Comorbidities in Patients with Antineutrophil Cytoplasmic Antibody-associated Vasculitis versus the General Population

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ABSTRACT. ***Objective.*** To evaluate the consultation rates of selected comorbidities in patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) compared with the general population in southern Sweden.

Methods. We used data from a population-based cohort of patients with AAV diagnosed between 1998 and 2010 in Southern Sweden (701,000 inhabitants). For each patient we identified 4 reference subjects randomly sampled from the general population and matched for year of birth, sex, area of residence, and index year. Using the population-based Skåne Healthcare Register, we identified relevant diagnostic codes, registered between 1998 and 2011, for selected comorbidities assigned after the date of diagnosis of AAV or the index date for the reference subjects. We calculated rate ratios for comorbidities (AAV:reference subjects).

Results. There were 186 patients with AAV (95 women, mean age 64.5 yrs) and 744 reference persons included in the analysis. The highest rate ratios (AAV:reference) were obtained for osteoporosis (4.6, 95% CI 3.0–7.0), followed by venous thromboembolism (4.0, 95% CI 1.9–8.3), thyroid diseases (2.1, 95% CI 1.3–3.3), and diabetes mellitus (2.0, 95% CI 1.3–2.9). For ischemic heart disease, the rate ratio of 1.5 (95% CI 1.0–2.3) did not reach statistical significance. No statistically significant differences were found for cerebrovascular accidents.

Conclusion. AAV is associated with increased consultation rates of several comorbidities including osteoporosis and thromboembolic and endocrine disorders. Comorbid conditions should be taken into consideration when planning and providing care for patients with AAV. (J Rheumatol First Release June 1 2016; doi:10.3899/jrheum.151151)

Key Indexing Terms:
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Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a group of chronic inflammatory vascular diseases involving multisystemic manifestations in the vast majority of patients. In addition to the negative effect of AAV-specific organ damage and the potential longterm morbidity of widespread inflammation, medications used to treat AAV may predispose patients to a wide variety of toxicities and comorbidities. Prior studies have suggested high rates of organ damage[1], thromboembolic diseases[2,3], and cardiovascular (CV) diseases (CVD) among patients with AAV[4]. Similar findings have been reported for patients with other systemic rheumatic diseases, including rheumatoid arthritis[5] and systemic lupus erythematosus[6]. Despite the availability of effective medications in AAV, which have certainly contributed to improved survival, patients with AAV still have high rates of morbidities and organ damage, attributable to both the disease and its treatment. For health providers and public health officials, it is important to assess the extent of problems of comorbidities among patients with systemic vasculitis. Previous reports on frequencies of comorbidities in AAV originated from either clinical trials or tertiary centers[7,8]. While such studies provided valuable knowledge, the study samples are not representative of either the usual and full spectrum of patients with these diseases or based on discrete population/geographic data. Further, studies

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with such small sample sizes present challenges with generalizability and low statistical power. We studied a relatively large cohort of patients with AAV using a regional register data that has been previously validated for a number of medical conditions and fractures[9,10,11,12,13].

The aims of our study were to determine the consultation rates (here referred to as "comorbidity rates") in a population-based cohort of patients with AAV and to compare these rates with those of randomly sampled reference subjects from the general population matched for age, sex, area of residence, and index year.

MATERIALS AND METHODS

The study area and population. The study was conducted in a well-defined geographical area in southern Sweden, which has previously been described in detail[14]. The population at the time of December 2009 was 701,000. The study area consisted of 2 healthcare districts in the Skåne region (central and southwest) containing 14 municipalities. Women made up 50.4% of the population, and the age distribution was as follows: 0–14 years, 18.8%; 15–54 years, 54.6%; and > 55 years, 26.6% (www.scb.se).

