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Arthritis Rheumatol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Arthritis Rheumatol. 2017 December ; 69(12): 2338–2350. doi:10.1002/art.40313.

The epidemiology of ANCA associated vasculitis in Olmsted County, Minnesota (USA): a 20 year population-based study

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Abstract

Objective—To estimate the incidence, prevalence and mortality of ANCA-associated vasculitis (AAV) and its subsets, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA), in a U.S. based adult population.

Methods—All medical records of patients with a diagnosis or suspicion of AAV in Olmsted County, Minnesota from January 1, 1996 to December 31, 2015 were reviewed. Incidence rates were age- and sex-adjusted to the 2010 US white population. Age- and sex-adjusted prevalence was calculated on January 1, 2015. Survival rates were compared with expected rates in the Minnesota population.

Results—Of 58 incident cases of AAV, 23 (40%) were GPA, 28 (48%) MPA, and 7 (12%) EGPA. Overall, 28 (48%) were women, 57 (98%) were Caucasian, with a mean±SD age at diagnosis of 61.1±16.5 years. Thirty-four patients (61%) were MPO-ANCA and 17 (30%) were PR3-ANCA positive; 5 (9%) were ANCA-negative.

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DISCLOSURE INTEREST: Disclosure statement for all authors: The authors have no financial or non-financial potential conflicts of interest to declare related to this project.

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The annual incidence of AAV was 3.3/100,000 population (95%CI: 2.4–4.1). GPA, MPA and EGPA incidence was 1.3 (95%CI: 0.8–1.8), 1.6 (95%CI: 1.0–2.2), and 0.4 (95%CI: 0.1–0.6), respectively. Overall prevalence of AAV was 42.1/100,000 (95%CI: 29.6–54.6). Mortality for AAV overall, and EGPA, MPA and MPO-ANCA was increased ($p<0.05$); mortality of GPA, PR3-ANCA and ANCA-negative patients did not differ from general population.

Conclusion—The annual incidence of AAV in Olmsted County is 3.3/100,000, with prevalence of 42.1/100,000, substantially higher than reported in other areas worldwide. The incidence of GPA and MPA is similar. Mortality of MPA and EGPA, but not GPA, is higher than the general population; MPO-ANCA is a marker of poor survival.

Keywords

ANCA-associated vasculitis; epidemiology; incidence; prevalence; mortality; MPO; PR3; GPA; MPA; EGPA; ANCA-negative; United States; U.S.

INTRODUCTION

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) are systemic, necrotizing vasculitides affecting small and medium-sized blood vessels collectively called ANCA-associated vasculitides (AAV), because of their frequent association with circulating antineutrophil cytoplasmic autoantibodies (ANCA) targeting either proteinase 3 (PR3) or myeloperoxidase (MPO) (1). Association of PR3-ANCA and MPO-ANCA with clinical diagnoses (GPA, MPA, EGPA) is variable, and evidence is mounting in support of integrating the presence and specificity of ANCA into the categorization of patients as it conveys clinical and prognostic information (2–4).

Overall, AAV are rare, with a worldwide reported annual incidence ranging from 1.2 to 2.0 cases per 100,000 individuals and a prevalence of 4.6–18.4 cases per 100,000 individuals (5). There appears to be some geographic variation in AAV, with higher incidence of GPA in northern Europe and Australia, and a higher frequency of MPA in southern Europe and Asia (5–11) (12–17). To date, precise data on AAV incidence, prevalence, and mortality are lacking in the United States (US).

In the US, the only population-based analysis of AAV frequency showed that the annual adjusted (to the US population) incidence of GPA was 0.83 cases per 100,000 population (95% confidence interval [CI], 0.25–1.42), roughly similar to estimates from northern Europe (18). Previous epidemiological studies from the US reported discrepant prevalence for GPA, between 3.2 and 9.1 per 100,000 population (19, 20). The only published data on GPA mortality in the US are derived from a non-population based study, which reported an annual mortality rate of 0.08 per 100,000 population (20). To date, the only available data on MPA from the US reported a prevalence of 1.3 per 100,000 population (19), whilst there are no data on EGPA epidemiology in the US. Taken altogether, most information about the epidemiology of GPA, MPA and EGPA are derived from European and other non-US studies, while little is known about the epidemiology of AAV in the US. Further information on published U.S. epidemiology data are provided in Supplementary Table 1.

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The aim of the present study was to determine the annual incidence, prevalence and mortality of GPA, MPA and EGPA in the US from 1996 through 2015 in a population based cohort of patients from Olmsted County, Minnesota, and to characterize AAV epidemiology by clinical diagnosis as well as ANCA specificity at diagnosis.

METHODS

Study design and case ascertainment

For this population based study, all patients were residents of Olmsted County, Minnesota. This population is well suited for investigation of the epidemiology of AAV. The Rochester Epidemiology Project (REP), a medical records linkage system, allows ready access to the complete (inpatient and outpatient) records from all healthcare providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes and the few private practitioners. The potential of this data system for population-based research and the generalizability of its results have been previously described (21, 22). This system ensures virtually complete clinical information on all clinically recognized cases of AAV among Olmsted County residents. The total population of Olmsted County was 106,470 in 1990 and rose to 144,248 in 2010 with 72.3% and 74.7% aged ≥18 years, respectively. The ethnic distribution was 95.7% White in 1990 and by 2010 was 85.7% White with 4.2% Hispanic, 4.8% African-American, 5.5% Asian/Native Hawaiian/Pacific Islander, and 0.2 % American Indian/Alaska Native. The study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

The potential cases were all residents of Olmsted County, Minnesota on January 1, 2015 for the prevalence cohort, or at the time of their initial diagnosis from January 1, 1996 to December 31, 2015 for the incident cohort. Patients were selected based on diagnostic codes for AAV (ICD-9: 446.0, 446.4; ICD-10: M31.30, M30.1, M31.31, M31.7). To ensure a complete detection of all potential cases, we also searched the laboratory database for positive ANCA test results, detected by both ELISA technique and conventional immunofluorescence (Figure 1).

