexes within the vessel wall [9] or by the targeting of epitopes on endothelial cells by immune effectors via molecular mimicry [10]. ANCA can be present years before the onset of AAV symptoms [11], and infectious agents might enhance pre-existing autoimmunity, for example through increased expression of ANCA antigens on the cell surface [12], facilitating progression of subclinical autoimmunity to active disease. Lack of suppression by regulatory T cells has been shown to be associated with the development of AAV [13], indicating interplay between adaptive and innate immune mechanisms in its pathogenesis.

Considerable differences between PR3- and MPO-ANCA-associated disease have been described, including age and renal function at diagnosis, sex distribution [14], pattern of organ involvement and prognosis [15], as well as geographic distribution [16] and genetic associations [6]. As the relationship of infection with ANCA is largely unknown, we investigated the occurrence of infection prior to the diagnosis of AAV in a large population-based cohort. We also sought to determine whether patients with infection prior to AAV diagnosis differed in disease phenotype, organ involvement or disease outcome.

Methods

Study area

The study area comprises two healthcare districts in Skåne, the southernmost region of Sweden, and included 14 municipalities with a total population of 790 000 [17], including rural areas, small towns, and the cities of Lund and Malmö. The area is served by the Skåne University Hospital—a tertiary care centre for the entire area with main campuses in Lund and Malmö, Trelleborg Hospital and Landskrona Hospital. Sweden’s healthcare system provides universal access to primary and hospital care to all residents. Every resident of Sweden is identified by a unique 10-digit number that enables linking data among administrative and healthcare registries.

Data sources

Skåne healthcare register

The Skåne Healthcare Register (SHR) is a centralized administrative healthcare database established in 1998 [18] and includes information from medical records and other administrative sources derived from all healthcare consultations with physicians, nurses and allied health professionals, public or private, in the Skåne region. It provides data on sex, age, place of residence, date of visit and healthcare provider, as well as up to eight diagnostic International Classification of Diseases, 10th edition (ICD-10) codes for every consultation. The proportion of physician consultations that have an assigned diagnosis code has been near 100% for hospital care, but for primary care this proportion was lower before 2004 and has since been ≥80% [18].

Patients

The study comprised a population-based cohort of patients with AAV diagnosed from 1997 through 2016 [19]. Case ascertainment, diagnosis and classification of AAV disease phenotypes has been described [20]. In brief, diagnosis of small vessel vasculitis was verified by histologic features of vasculitis or granuloma, ANCA positivity, or surrogate markers for vasculitis or granuloma. Disease was classified into three AAV disease phenotypes according to the algorithm of the European Medicines Agency [21].

Study design

This study was conducted in two segments, an initial population-based case-control study to determine whether exposure to infection was associated with later occurrence of AAV, followed by a cohort study to investigate the potential impact of infection prior to AAV onset on disease characteristics and outcome.

The case–control study

As data in the SHR are only available from 1998, to allow for a 2-year exposure period, data of previous infections were collected for patients diagnosed with AAV from 1 January 2000. A total of 270 patients (48% female) were included. Using the SHR, 10 controls from the general population were randomly selected for each AAV patient matched with respect to sex, age and place of residence. Controls must have consulted a physician sometime during the year that their respective case received an AAV diagnosis and were crosschecked in the SHR to preclude assignment of any ICD-10 code for AAV. Each control was assigned an index date corresponding to the diagnosis date of their respective AAV case. If patients and controls experienced more than one infection prior to the diagnosis/index date, only the infection closest to the index date was included in analysis. As some non-specific and early symptoms of
vasculitis can be misinterpreted as infection or occur in combination with infection, a 3-month latency period from date of infection to the date of AAV diagnosis/index date was applied, based on earlier studies of diagnosis delay in this cohort [22].

The cohort study
The cohort of patients with AAV (n = 270) was divided into patients with and without prior infection. Demographics, clinical, laboratory characteristics and outcome were analysed and compared between groups. Patients in the AAV cohort were followed from date of diagnosis to death or end of study, December 2016.

Data collection
For the case–control study, all episodes of infection prior to diagnosis/index date for controls were identified. To be classified as infection, diagnosis must have been made and ICD-10 code assigned by a physician in either in- or out-patient setting.