The Skåne Healthcare Register (SHR). The SHR is a central database to which all information on healthcare contacts are transferred. The SHR receives data from all levels of healthcare (from the primary outpatient care to the highly specialized in-hospital care). Each single healthcare consultation (public and private) at any level (physicians or paramedics) generates data entries by the healthcare provider that are transferred to the SHR[11]. The diagnostic codes are included for the public healthcare providers and are classified according to the International Classification of Diseases, 10th ed (ICD-10). All inpatient care is public, while about 30% of all outpatient healthcare is provided by private practitioners.

The AAV cohort. A total of 186 incident cases of AAV (95 women) with patients diagnosed during a 13-year period (1998–2010) were included in our study. Case retrieval, diagnosis, and classification had been described[14]. Patients were identified from clinical and serology registers at all the hospitals in the study area. All available medical records of patients living in the study area at the time of diagnosis were thoroughly reviewed to establish a diagnosis of small-vessel vasculitis. The patients were classified into the 3 AAV phenotypes [granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA)] according to the 2007 European Medicine Agency algorithm[15]. Case ascertainment, review of case records, and data collection were carried out by the last author (AJM). When classification difficulties arose, consensus was reached between 2 authors (AJM and MS).

Demographics and clinical data were collected from time of diagnosis and included age at diagnosis and signs and symptoms at onset. Laboratory data included ANCA serology and organ involvement at diagnosis.

The reference cohort. For each patient with AAV, we randomly sampled 4 reference subjects from the background population and matched for age, sex, area of residence, and index year. To minimize the potential bias of greater healthcare consumption in general by patients with AAV, we included reference subjects from the population who had had at least 1 healthcare encounter during the study period, i.e., not a completely random sample of subjects from the resident population. Reference subjects had to have at least 1 clinic visit during the study period with a diagnosis (any) by any physician in the SHR. We further required that the reference subjects should not have been assigned any of the ICD codes for AAV (i.e., unexposed to the disease).

Linking of data sources. Using the subjects' personal identification number, both the patients with AAV and the reference subjects were linked to the SHR to identify all healthcare visits and all assigned ICD codes. The municipality of the patients' residence address and references were checked against the Swedish Tax Agency on December 31 of each calendar year to verify that the subjects were still residents in the study area. The resulting data included all healthcare contacts for AAV and their reference subjects since diagnosis (or index year). The data included details regarding the site and type of contact, including inpatient or outpatient setting, hospital, specialized ward, length of inpatient stay for each hospitalization, and all assigned ICD-10 diagnosis codes up to a maximum of 8 diagnosis codes at each healthcare contact. The healthcare system in the Skåne region has been using the 10th edition of the ICD codes since 1998. The period searched to identify codes assigned for comorbidities was from January 1, 1998, until December 31, 2011.

The comorbidities. In our study, we counted only the first occurrence of the physician's diagnostic code of a given comorbidity that had to be registered in the SHR after the date of AAV diagnosis for cases and the corresponding index date for reference subjects. These consultation rates are here referred to as "comorbidity rates." The ICD codes searched in our study are listed in Table 1. Ischemic heart diseases (IHD) are referred to any or combinations of angina pectoris, myocardial infarction (or reinfarction), and chronic IHD. Cerebrovascular accidents (CVA) included any condition leading to stroke, including cerebral infarct or bleeding, subarachnoid bleeding, or any cerebrovascular abnormalities that result in stroke. The venous thromboembolic (VTE) diseases in our study included any or both of deep vein thrombosis and pulmonary embolism. We also studied a select number of common osteoporosis-related fractures in the following bones: clavicles, spine, femur, and radius bone. For IHD, CVA, and VTE diseases, only diagnosis codes assigned after hospitalization were included in our analyses to increase the reliability of the diagnosis.