Patients had to meet the criteria of at least one of the following classification schemes to be included: American College of Rheumatology (ACR) classification criteria or the modified ACR criteria for GPA (23) (24), ACR criteria for EGPA (25), Chapel Hill Consensus Conference (CHCC) definition (26), or European Medical Agency (EMA) algorithm (27). The review of medical records, case identification, and data collection was carried out by the investigators, all with expertise in vasculitis. The date of first diagnosis was collected and all patients followed-up until January 1, 2015, or death. Dates of death are routinely tracked and documented by each healthcare provider in the REP with augmentation from electronic Minnesota State Death Certificates and the National Death Index for those who migrate out of the region and die outside Minnesota (28).

All individual medical records from identified patients were reviewed. Information on patient demographics, clinical manifestations, laboratory findings, histopathology, radiology, and disease activity at baseline were retrieved. The Modification of Diet in Renal Disease

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(MDRD) was used for the estimation of glomerular filtration rate (eGFR). Hyper-eosinophilia was defined as >10% and/or >1500 cells/μL. Data required to compute Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) (29) at AAV diagnosis were also abstracted from the medical records.

Statistical analyses

Descriptive statistics (means, medians, interquartile ranges (IQR), percentages, etc.) were used to summarize the data. Comparisons of patient features between clinical diagnosis or antibody type groups were performed using Chi-square and rank sum tests. Age- and sex-specific annual incidence rates were calculated using the number of incidence cases as the numerator and population estimates for adults (age ≥18 years) based on decennial census counts as the denominator, with linear interpolation to estimate population size for intercensal years. Prevalence rates on January 1, 2015 were calculated using the number of prevalent cases as the numerator and the population estimates for adults (age ≥18 years) from the census as the denominator. Overall incidence and prevalence rates were age- and sex-adjusted to the 2010 US white population. Trends in annual incidence rates were examined using Poisson regression methods with smoothing splines for age and calendar year. The annual incidence rates were graphically illustrated using a 3-year, centered, moving average to reduce the random fluctuations over time.

Survival following the diagnosis of AAV and of the different subgroups (GPA, MPA, EGPA and PR3-ANCA, MPO-ANCA, ANCA-negative) was estimated using Kaplan-Meier methods. Observed and expected survival rates were compared using the log-rank test, where expected survival for persons of the same age, sex and calendar year was estimated using Minnesota population life tables. The ratio of observed number of deaths to the expected number, the standardized mortality ratio (SMR), was estimated. Ninety-five percent confidence intervals (CI) were computed for the SMR assuming that the expected rates are fixed and the observed number of deaths follows a Poisson distribution. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic, clinical and laboratory findings of the incidence cohort at diagnosis

Demographic and clinical characteristics of the 58 patients who received a new diagnosis of AAV (23 GPA, 28 MPA and 7 EGPA; 30 men and 28 women) in Olmsted County between 1996 and 2015 are summarized in Table 1. Patients with MPA were more than 10 years older on average than those with GPA or EGPA (67.7±16.2 years vs 56.1±15.1 and 51.5±13.4 years, respectively). The majority of the patients were Caucasians (98%), and only 1 patient was native American.

A summary of clinical manifestations at diagnosis for each disease entity is provided in Table 1. In GPA, the most common disease features at diagnosis were otorhinolaryngological (74%), followed by “general” (57%) and pulmonary (48%) manifestations. Renal involvement was by far the most common finding at diagnosis in MPA

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(82%), with significantly impaired renal function by mean baseline eGFR and creatinine levels compared to patients with GPA and EGPA. Asthma and pulmonary involvement other than asthma were each present at diagnosis in 86% of patients with EGPA. Cutaneous involvement and general manifestations were each present in 71% of patients with EGPA, and renal involvement was present in 57%. All the patients with EGPA had hypereosinophilia at diagnosis, and nasal polyposis was observed in 29% of these cases. Overall, patients with GPA and MPA had similar BVAS/WG scores at diagnosis (median [IQR] 5.0 [3.0,8.0] versus 6.0 [4.0,7.0], respectively).

ANCA antibody testing was performed in almost all patients at diagnosis (Table 1). Overall, ANCA testing was negative at initial evaluation in 9% of the entire AAV cohort, in 14% of GPA cases and in 33% of the EGPA cases. In contrast, MPO-ANCA was present in 100% of MPA cases. There was 100% concordance between the immunofluorescence findings (cytoplasmic (c)-ANCA versus p-ANCA) and antigen-specific immunoassay findings (PR3-ANCA versus MPO-ANCA) in all ANCA-positive patients.

Incidence of AAV in the general population

The overall annual incidence rate for AAV was 3.3 (95%CI: 2.4–4.1) per 100,000 adults adjusted for age and sex to the US population (Table 2). Annual incidence was overall higher in males compared to females, mainly in patients between 45 and 74 years of age.

The age- and sex-adjusted annual incidence rate of GPA for the adult population was 1.3 (95%CI: 0.8–1.8) per 100,000 population. The overall age- and sex-adjusted annual incidence rate in adult women was 1.2 (95%CI: 0.5–2.0) and in adult men 1.3 (95%CI: 0.5–2.0) per 100,000. The age- and sex-adjusted annual incidence rate for MPA for the adult population was 1.6 (95%CI: 1.0–2.2) per 100,000 population; for women it was 1.5 (95%CI: 0.7–2.3) and for men 1.8 (95%CI: 0.8–2.8) per 100,000 population. Unlike GPA, annual incidence in MPA increased progressively with age, culminating at 7.2 per 100,000 in individuals aged 75 years or more. In EGPA, the age- and sex-adjusted annual incidence for the adult population was 0.4 (95%CI: 0.1–0.6) per 100,000 population; 0.1 (95%CI: 0.0–0.3) for women and 0.7 (95%CI: 0.1–1.2) per 100,000 for men.