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For the cohort study, medical records were reviewed, and the following data were recorded from time of AAV diagnosis or during follow-up: patient demographics, clinical manifestations and laboratory data including ANCA serology. Vasculitis disease activity (at diagnosis) was calculated based on the BVAS [23]. Organ damage at 12 months post-AAV diagnosis was calculated based on the Vasculitis Damage Index (VDI) [24]. Data of renal function, occurrence of end-stage renal disease, and survival was collected as well as date and cause of death. Estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula [25]. Data of selected comorbidities diagnosed after the onset of AAV were collected by case record review and acquired via regional registries, and included severe infection requiring hospitalization and intravenous antimicrobials, venous thromboembolism, stroke and myocardial infarction.

Ethics
The study was conducted in accordance with the declaration of Helsinki and approved by the Regional Ethical Review Board in Lund, Sweden (2010/517). Informed consent was not required.

Statistical analysis
In the case–control study, a conditional logistic regression model was used to estimate odds ratios (OR) and 95% confidence intervals (CI), yielding an approximation of the relative risk of developing AAV following infection. Exposure was defined as any episode of infection diagnosed by a physician in either in- or outpatient setting and the diagnosis of AAV as the outcome. All infections diagnosed within 3 months of AAV diagnosis were excluded. The conditional regression analysis was carried out in two steps. First, all patients with AAV were included with all controls who were matched for age, sex and place of residency. Second, the AAV cohort was stratified according to ANCA serology; PR3- and MPO-ANCA. The analyses were then carried out comparing each serology group with their respective matched controls.

To quantify a potential dose–response relationship between prior infection and occurrence of AAV, we calculated odds ratios for frequency of prior infections in a logistic regression model. Prior infections were categorized into four groups: 0 (no infection, the reference in this model), 1, 2–4, or 5 or more prior infection events. To assess the effect of number of infections prior to AAV, a test for trend was employed.

In the cohort study, continuous and normally distributed data are presented as means with s.d. with group comparisons using Student’s t-test. Non-normally distributed data are presented as median with interquartile range (IQR). The Mann–Whitney test was used for group comparison. Categorical data was analysed using a $\chi^2$ test. All statistical analyses were performed using IBM SPSS v. 26 for Windows. A P-value <0.05 was considered significant.

Results

The association of prior infection with AAV
A total of 146 patients (54%) had suffered at least one episode of infection prior to diagnosis of AAV compared with 1282 controls (48%) (P = 0.04), 98% of infections were from an outpatient setting. The time period from infection event to diagnosis/index date was shorter in AAV cases than in controls (Table 1).

Infection at any site was associated with a subsequent diagnosis of AAV OR of 1.43 (95% CI 1.06, 1.92). For upper respiratory tract infection OR was 1.57 (95% CI 1.18, 2.19) and for pneumonias was 1.68 (95% CI 1.02, 2.77). There was a non-significant increase in OR for AAV after ENT infections (OR 1.39, 95% CI 0.80, 2.42), with no such trend seen for urinary tract infection (OR 0.93, 95% CI 0.47, 1.82) (Fig. 1).

Results of ANCA serology were available for 251 patients: 134 were PR3-ANCA positive and 117 MPO-ANCA positive; 19 patients tested negative for ANCA. Patients that developed MPO-ANCA-associated vasculitis were more likely to have experienced an infectious event prior to AAV diagnosis, with an OR of 1.99 (95% CI 1.25, 3.1) for infection at any site, OR 1.7 (95% CI 1.03, 2.89) for pneumonia, and 2.39 (95% CI 1.13, 5.04) for ENT infections. No association with infection was observed for PR3-ANCA vasculitis [OR 1.0 (95% CI 0.61, 1.52)] (Fig. 2a and b). Results apply for a 3-month latency period between infection and AAV diagnosis, but similar results were observed with a 6-month period (data not shown).