Statistical analyses. We calculated the comorbidity rate by dividing the number of patients or reference persons being diagnosed with the comorbidity of interest by the sum of person-time during the followup period. The person-time was defined as the number of days each person was followed from the date of the diagnosis for AAV or index date for reference person to the end of followup, as previously described[16]. The followup time was calculated from date of diagnosis or index date for reference until the earliest of the following: (1) date of consultation for the comorbidity, (2) death, (3) the date when the case or reference person moved outside the study area, or (4) December 31, 2011. The comorbidity rate ratio was calculated by dividing the comorbidity rate for patients with AAV by the corresponding rate for the reference subjects. A rate ratio of > 1 indicates a higher comorbidity rate in the patients with AAV than among reference subjects. Consequently, a rate ratio of < 1 equals a lower comorbidity rate than for the reference subjects.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board in Lund, Sweden (301-2007 and 2010-517).

Table 1. The ICD-10 codes searched for identification of comorbidities among patients with AAV and the reference population.

Diseases	ICD-10 Codes
Ischemic heart diseases*	I20–I25
Cerebrovascular diseases*	I60–I69
Hypertensive diseases	I10–I15
Diabetes mellitus	E10–E14
Disorders of the lipoprotein metabolism	E78
Venous thromboembolism*	I80.0–I80.9 and/or I26.0–I26.9
Thyroid diseases	E00–E07
Psychological disorders	F00–F99
Osteoporosis	M80–M85

* Comorbidities diagnosed after inpatient (hospitalization). ICD-10: International Classification of Diseases, 10th ed; AAV: antineutrophil cytoplasmic antibody–associated vasculitis.

RESULTS

Our study included data from 186 patients with AAV (95 women). Ninety-two patients were classified as having GPA, 83 patients with MPA, and 11 with EGPA. The mean age of patients with AAV at diagnosis was 64.5 ± 15.8 years. The mean time of followup from date of diagnosis to death or December 31, 2011, was 5.3 ± 3.9 years. The diagnosis was confirmed by histopathology findings in 139 patients (75%). The clinical, demographic, and laboratory characteristics of the AAV cohort are summarized in Table 2. A total of 744 reference subjects were sampled and matched according to the study criteria.

Comorbidity rates. The highest absolute comorbidity rate among patients with AAV (Table 3) was found for hypertension [HTN; 98.8/1000 person-yrs (PY), 95% CI 78.1–123.3], followed by any psychological diagnoses (62.1/1000 PY, 95% CI 46.6–81.0), osteoporosis (47.0/1000 PY, 95% CI 34.0–63.3), diabetes mellitus (DM; 44.3/1000 PY, 95% CI 31.6–60.3), and IHD (30.9/1000 PY, 95% CI 21.0–43.9). The highest absolute comorbidity rate for the reference subjects (Table 3) was HTN (72.2/1000 PY, 95% CI 64.0–81.1), followed by any psychological diagnoses (59.1/1000 PY, 95% CI 51.9–67.0), DM (22.2/1000 PY, 95% CI 18.1–27.0), IHD (20.3/1000 PY, 95% CI 16.5–24.9), and dyslipoproteinemias (19.1/1000 PY, 95% CI 15.4–23.5).

The rate ratios. The rate ratios of comorbidities in AAV are shown in Table 3. The highest rate ratios were obtained for osteoporosis (4.6, 95% CI 3.0–7.0), followed by VTE (4.0, 95% CI 1.9–8.3), thyroid diseases (2.1, 95% CI 1.3–3.3), and DM (2.0, 95% CI 1.3–2.9). The rate ratio of dyslipoproteinemias was significantly lower among patients with AAV than among the reference subjects (0.6, 95% CI 0.3–1.01). There was no increase in the rate ratio of CVA (1.1, 95% CI 0.56–2.0). For the IHD, the rate ratio was 1.5 (95% CI 1.0–2.3), but was not statistically significant. The rate ratio for myocardial infarction was increased to 2.0 (95% CI 1.0–3.6).