Annual Incidence rates were then calculated based on ANCA type. PR3-ANCA was present in 17 patients, MPO-ANCA in 34 patients, and 5 patients had no detectable ANCA (Table 2). The age- and sex-adjusted annual incidence rate of PR3-AAV for the adult population was 0.9 (95%CI: 0.5–1.4) per 100,000 population, with an annual incidence rate in adult women of 0.8 (95%CI: 0.2–1.3) per 100,000, and in adult men of 1.1 (95%CI: 0.4–1.8) per 100,000. Age- and sex-adjusted annual incidence rate in adults for MPO-AAV was 2.0 (95%CI: 1.3–2.6) per 100,000 population, with an incidence for women of 1.7 (95%CI: 0.8–2.5), and for men of 2.4 (95%CI: 1.3–3.5) per 100,000 population. Notably, the annual incidence of diagnosis of PR3-AAV was higher between 45–65 years of age, whereas the rate of MPO-AAV progressively increased after 45 years of age (Table 2). Annual incidence of ANCA-negative AAV was 0.3 (95%CI: 0.0–0.5) per 100,000 population, 0.3 (95%CI: 0.0–0.7) for women and 0.2 (95%CI: 0.0–0.6) for men.

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The evolution of age- and sex-adjusted annual incidence rates of AAV in aggregate, and GPA and MPA over the 20 years of the study are shown in Figure 2A. The EGPA incidence trend was not examined because of small number of patients. Even though there is some variation by sex, globally there was similar fluctuation in annual incidence of either AAV or its subsets, GPA and MPA, with a peak around 2005. Overall, annual incidence did not significantly change during the years from 1996 through 2015 ($p>0.05$ in all cases). Figure 2B shows the annual age- and sex-adjusted annual incidence per 100,000 of PR3-ANCA and MPA-ANCA AAV in adults. The ANCA-negative AAV incidence trend was not examined because of its small sample size. Similar fluctuations in annual incidence as observed in AAV, GPA and MPA could be seen in patients with PR3-ANCA and MPO-ANCA, with a similar peak around 2005. Albeit an overall increase of PR3-AAV incidence during the last 2 decades ($p<0.01$), global annual incidence of all AAV and MPO-AAV remained stable.

Mortality of patients with AAV compared to the general population

There were 20 deaths among the 58 patients in this AAV incident cohort (Table 3). Age- and sex-adjusted mortality was compared to the general population over a median [IQR] follow-up of 6.0 [2.8, 11.2] years. With 9.8 expected deaths, the SMR for the entire AAV incident cohort 1996–2015 was 2.04 (95%CI: 1.24–3.14) (Figure 3A). A significantly higher SMR was observed in MPA (2.04; 95%CI: 1.09–3.49) and EGPA 16.60 (95%CI: 4.52–42.50), with a 5- and 10-year survival rate of 73% (95%CI: 57–92%) and 50% (95%CI: 33–78%) for MPA (Figure 3B) and 86% (95%CI: 63–100%) and 43% (95%CI: 15–100%) for EGPA. Survival of patients with GPA was not significantly different than that of the general population (0.93; CI95%: 0.19–2.73) (Figure 3C), with stable 5- and 10-year survival rates of 90% (95%CI: 78–100%).

When the cohort was stratified for ANCA type, the SMR for patients with PR3-ANCA and MPO-ANCA was 1.09 (95%CI: 0.13–3.95) and 2.17 (95%CI: 1.24–3.52), respectively. The 5- and 10-year survival rate was 74% (95%CI: 59–91%) and 51% (95%CI: 34–75%) for MPO-ANCA patients (Figure 3D), 93% (95%CI: 82–100%) and 86% (95%CI: 70–100%) for PR3-ANCA patients (Figure 3E). There were no deaths among the ANCA negative patients.

Prevalence of AAV

A total of 44 patients with a diagnosis of AAV were living in Olmsted County on January 1, 2015. Most were women (59%), white (98%), with a mean (±SD) age of 63.6±17.4 years and a mean disease duration of 8.8±6.5 years with no significant difference between GPA, MPA and EGPA. C-ANCA/PR3-ANCA were positive in 47% of cases, p-ANCA/MPO-ANCA in 47% of cases, and ANCA were negative in 7% of cases. Further detail is provided Supplementary Table 2.

On January 1, 2015, the age- and sex-adjusted prevalence of AAV in adults (age ≥18 years) was 42.1 (95%CI: 29.6–54.6) per 100,000 population (Supplementary Table 3); 45.2 (95%CI: 27.8–62.6) among women, 38.6 (95%CI: 20.5–56.6) per 100,000 among men. The age- and sex-adjusted prevalence of GPA was 21.8 (95%CI: 12.9–30.8) per 100,000 population, with no difference between women and men. The age- and sex-adjusted

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prevalence of MPA was 18.4 (95%CI: 10.1–26.7) per 100,000. The age- and sex-specific prevalence of MPA was higher in older patients, with an overall female prevalence of 24.3 (95%CI: 11.5–37.0) per 100,000, compared to male prevalence of 11.5 (95%CI: 1.3–21.6) per 100,000. The overall age- and sex-adjusted prevalence of EGPA was 1.8 (95%CI: 0.0–4.4) per 100,000, and was similar in men (2.1 per 100,000; 95%CI: 0.0–6.1) and women (1.6 per 100,000; 95%CI: 0.0–4.8).