We observed a dose–response relationship between the number of prior infection episodes and subsequent
occurrence of AAV with the strength of the association increasing with the number of prior infections: OR 1.49 (95% CI 1.03, 2.17) for two to four infections to 2.17 (95% CI 1.39, 3.38) for those with five or more prior infections. This association was observed for the MPO phenotype, OR 1.89 (95% CI 1.04, 3.39) for two to four infections and OR 3.37 (95% CI 1.81, 6.28) for five or more prior infections, but not for the PR3 phenotype (Fig. 3).

Prior infection, disease phenotype and outcome of AAV

Patients who suffered infections prior to AAV diagnosis exhibited higher vasculitis disease activity at diagnosis with a BVAS of 15 (IQR 10–19) vs 14 (IQR 11–16).
A total of 128 (47%) patients developed at least one of the following comorbidities during follow-up time: myocardial infarction, deep venous thrombosis, pulmonary embolism, stroke or severe infection (Table 3). The composite outcome of any comorbidity occurred in 72 (49%) patients with prior infection and in 56 (45%) patients without prior infection. This difference can be attributed to higher renal BVAS score for patients with prior infections. We did not observe a difference for other organ systems (Table 2).

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without ($P = 0.84$). There were no differences in the occurrence of any of the studied comorbidities.

**Discussion**

In this population-based study comprising 270 cases of AAV and utilizing a comprehensive administrative registry of all healthcare contacts, we found that exposure to infection was associated with later development of AAV with an OR of 1.43. This was especially evident for respiratory infections, which showed an OR of 1.57 for prior upper respiratory tract infections and 1.68 for prior pneumonia. This association could be observed for MPO-ANCA but not PR3-ANCA.

Patients with immune system deficiencies or dysregulation might be prone to infection as well as to autoimmunity, and the association of infection with AAV may not be causal. Subclinical vasculitic processes in the airway or such vasculitic manifestations as interstitial lung
### Table 2: Demographics, clinical characteristics, and outcome in 270 AAV patients with and without prior infections (cohort study analysis)

|                                      | All patients (n = 270) | AAV with prior infection (n = 146) | AAV with no prior infection (n = 124) | P   |
|--------------------------------------|------------------------|-----------------------------------|--------------------------------------|-----|
| Age, mean (s.d.), years              | 65 (16)                | 64 (17.5)                         | 65 (15.5)                           | 0.14|
| Female, n (%)                        | 129 (48)               | 76 (52)                           | 53 (43)                              | 0.10|
| GPA, n (%)                           | 139 (51.5)             | 71 (48.6)                         | 68 (54.8)                           | 0.22|
| MPA, n (%)                           | 110 (40.7)             | 60 (41.1)                         | 50 (40.3)                           | 0.22|
| EGPA, n (%)                          | 21 (7.8)               | 15 (10.3)                         | 6 (4.8)                              | 0.22|
| PR3-ANCA positive                    | 134 (50)               | 62 (42.5)                         | 72 (58.1)                           | 0.01|
| MPO-ANCA positive                    | 117 (43)               | 72 (49.3)                         | 45 (36.3)                           | 0.07|
| BVAS 0M, median, IQR                 | 15 (11–18)             | 15 (10–19)                        | 14 (11–16)                          | 0.04|
| Renal BVAS score (max 12), median, IQR | 0                      | 0                                 | 0                                    | 0.54|
| General                              | 209 (77)               | 108 (74)                          | 101 (82)                             | 0.14|
| Skin                                 | 30 (11)                | 20 (14)                           | 10 (8)                               | 0.14|
| Mucous membranes                     | 20 (7)                 | 12 (8)                            | 8 (7)                                | 0.58|
| ENT                                  | 105 (39)               | 57 (39)                           | 48 (39)                              | 0.96|
| Chest                                | 137 (51)               | 80 (55)                           | 57 (46)                              | 0.15|
| Cardiovascular                       | 18 (7)                 | 8 (6)                             | 10 (8)                               | 0.40|
| Abdominal                            | 7 (2.6)                | 2 (1)                             | 5 (4)                                | 0.17|
| Renal                                | 182 (67)               | 98 (67)                           | 84 (68)                              | 0.91|
| Nervous                              | 32 (12)                | 18 (12)                           | 14 (11)                              | 0.79|
| Number of organs involved, n (%)     | 1–2                    | 115 (43)                          | 60 (41)                              | 55 (44)                             | 0.59|
| Outcome VDI 12M, median, IQR         | 1 (0–2)                | 1 (0–3)                           | 1 (0–2)                              | 0.41|
| ESRD(during follow up), n (%)         | 38 (14)                | 17 (11.6)                         | 21 (16.9)                            | 0.21|
| Death, n (%)                         | 110 (41)               | 55 (37.7)                         | 55 (44.4)                            | 0.27|
| Mortality 1 year post-AAV diagnosis, n (%) | 33 (12)                | 19 (13)                           | 14 (11)                              | 0.30|