Sex-specific rates. As shown in Table 4, there are some differences in the rates and rate ratios of a number of comorbidities when the cohort was stratified by sex. Among men, the highest rate ratio was obtained for osteoporosis, followed by VTE. However, among women, the highest rate ratio was obtained for VTE, followed by osteoporosis, DM, and thyroid diseases. The rate ratio of dyslipoproteinemias was only significantly decreased among men (Table 4).

Table 2. Demographic, laboratory, and clinical characteristics of 186 patients with AAV. Values are n (%) unless otherwise specified.

Characteristics	Values, n = 186
PR3:MPO-ANCA+, n	92:78
Diagnosis of GPA, MPA, EGPA, n	92, 83, 11
Age at diagnosis, yrs, mean (SD)	64.5 (15.8)
Diagnosis delay, mos, median (IQR)	2 (1–5)
Laboratory results	
CRP, mg/dl, median (IQR)	8.7 (2.2–14.8)
ESR, mm/h, mean (SD)	67 (33)
Hemoglobin, g/dl, mean (SD)	11.0 (1.9)
Thrombocyte count, × 10^9/l, mean (SD)	381 (135)
WBC count, × 10^9/l, median (IQR)	11 (9–14)
Creatinine, mg/dl, median (IQR)	1.73 (0.84–3.47)
Patients with ≥ 3 organ systems involved	124 (67)
Deaths during followup	66 (36)
Endstage renal disease*	32 (17)
Organ systems involved at diagnosis	
General	160 (86)
Ear, nose, and throat	79 (42)
Chest	88 (47)
Nervous	23 (12)
Cutaneous	15 (8)
Mucocutaneous and eyes	11 (6)
Cardiovascular	11 (6)
Abdominal	12 (6)
Renal	134 (72)

* Information on endstage renal disease defined as either commencement of chronic dialysis or renal transplantation at any time during the followup from diagnosis to December 2011. ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; IQR: interquartile range; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell.

DISCUSSION

In our population-based cohort study, we found a substantial increase in the consultation rate of several comorbidities in patients with AAV. Patients with AAV consult for osteoporosis and pathologic fractures, deep vein thrombosis, DM, and thyroid disease at higher rates compared with age- and sex-matched reference subjects from the same geographic area.

Compared with the reference population, patients with AAV also had an increase in the rate of IHD, though this finding was not statistically significant. A high rate of CVD in AAV compared with patients with noninflammatory chronic kidney disease has been reported previously[4] and was associated with a previous history of CV events, dialysis dependency, low renal function at remission, and smoking[4]. Patients with AAV also have a higher rate of metabolic syndrome[8]. Of patients with GPA and MPA enrolled in 4 clinical trials conducted by the European vasculitis study group, 14% developed CVD during the first 5 years after the diagnosis[7]. Comparison of these results should be made with caution because patients enrolled in clinical trials are highly selected for severe disease, often including severe kidney disease[17]. In our study, the rate ratio of stroke was not increased, a finding similar to what has been reported from a tertiary center in Denmark[18]. Because of the inflammatory characteristic of AAV and higher rates of other risk factors, we would expect significant differences in the rate of CV events between AAV and reference subjects. The intensive antiinflammatory treatment routinely administered to patients with AAV might attenuate this rate and decrease the risk and effects of atherosclerosis[19,20].

Table 3. Rate of a number of comorbidities (per 1000 yrs of followup) among 186 patients with AAV compared to 744 age-, sex-, and index year–matched reference persons from the background population.