When patients were stratified based on the ANCA type (Supplementary Table 3), the PR3-AAV age- and sex-adjusted prevalence in adults was 19.0 (95%CI: 10.6 –27.3) per 100,000, with a similar prevalence by sex. Prevalence of MPO-AAV was 19.2 (95%CI: 10.8–27.7) per 100,000, 22.5 (95%CI: 10.3–34.8) among women and 15.3 (95%CI: 3.8–26.8) per 100,000 among men. Finally, the age- and sex-adjusted prevalence in adults with ANCA-negative disease was 2.8 (95%CI: 0.0–6.1) per 100,000, with a female predominance (female 5.3 per 100,000, 95%CI: 0.0–11.2; male 0.0 per 100,000).

DISCUSSION

The current study is the first to describe the annual incidence, prevalence and mortality rates of AAV in a geographically well-defined region in the US, and their evolution over a period of 20 years. To the best of our knowledge, this is also the first population-based study that systematically compares the epidemiological features of these patients by conventional clinical diagnosis, namely GPA, MPA and EGPA, and by ANCA status and specificity over such a long period of time. This is the highest incidence and prevalence ever reported for AAV, with rates above what was previously published, following only giant cell arteritis among systemic vasculitides (30). Overall, the estimated annual incidence of AAV in Olmsted County in 1996–2015 was 3.3 per 100,000 population, remarkably higher than the previous reports, without a significant change in incidence over the two decade period of the study. Prevalence was estimated around 42.1 per 100,000 population, and the overall mortality rates were significantly higher than the expected rates in the general population, although the base population is relatively small. Interestingly, we observed a higher GPA incidence compared to the previous US (18) and non-US published data (5–11). In particular, compared to the previous report, the annual US-adjusted annual incidence of GPA increased from 0.83 cases per 100,000 in the early 1990s to 1.3 cases per 100,000 in the last two decades. An increased incidence of GPA has been reported in other parts of the world in the 1990s and early 2000s, possibly related to the increasingly widespread use of ANCA testing and physician awareness for this spectrum of diseases (6, 11, 31, 32). Results from the current study suggest that, while disease detection probably increased just after the introduction of ANCA testing when compared to the previous decades, the incidence trends have been stable over the past 20 years.

Surprisingly, we found that the annual incidence of MPA is similar to the incidence of GPA. This result is intriguing and challenges the prevailing notion that incidence of GPA is higher than MPA in the Western world (5, 7, 11, 12, 33), in contrast to Japan, where MPA frequency is two to three times higher than GPA (8). The proportion of GPA cases among total AAV cases is even higher among the populations of northern Europe (10, 31, 34), which share most of the genetic background with the US and particularly Olmsted County

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populations. However, in a recent mixed ethnicity incident cohort from the United Kingdom (UK), MPA also accounts for almost 60% of the cases, and MPO-ANCA for 51%, congruent with our results (35). A study from Sweden reported an annual incidence of GPA 0.98 per 100,000, and for MPA of 1.01 per 100,000 population (33). These results are similar to those of the current study and are consistent with other publications from Northern Europe reporting similar rates for MPA and GPA, whereby the overall incidence of AAV in Olmsted County is somewhat higher than estimates from other reports.

This study sheds new light on the epidemiology of AAV and particularly of MPA in the US, with findings of a higher than expected incidence of MPA, which falls between the estimates from European and Japanese cohorts. These findings suggest an important role of geographical and environmental factors as well as genetic factors (36–39) for the development of GPA and MPA. The influence of environment is perhaps also supported by the observation that the annual incidence of AAV in black and non-white UK residents was not significantly different from Caucasian residents after adjustment for age and sex in a well-defined population (35). Additional epidemiological research is needed to identify potential environmental factors that may contribute to disease expression of AAV.

The prevalence of AAV was also higher than previously reported in the US (19, 20) and outside the US (5, 6, 9, 10, 40, 41). Reported prevalence of GPA in other US cohorts between 1986 and 1990 was 3.2 cases/100,000 population (New York State) (20) and between 1993 and 2006 was 9.1 cases per 100,000 population (Western Montana) (19), compared to 21.8 per 100,000 in the present study. The sole estimation of the prevalence of MPA in the US was reported as 1.3 cases per 100,000 population (19), a figure which appears inconsistent with the prevalence of GPA from the same report (7 times higher), and maybe a consequence of the methodological limits of this study (hospital-based study). When compared to these data, the prevalence of AAV is consistently higher, especially for GPA and MPA. This could also be due to the ability to capture all cases of AAV using the REP, which allowed complete full access to a comprehensive coding system and to all individual medical records of the screened patients, permitting exhaustive case detection in the general population living in Olmsted County, including patients with mild/localized AAV. Other potential factors accounting for dissimilarities in estimates of disease in populations can include but certainly are not limited to differences in population demographics, environment, the population used as denominator (total or only adult population), healthcare access and secular trends in both disease occurrence and disease severity. Indeed, while the incidence of GPA and MPA reported in this study is slightly higher than previously reported elsewhere, the prevalence of these diseases is more substantially increased (11, 12, 32, 34). While the reasons for this finding remain unclear, it is conceivable that the prevalence of AAV may be increasing because of an improved life expectancy in recent decades with improved treatments, possibly less severe or earlier disease detection and management, or better access to healthcare in Olmsted County (42, 43). The ultimate causes, eventually, remain unknown.

There are scarce epidemiological data on EGPA, which represent only 10–20% of AAV cases (5, 11). Reported prevalence in our study was 1.8 per 100.000 inhabitants, not greatly different from those reported for white, Middle Eastern or Asian populations, with the

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highest rate reported in Northern of Germany, 2.4 per 100.000 (5, 11,) (9, 41) (32). However, incidence (0.4 per 100,000 inhabitants) resulted the highest ever reported for this disease (previously, the highest rate was reported in Norwich (UK), 0.27 per 100,000) (12).

The mortality in patients with incident AAV in Olmsted County was overall higher that the general population. This result was driven by the mortality of MPA and EGPA. Previous studies showed that survival among individuals with AAV was significantly reduced compared to sex and aged-matched populations (6, 8, 44–47), with older age as the most reported risk factor (9, 48), mainly due to lower survival among patients with MPA (47). This finding could also have been influenced by an often compromised renal function of MPA patients, which has been demonstrated to be a predictor of mortality (49).