BVAS range 0–63. AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; IQR: interquartile range; VDI: Vasculitis Damage Index (range 0–64); ESRD: end stage renal disease.

### Table 3: Selected comorbidities diagnosed after AAV diagnosis

|                                      | All, n = 270 (%) | Infection prior to AAV, n = 146 (%) | No infection prior to AAV, n = 124 (%) | P   |
|--------------------------------------|----------------|------------------------------------|----------------------------------------|-----|
| Any comorbidity                      | 128 (47)       | 72 (49)                            | 56 (45)                                | 0.52|
| Myocardial infarction                | 19 (7)         | 10 (7)                             | 9 (7)                                  | 0.96|
| Stroke (ischaemic)                   | 16 (6)         | 10 (7)                             | 6 (5)                                  | 0.49|
| Deep vein thrombosis                 | 18 (7)         | 9 (6)                              | 9 (7)                                  | 0.72|
| Pulmonary embolism                   | 12 (4)         | 7 (5)                              | 5 (4)                                  | 0.77|
| Serious infection                    | 109 (40)       | 61 (41)                            | 48 (39)                                | 0.61|

Serious infection defined as those requiring hospitalization or treatment with intravenous antimicrobials. AAV: ANCA-associated vasculitis.
disease in MPO-positive vasculitis may facilitate infection, especially respiratory infections, in patients not yet diagnosed with AAV.

Association of infection with other types of vasculitis has been previously reported. Our group recently demonstrated association of infections, especially respiratory infections, with an increased risk of subsequent development of GCA [26]. Similar findings have been reported for systemic autoimmune disorders such as idiopathic inflammatory myopathies [27] and SS [28]. Several infectious agents have been implicated as playing a role in pathogenesis of IgA vasculitis, an immune complex vasculitis [29].

Although clinical, as well as experimental, data indicate an important role of ANCA in the pathogenesis of AAV [30], low levels of natural ANCA have been observed in healthy individuals [31], and seropositivity for both PR3- and MPO-ANCA has been found years before onset of AAV symptoms [11, 32], implying that the presence of ANCA is not universally pathogenic and that additional triggers are needed to overcome tolerance. Infection could be such a trigger, transforming a subclinical autoimmune process to active disease. Seropositivity for pathologic antibodies in advance of disease manifestation has been described in other autoimmune diseases, including RA [33] and SLE [34].

Chronic infection or colonization with infectious agents might lead to a loss of tolerance and antibody formation. In patients with cystic fibrosis, a disorder with chronic bronchial inflammation and suppuration, chronic infection with *Pseudomonas aeruginosa* is observed in a majority of patients [35]. Formation of bactericidal permeability increasing (BPI) protein-ANCA positivity is common [36] and linked to *P. aeruginosa* colonization [37]. The BPI-ANCA levels drop significantly after lung transplant, with the accompanying elimination of the bacteria [38].