Comorbidities	Patients with AAV, n = 186			Reference Subjects, n = 744			Rate Ratios	95% CI	p
	n	Person-yr	Rate	n	Person-yr	Rate			
IHD*	31	1002	30.9	95	4670	20.3	1.5	1.0–2.3	0.07
MI*	16	1064	15.0	37	4867	7.6	2.0	1.0–3.6	0.06
CVA*	14	1057	13.2	59	4828	12.2	1.1	0.6–2.0	0.7
HTN	78	789	98.8	284	3934	72.2	1.4	1.1–1.8	0.02
DM	40	903	44.3	101	4554	22.2	2.0	1.3–2.9	0.003
Dyslipoproteinemias	12	1064	11.3	89	4654	19.1	0.6	0.3–1.1	0.04
VTE*	16	1025	15.6	19	4926	3.9	4.0	1.9–8.3	0.003
Thyroid diseases	27	968	27.9	63	4748	13.3	2.1	1.3–3.3	0.009
Psychological disorders	54	870	62.1	243	4110	59.1	1.0	0.8–1.4	0.7
Osteoporosis	43	915	47.0	49	4795	10.2	4.6	3.0–7.0	< 0.001
Fractures	22	1042	21.1	92	4676	19.7	1.1	0.6–1.7	0.7

* Only diagnoses assigned after hospitalization. AAV: antineutrophil cytoplasmic antibody–associated vasculitis; IHD: ischemic heart diseases; MI: myocardial infarction; CVA: cerebrovascular accidents; HTN: hypertension; DM: diabetes mellitus; VTE: venous thromboembolism.

Table 4. Rate of selected comorbidities (per 1000 yrs of followup) among 95 women and 91 men with AAV compared with 380 and 364 age- and index year–matched reference persons from background population.

Comorbidities	Rate Cases	Rate Reference Population	Rate Ratio	95% CI	p
IHD*					
Men	40.0	25.5	1.6	0.9–2.7	0.1
Women	23.5	15.7	1.5	0.7–2.8	0.2
CVA*					
Men	12.2	15.2	0.8	0.3–1.9	0.5
Women	14.2	9.5	1.5	0.6–3.5	0.3
HTN					
Men	117.4	79.5	1.5	1.0–2.1	0.05
Women	84.7	65.9	1.3	0.9–1.8	0.2
DM					
Men	41.5	27.0	1.5	0.8–2.7	0.1
Women	46.6	17.9	2.6	1.5–4.4	0.004
Dyslipoproteinemias					
Men	8.1	24.8	0.3	0.1–0.9	0.002
Women	14.0	14.1	1.0	0.4–2.2	0.9
VTE*					
Men	17.1	5.1	3.4	1.2–9.2	0.05
Women	14.3	2.7	5.3	1.7–19.5	0.02
Thyroid disease					
Men	8.1	4.7	1.7	0.4–6.2	0.4
Women	48.3	21.6	2.2	1.3–3.7	0.01
Psychological disorders					
Men	52.5	47.7	1.1	0.7–1.8	0.6
Women	70.9	70.6	1.0	0.7–1.5	0.9
Osteoporosis					
Men	30.6	3.4	9.0	3.5–26.7	0.001
Women	63.4	16.8	3.8	2.3–6.2	< 0.001
Fractures					
Men	14.3	16.9	0.8	0.3–1.9	0.6
Women	27.1	22.4	1.2	0.6–2.2	0.5

* Only diagnoses assigned after hospitalization. AAV: antineutrophil cytoplasmic antibody–associated vasculitis; IHD: ischemic heart diseases; CVA: cerebrovascular accidents; HTN: hypertension; DM: diabetes mellitus; VTE: venous thromboembolism.

The occurrence of DM and HTN among patients with AAV is understandable, given that these diseases might each be a direct consequence of the prolonged use of glucocorticoids or from renal damage because of vasculitis[21]. In a study on the prevalence of irreversible organ damage among 86 prevalent cases of AAV and polyarteritis nodosa from our group, HTN was found to be the most common disease-associated damage[22].