Surprisingly, we observed that GPA related mortality is no longer increased compared to the general population (6, 50–54). Reasons for this observation of improved survivorship are uncertain but probably influenced by improved case identification, as shown by the increased incidence, and likely by close and consistent multi-specialty follow-up in a tertiary care center once diagnosis was established. Moreover, complete case ascertainment using the REP allowed capture of patients with mild/localized GPA with better prognosis.

Interestingly, in our cohort the survival rate for EGPA and MPA continued to decrease during the 10 years after diagnosis, in contrast with previous reports that attributed a higher AAV mortality to the first year (6, 53). This finding may reflect modern immunosuppressive strategies for AAV (42, 43, 50), leading to remission in more than 90% of cases and thus improved survival in the first year, although survivorship in EGPA and MPA is overall still lower than for GPA.

Purely electronic-based dataset analyses, even using complex algorithms, are not totally satisfactory for case ascertainment and verification (20). In fact, the use of only diagnostic codes leads to the inclusion of patients without confirmed disease. Specificity may be enhanced by adding supplemental information in more complex algorithms (as for instance presence of eosinophilia or physician specialty), as elegantly showed by Sreih et al (55), but this may lower the sensitivity of the screening method. The present study did not rely on a purely automated case-finding algorithm, but included screening of cases without an AAV diagnostic code but with concordant ANCA tests (MPO/p-ANCA or PR3/c-ANCA) identified on the basis of laboratory results review. Diagnosis specificity was increased by excluding those patients not fulfilling classification ACR/CHCC/EMA criteria on detailed review of the individual medical record. This broader screening method and detailed chart review enhanced the sensitivity and specificity of case retrieval.

A further strength of the current study is the evaluation of data by both clinical diagnosis classification as well as the ANCA-type classification. Despite the much higher incidence of MPO-AAV compared to PR3-AAV (2.0 per 100,000 vs 0.9 per 100,000), their prevalence is similar (19.2 per 100,000 vs. 19.0 per 100,000), due to the increased mortality of MPO-AAV patients. Hence, MPO-AAV patients represented 61% of the incident cohort versus only 47% of the patients at the prevalence date. Presence of MPO-ANCA could be therefore

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considered as marker of low survival compared to PR3-ANCA positivity and ANCA-negative state among all patients, including those with EGPA.

The results of this study can be generalized to adult subjects with similar age, sex, race/ethnicity, living in the Midwest or northern states of the US. They may or may not reflect AAV in communities with a different racial/ethnic composition, as those with high prevalence of African Americans or Asians. Other limitations include the retrospective and descriptive nature of the study, and the inability to examine the influence of treatment on prevalence and mortality trends.

In summary, the annual incidence of AAV in this US population is 3.3 per 100,000 and its prevalence in 2015 is 42.1 per 100,000, remarkably higher than previously reported. The incidence and prevalence of overall AAV, and GPA, MPA, EGPA are higher than most of previous reports. In contrast with most of the previous European studies, GPA and MPA have similar incidence rates. Finally, mortality of MPA, EGPA and MPO-ANCA patients is higher than in the general population, whereas mortality of GPA does not substantially differ from the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Divi Cornec received fellowship grants from the French Society of Rheumatology and from Brest University Hospital, France. Funding: This study was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health under Award Number R01AG034676, and CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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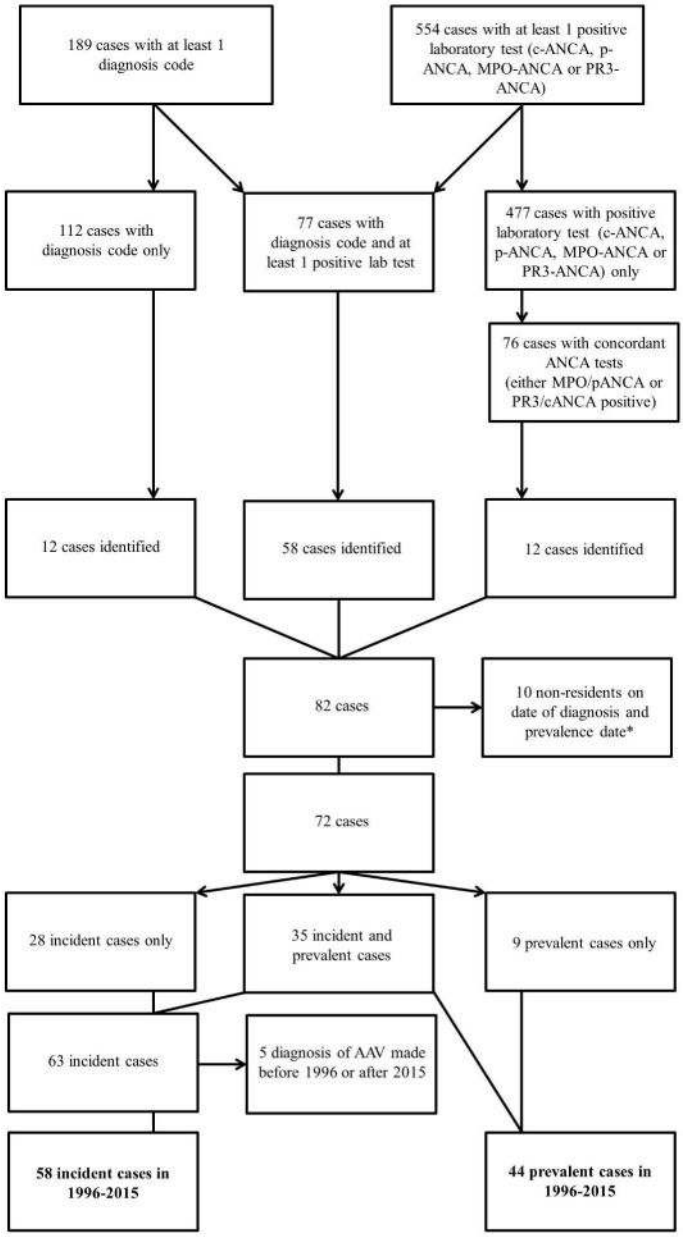

Figure 1.