Previous studies have investigated the relationship between prior infection and the occurrence of AAV, primarily association with GPA, as nasal carriage of *Staphylococcus aureus* is found to be more common in patients with GPA compared with healthy individuals, and is associated with increased risk for relapse [39]. This is supported by studies showing that treatment with co-trimoxazole reduces relapse rates in patients with localized GPA [40]. Alterations in microbiota homeostasis have been implicated in the pathogenesis of autoimmune and chronic inflammatory diseases [41]. In recent years several studies have examined and characterized the microbiome in patients with GPA. Rhee *et al.* observed differences in the fungal and bacterial composition of nasal microbiome in GPA patients compared with healthy controls [42]. Another study showed differences in the abundance of *S. aureus* in relation to disease activity [43]. Another possible mechanism of infection triggering AAV/autoimmunity is the production of proinflammatory cytokines such as TNF-α and IL-1β. Increased neutrophil turnover, together with microbial cofactors, might trigger formation and presentation of MPO and PR3 on cell surfaces with subsequent neutrophil activation, including neutrophil extracellular traps (NETs) formation and endothelial damage [30]. Neutrophils appear to play a key role in pathogenesis, being the target of autoantibodies on one hand and effector cells inducing tissue damage on the other. Neutrophil extracellular traps have been implicated in the pathogenesis of AAV after being identified within vasculitis lesions; moreover, AAV patients exhibit increased blood levels of NETs, and ANCA have been shown to induce NETosis [44]. In a study on the relationship between AAV and molecular mimicry between LAMP-2 (lysosomal membrane protein-2) and an adhesin located at bacterial fimbrae in certain Gram-negative bacteria, the researchers reported microbiologically confirmed diagnoses with *Escherichia coli* and *Klebsiella* in the 12 weeks before onset of pauci-immune glomerulonephritis [10]. We could not identify an association between prior urinary tract infection and subsequent AAV development in this study, but comparisons between these studies are difficult; we employed a 3 months latency period, excluding infections in this period; and furthermore, microbiologic data were not available in our study.

Time from infection event to AAV diagnosis was shorter than the time from infection to index date in the reference group, potentially through infection-induced immune activation in susceptible individuals as discussed. We observed higher disease activity at onset of AAV in patients with prior infection but no other differences in terms of clinical presentation or outcome.

The association of infection with subsequent development of AAV was significant only for patients with MPO-ANCA-associated vasculitis, the association of infection at any site with AAV was mainly driven by ENT and respiratory infections.

While information about differences in the pathogenesis of MPO- vs PR3-ANCA-associated disease is scarce, research has revealed common pathways such as the priming of neutrophils [7]. Infection has been implicated in clinical studies and experimental settings. In a systematic review, Kakoullis *et al.* [45] identified cases of infection-induced anti-MPO formation and subsequent AAV development for a variety of pathogens. Upon resolution of the infection, vasculitis regressed in about 50% of patients, and ANCA levels decreased in a majority of cases.

We observed no differences in demographic or outcome parameters such as mortality or the development of common comorbidities in AAV patients with and without preceding infection. Prior infection was not associated with severe infection after diagnosis of AAV. However, AAV patients with prior infection showed higher disease activity. MPO-positive individuals are known to exhibit greater renal involvement [46], which has a high impact on BVAS. These patients exhibit less extensive involvement in organs overall [15].

There are limitations to this study. Infections were identified by ICD-10 codes, but no ascertainment of the accuracy of diagnosis or prescribed antimicrobials was made. However, patients and controls were matched for age and sex, and the consultations took place months
before the diagnosis of vasculitis. We therefore expect that the diagnosis and treatment of patients later diagnosed with AAV did not differ from that of those who were not. Data were collected retrospectively, raising the potential for missing data, especially in assessment of disease activity and irreversible organ damage. Wide CIs were observed in some analyses, probably due to the small number of events.

The study has several strengths, including the large number of patients and controls from the same background population. We studied all sites and types of infections diagnosed in both outpatient and hospital settings. All data on comorbidities after diagnosis of AAV were accessed by case-record review.

We found that infection is associated with later development of AAV and that MPO-positive AAV patients are more likely to have experienced infections before the onset of vasculitis than are PR3-positive patients. We also found that number of prior infections was positively associated with higher odds for AAV diagnosis. Prior infection was associated with higher disease activity at diagnosis but showed no impact on organ damage after 1 year or on patient and renal survival.

Further studies are needed to replicate our findings in other AAV patients; in addition, more research on the link between infection and development of autoimmune disease is needed.

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Data availability statement

Data are protected by the confidentiality laws in Sweden and cannot be shared. All data relevant to the study are included in the article. Please contact the corresponding author.

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