Another notable finding of our study is the lower rate of disorders of lipoprotein metabolism (the dyslipoproteinemias) among patients with AAV (especially among men) compared with the reference population. To the best of our knowledge, this relationship between dyslipoproteinemias and AAV has not been previously reported. Of the 12 cases of AAV who had dyslipoproteinemias, only 1 patient had endstage renal disease (ESRD). Although there were no data on the temporal sequence of ESRD and dyslipoproteinemias in this cohort, this finding indicates that the low rate ratio of dyslipoproteinemias is related to renal insufficiency. However, in the regional treatment guidelines for AAV, statins are not routinely recommended for new cases of AAV. Similarly, the European League Against Rheumatism or the British Society of Rheumatology recommendations for treatment of small-vessel vasculitis did not recommend the routine use of lipid-lowering agents in the management of AAV[23,24]. In a case-control study of 91 patients with AAV, there were no significant differences in percentage of patients with low levels of high-density lipoproteins or high level of triglycerides between patients and controls, despite a higher frequency of metabolic syndrome among patients with AAV[8].

Our study also clearly suggested a higher rate of VTE diseases among patients with AAV compared with the reference subjects. When analyses were repeated for diagnoses assigned as outpatient visits (data not shown), the rate of deep vein thrombosis (DVT) was still significantly higher among patients, but the rate ratio decreased, a finding possibly explained by a bias to refer patients with AAV to a hospital when DVT is diagnosed or suspected. The association of AAV and VTE diseases has been reported[2,3,18,25]. VTE in AAV have been strongly associated with periods of active vasculitis despite no differences in classic risk factors, indicating that vasculitis disease activity is an important predisposing factor for VTE[2,26]. Better and earlier control of disease activity in AAV might have reduce the risk of VTE.

In line with prior reports, our study also found a significantly higher rate of thyroid diseases among patients with AAV, mainly among women[27,28]. However, the feature of the association between AAV and thyroid disease needs further attention.

We found a higher rate of osteoporosis diagnosed in our patients with AAV compared with the reference subjects. Data on osteoporosis in AAV are scarce. In a cross-sectional study of bone density in a cohort of patients with AAV from a tertiary center in the Netherlands, the prevalence of osteoporosis was 21% and of osteopenia, 57%[29]. Osteoporosis occurred in 15% of patients with AAV and polyarteritis nodosa previously reported from our group[22]. In southern Sweden, treatment with bisphosphonates is recommended for all patients with AAV if there are no contraindications. Despite a higher rate of osteoporosis among the patients with AAV, our study did not find an increased rate of fractures. A possible explanation for this finding is that physicians may more likely order bone density examination for patients with chronic diseases such as AAV than for the patients in the reference population.

Our study has important limitations. Diagnosis codes of comorbidities are usually recorded by physicians according to their clinical judgment and we did not verify individual medical records. Because we had no means to evaluate the first occurrence of the comorbidities under study, we cannot exclude the possibility that a comorbidity occurred before the onset of AAV. Additionally, the increased rates of comorbidities in AAV might also be explained by an increased propensity to seek care among patients with AAV and surveillance bias from increased monitoring/doctors' examinations compared with patients with less serious or nonchronic medical conditions. Physicians might also be more prone to admit patients to the hospital who have more serious conditions such as AAV compared with persons with relatively less severe diagnoses. Another limitation is that we could not obtain the diagnostic codes from outpatient private practitioners. However, because the distribution of public and private visits is largely the same in the 2 cohorts, we expect the potential bias to be minimal. Further, many of the diagnoses investigated are typically determined during inpatient care, which is public and hence not affected.

Our study has important strengths. We used a population-based sample including a large and well-characterized validated cohort of patients with AAV and matched references. Moreover, our study includes an inception cohort of subjects with AAV, therefore identifying a wider spectrum of the natural history of AAV compared with cohorts of patients enrolled in clinical treatment trials.

We report high consultation rates of important comorbidities in patients with AAV compared with a reference population without AAV. Healthcare planners, researchers, and physicians with a special interest in vasculitis should take the results of our study into consideration when planning and providing healthcare for such patients. Increased awareness by clinicians of the high rate of comorbidities among patients with AAV, frequent risk assessment, and early preventive steps after diagnosis of AAV might have important effects on the outcome for patients.

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