Algorithm representing the screening process for the identification of the patients with ANCA-associated vasculitis diagnosed in Olmsted County, Minnesota (USA) from 1996 to 2015.

Footnotes: *All the patients aged < 18 years were excluded due to residency coincidentally.

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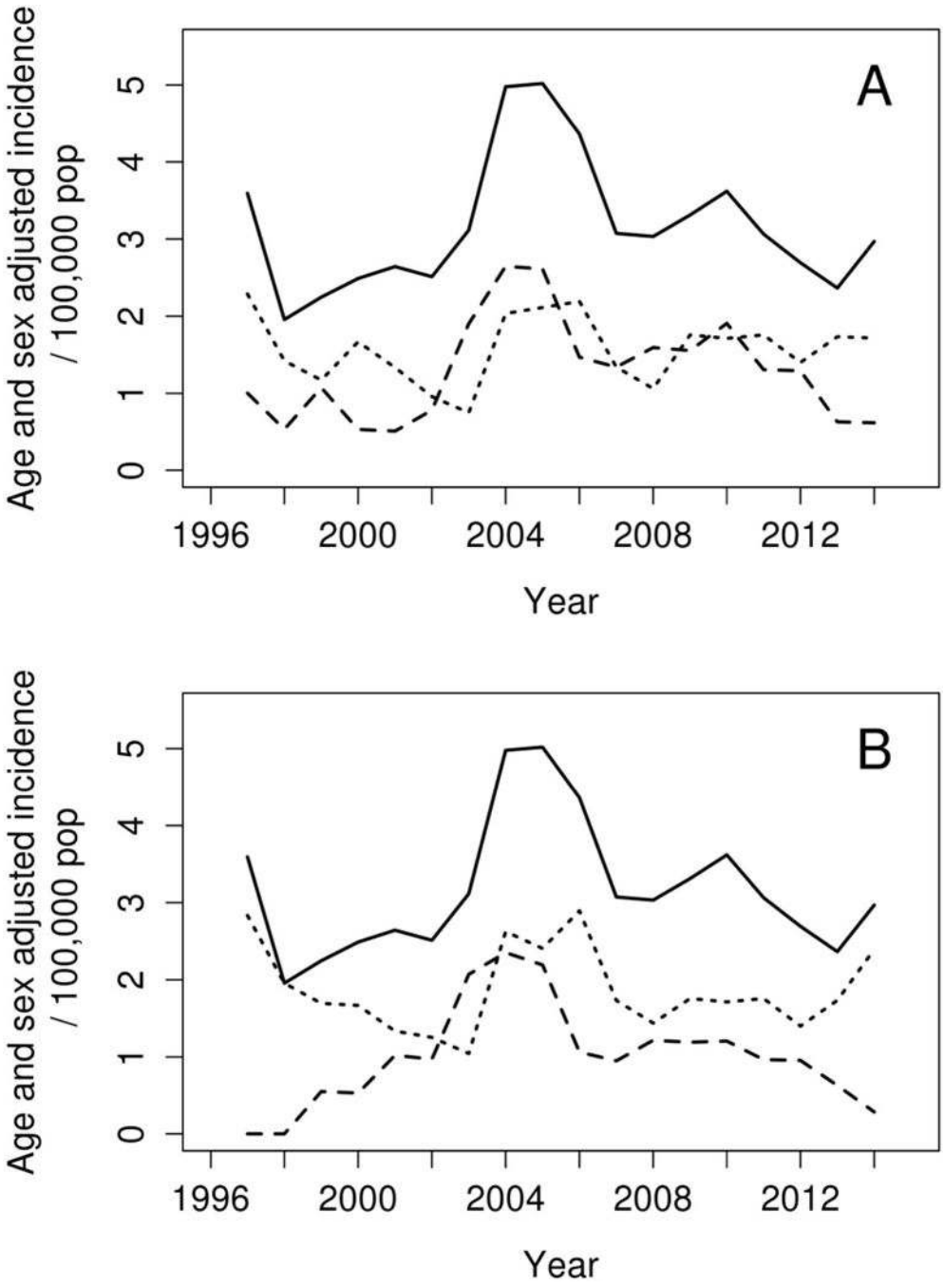

Figure 2.

Age- and sex-adjusted incidence rates of ANCA-associated vasculitis in adults (age ≥18 years) in Olmsted County, Minnesota. (**A**) Annual incidence of the entire AAV cohort (solid line), GPA (dashed line) and MPA (dotted line). (**B**) Annual incidence of the entire AAV cohort (solid line), PR3-ANCA patients (dashed line) and MPO-ANCA patients (dotted line). Annual incidence trends of EGPA and ANCA-negative patients were not examined due to small sample size.

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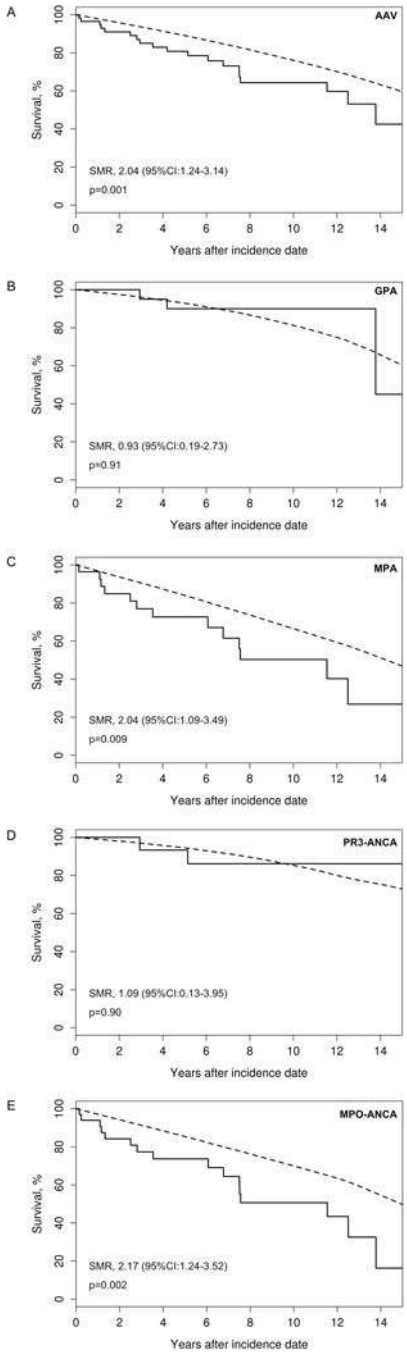

Figure 3.

Survival rates of Olmsted County residents with ANCA-associated vasculitis compared to expected rates from Minnesota lifetables (observed, solid line; expected dashed line): entire AAV cohort (**A**), stratified by diagnosis (**B, C**) or by ANCA status and specificity (**D, E**). Survival rates of EGPA and ANCA-negative patients were not examined due to small sample size.

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Table 1

Features of patients with incident ANCA associated vasculitis diagnosed in Olmsted County, Minnesota 1996 to 2015.

Characteristic	GPA (N=23)	MPA (N=28)	EGPA (N=7)	Total (N=58)	p value
Age, years, mean (SD)	56.1 (15.1)	67.7 (16.2)	51.5 (13.4)	61.1 (16.5)	**0.004**
Sex, female	12 (52%)	15 (54%)	1 (14%)	28 (48%)	0.158
Ethnicity, Caucasian †	23 (100%)	27 (96%)	7 (100%)	57 (98%)	0.580
Biopsy, performed	18 (78%)	19 (68%)	6 (86%)	43 (74%)	0.530
Biopsy, positive	10 (56%)	15 (79%)	5 (83%)	30 (70%)	0.222
BVAS, median [IQR]	5.0 [3.0, 8.0]	6.0 [4.0, 7.0]	9.0 [7.0, 12.0]	6.0 [3.0, 8.0]	0.071
General *	13 (57%)	11 (39%)	5 (71%)	29 (50%)	0.227
Cutaneous *	4 (17%)	4 (14%)	5 (71%)	13 (22%)	**0.004**
Mucous membrane/Eyes *	2 (9%)	0 (0%)	0 (0%)	2 (3%)	0.207
Ear, Nose and Throat *	17 (74%)	4 (14%)	2 (29%)	23 (40%)	**<0.001**
Pulmonary *	11 (48%)	12 (43%)	6 (86%)	29 (50%)	0.123
Gastrointestinal *	–	–	–	–	–
Renal *	10 (43%)	23 (82%)	4 (57%)	37 (64%)	**0.016**
Cardiovascular *	1 (4%)	0 (0%)	0 (0%)	1 (2%)	0.461
Nervous System *	5 (22%)	3 (11%)	5 (71%)	13 (22%)	**0.003**
Asthma	–	–	6 (86%)	–	–
Hemoglobin ** (SD), g/dL	12.1 (2.4)	10.4 (1.6)	10.5 (1.0)	11.1 (2.0)	**0.040**
WBC ** (SD), 10^9/L	10.1 (4.2)	10.6 (4.2)	16.3 (7.8)	11.0 (5.0)	0.152
Eosinophils ** (SD), 10^9/L	–	–	6.8 (4.7)	–	–
Platelets ** (SD), 10^9/L	337.5 (123.2)	313.0 (140.4)	368.0 (124.3)	328.3 (131.3)	0.412
ESR ** (SD), mm/1 hr	31.6 (26.6)	57.7 (37.2)	59.0 (42.9)	48.0 (36.0)	0.055
CRP ** (SD), mg/L	35.7 (56.4)	50.1 (80.7)	54.8 (53.9)	45.1 (66.9)	0.458
Creatinine ** (SD), mg/dL	1.7 (1.5)	2.4 (1.6)	1.2 (0.7)	2.0 (1.5)	**0.035**
eGFR ** (SD), mL/min/1.73 m^2	60.9 (34.6)	39.3 (29.1)	73.3 (26.4)	51.8 (33.2)	**0.021**

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Characteristic	GPA (N=23)	MPA (N=28)	EGPA (N=7)	Total (N=58)	p value
ANCA groups[***]					**<0.001**
ANCA-negative	3 (14%)	0 (0%)	2 (33%)	5 (9%)	–
p-ANCA/MPO-ANCA	3 (14%)	28 (100%)	3 (50%)	34 (61%)	–
c-ANCA/PR3-ANCA	16 (73%)	0 (0%)	1 (17%)	17 (30%)	–

[†] All but one patient (a Native American) were Caucasian

[*] System involvement was detailed according to the BVAS items.

[**] General laboratory data not available in all patients (Hb, WBC, platelets missing in 2 GPA and 1 EGPA patient; ESR missing in 5 GPA, 4 MPA and 1 EGPA patients, CRP missing in 8 GPA, 11 MPA and 1 EGPA patients).

[***] No data on ANCA testing at diagnosis was available for 1 patient with GPA and 1 with EGPA

Abbreviations: ANCA=anti-neutrophil cytoplasmic antibodies; c-ANCA=cytoplasmic ANCA; p-ANCA=perinuclear ANCA; BVAS/WG=Birmingham Vasculitis Activity Score for Wegener's Granulomatosis; CRP= C-reactive protein; EGPA=eosinophilic granulomatosis with polyangiitis; ESR=erythrocyte sedimentation rate; eGFR=estimated glomerular filtration rate, by means the Modification of Diet in Renal Disease (MDRD) study equation; GPA=granulomatosis with polyangiitis; MPA-microscopic polyangiitis; MPO=myeloperoxidase;N=number; PR3=proteinase-3; SD=standard deviation; WBC=white blood cells.

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Table 2

Annual incidence of ANCA-associated vasculitis among residents of Olmsted County, Minnesota in 1996–2015 by sex and age group, per 100,000 population age ≥18 years.

		Clinical Diagnosis								ANCA Type*					
		Overall AAV		GPA		MPA		EGPA		PR3-ANCA		MPO-ANCA		ANCA negative	
	Age group	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Overall	**18–44**	11	1.1	4	0.4	4	0.4	3	0.3	3	0.3	6	0.6	1	0.1
	45–54	8	2.1	6	1.5	1	0.3	1	0.3	6	1.5	1	0.3	1	0.3
	55–64	13	4.9	7	2.6	4	1.5	2	0.8	5	1.9	6	2.3	2	0.8
	65–74	13	7.9	4	2.4	8	4.8	1	0.6	2	1.2	10	6.1	1	0.6
	75+	13	8.5	2	1.3	11	7.2	0	0.0	1	0.7	11	7.2	0	0.0
	Overall [a] (95% CI)	**58**	**3.3 (2.4, 4.1)**	**23**	**1.3 (0.8, 1.8)**	**28**	**1.6 (1.0, 2.2)**	**7**	**0.4 (0.1, 0.6)**	**17**	**0.9 (0.5, 1.4)**	**34**	**2.0 (1.3, 2.6)**	**5**	**0.3 (0.0, 0.5)**
Female	**18–44**	7	1.4	3	0.6	3	0.6	1	0.2	3	0.6	3	0.6	1	0.2
	45–54	3	1.5	2	1.0	1	0.5	0	0.0	2	1.0	1	0.5	0	0.0
	55–64	4	2.9	3	2.2	1	0.7	0	0.0	1	0.7	2	1.5	1	0.7
	65–74	6	6.8	2	2.3	4	4.5	0	0.0	1	1.1	4	4.5	1	1.1
	75+	8	8.5	2	2.1	6	6.3	0	0.0	1	1.1	6	6.3	0	0.0
	Overall [b] (95% CI)	28	**2.9 (1.8, 3.9)**	12	**1.2 (0.5, 2.0)**	15	**1.5 (0.7, 2.3)**	1	**0.1 (0.0, 0.3)**	8	**0.8 (0.2, 1.3)**	16	**1.7 (0.8, 2.5)**	3	**0.3 (0.0, 0.7)**
Male	**18–44**	4	0.9	1	0.2	1	0.2	2	0.4	0	0.0	3	0.6	0	0.0
	45–54	5	2.6	4	2.1	0	0.0	1	0.5	4	2.1	0	0.0	1	0.5
	55–64	9	7.0	4	3.1	3	2.3	2	1.6	4	3.1	4	3.1	1	0.8
	65–74	7	9.1	2	2.6	4	5.2	1	1.3	1	1.3	6	7.8	0	0.0
	75+	5	8.6	0	0.0	5	8.6	0	0.0	0	0.0	5	8.6	0	0.0
	Overall [b] (95% CI)	30	**3.8 (2.4, 5.1)**	11	**1.3 (0.5, 2.1)**	13	**1.8 (0.8, 2.8)**	6	**0.7 (0.1, 1.2)**	9	**1.1 (0.4, 1.8)**	18	**2.4 (1.3, 3.5)**	2	**0.2 (0.0, 0.6)**

[a] Age- and sex- adjusted to US white 2010 population

[b] Age- adjusted to US white 2010 population

* ANCA antibodies were not tested for 2 patients, who were excluded from this analysis

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Abbreviations: AAV=ANCA associated vasculitis; ANCA=anti-neutrophil cytoplasmic antibodies; CI=confidence interval; EGPA=eosinophilic granulomatosis with polyangiitis; GPA=granulomatosis with polyangiitis; MPA-microscopic polyangiitis; MPO=myeloperoxidase; N=number; PR3=proteinase-3

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Table 3

Mortality and Survival rates for Olmsted County residents with incident ANCA-associated vasculitis in 1996–2015.

Measure	All AAV	GPA	MPA	EGPA	PR3-ANCA*	MPO-ANCA*	ANCA negative*
Number of patients	58	23	28	7	17	34	5
Number of deaths	20	3	13	4	2	16	0
Expected number of deaths	9.8	3.2	6.4	0.2	1.8	7.4	0.3
Standardized mortality ratio (95% CI)	2.04 (1.24, 3.14)	0.93 (0.19, 2.73)	2.04 (1.09, 3.49)	16.60 (4.52, 42.50)	1.09 (0.13, 3.95)	2.17 (1.24, 3.52)	0 (0, 13.87)
1-sample log rank test p-value	0.001	0.91	0.009	<0.001	0.90	0.002	0.61
2 year survival rate (95% CI)	91 (84, 99)	100	85 (72, 100)	86 (63, 100)	100	84 (72, 98)	100
5 year survival rate (95% CI)	81 (71, 92)	90 (78, 100)	73 (57, 92)	86 (63, 100)	93 (82, 100)	74 (59, 91)	100
10 year survival rate (95% CI)	64 (51, 81)	90 (78, 100)	50 (33, 78)	43 (15, 100)	86 (70, 100)	51 (34, 75)	100

*ANCA antibodies were not tested for 2 patients, who were excluded from this analysis.

Abbreviations: AAV=ANCA associated vasculitis; ANCA=anti-neutrophil cytoplasmic antibodies; CI=confidence interval; EGPA=eosinophilic granulomatosis with polyangiitis; GPA=granulomatosis with polyangiitis; MPA-microscopic polyangiitis; MPO=myeloperoxidase; PR3=proteinase-3