Incidence and disease severity of anti-neutrophil cytoplasmic antibody-associated nephritis are higher than in lupus nephritis in Sweden

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ABSTRACT

Objectives. The objectives of this study were to compare incidence rates, renal and patient survival between lupus nephritis (LN) and anti-neutrophil cytoplasmic antibody-associated nephritis (AAN) during a 12-year period in two geographically defined populations in Sweden.

Methods. In the health care districts surrounding the Skåne University Hospital in Lund [mean population ≥18 years (1997–2008), 188,400] and the University Hospital in Linköping [mean population ≥18 years (1997–2008), 328,900] all patients with biopsy-proven LN and AAN during the period 1997–2008 were included in the study if they (i) were residing within the study areas at the time of onset of nephritis, (ii) had a clinical diagnosis of either SLE or ANCA-associated vasculitis (AAV) and (iii) experienced a first flare of biopsy-proven nephritis during the study period.

Results. Eighty-two patients (Lund 44 + Linköping 38) with biopsy-proven AAN were identified and 27 patients with LN (Lund 13 + Linköping 14). The annual incidence rate per million inhabitants aged ≥18 years in both study areas was estimated to be 13.2 (95% CI 10.4–16.1) for AAN and 4.3 (95% CI 2.7–6.0) for LN, P < 0.001. The patients were followed until January 2013. During the follow-up time 38 patients died (AAN 36, LN 2; P = 0.001), and 20 patients went into end-stage renal disease (AAN 19 and LN 1), P = 0.020.

Conclusions. In Sweden, AAN was three times more common than LN, and the outcome was considerably worse. SLE is often diagnosed before the onset of nephritis leading to earlier treatment, while AAN is still often diagnosed at a later stage.

Keywords: ANCA, end-stage renal disease, incidence, lupus nephritis, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are autoimmune inflammatory diseases characterized by involvement of multiple organ systems and by the production of autoantibodies. Even though considerable progress has been made in recent years regarding the pathogenesis, the aetiologies of both conditions are still largely unknown [1, 2]. There are many clinical differences between the conditions, but treatment modalities are similar, including the use of cytotoxic agents and corticosteroids for induction of remission and less toxic immunosuppressive agents as maintenance therapy [3]. In both conditions, renal involvement constitutes a feared manifestation with substantial
prognostic implications for the patient’s survival [4]. Early detection and treatment is of the utmost importance for the prognosis of glomerulonephritis in both SLE and AAV. The epidemiology of lupus nephritis (LN) and ANCA-associated nephritis (AAN) has been addressed in a number of studies, but to our knowledge they have never been compared simultaneously in the same geographical area. Worldwide, SLE is a more common disease than AAV, but nephritis is seen in a larger proportion of patients with AAV. Studies from Sweden and Norway have reported a falling incidence of LN and improved prognosis [5, 6].

The aim of this study was to compare the annual incidence rates of LN and AAN in two independent geographically defined populations in southern Sweden and to compare the outcome with regard to renal and patient’s survival.

METHODS

Study area and population

The study was carried out in two separate geographical areas in Sweden (Figure 1). Area A consists of a health care district in the county of Skåne, the southernmost county in Sweden. The total population aged ≥18 years in 1997 was 177,210 inhabitants, increasing to 199,606 in December 2008. The corresponding figures for Area B were 322,014 in 1997 and 335,780 in 2008. Area B consists of the entire county of Östergötland situated about 400 km north of Skåne (Area A). Both Skåne University Hospital in Lund and the University Hospital in Linköping are tertiary referral centres in their respective counties. The age and sex distributions are similar in both areas: 0–14 years 18%; 15–54 years 54% and >55 years 28% and the proportion of women is ~50% [7].

Case retrieval

Area A. At the Department of Rheumatology in Lund, longitudinal population-based studies of SLE started in the early 1980s [5, 8]. All diagnosed cases of SLE within the area were included in a cohort and new cases are added with regular updating [5]. The completeness of the retrieval procedure has been shown by capture–recapture methodology [8]. The diagnosis of SLE is verified by review of case records and all patients fulfil the American College of Rheumatology classification...
criteria for SLE [9]. Kidney biopsy reports were reviewed and all histopathology classifications were performed according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN [10].

A vasculitis registry was started in 2002 with the combined efforts of the Departments of Rheumatology and Nephrology in Lund; incident patients from 1997 and onward have been included retrospectively. A geographically defined cohort was generated covering an area, which included Area A, and new patients have been added by regular updates. The case retrieval and ascertainment of diagnosis and classification have been described previously [11, 12]. The classification of patients with AAV was made according to the European Medicines Agency algorithm [13].

Area B. The rheumatology clinic in Linköping is the only one in the county. A prospective follow-up program, KLURING (a Swedish acronym for ‘clinical lupus register in north-eastern Gothis’), was started in 2008 and includes both prevalent and incident cases. The patient material has been recently described in detail [14]. For this study, cases were also retrieved through the registry of clinical pathology in Linköping.

A vasculitis registry for Östergötland was started in 1997, and details concerning classification and case retrieval have been published previously [15].

Inclusion criteria

For inclusion in the study patients had to fulfil the following criteria: (i) reside within the study area, (ii) have a clinical diagnosis of either SLE or AAV and (iii) experience a first flare of biopsyped nephritis during the period 1997–2008. To calculate biopsy rate (data available only in Area B) the number of patients with biopsy-proven nephritis was divided by the number of patients with AAV and SLE who were judged to have active nephritis based on the following criteria: for AAV the presence of haematuria and active urinary sediment giving a score ≥1 in the Birmingham Vasculitis Activity Score (BVAS) renal domain [16], and for SLE diagnosis of LN was based on the clinical and laboratory findings including the presence of haematuria and proteinuria according to the SLE Disease Activity Index (SLEDAI) [17]. Demographics, clinical and laboratory data and results of histopathology investigations were collected retrospectively by review of case records. In addition, information on renal outcome was registered, either as creatinine at the end of the study or end-stage renal disease (ESRD) or death during the follow-up. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation [18].

Treatment

The vast majority of patients were treated in a uniform fashion, according to local guidelines. The first-line treatment for LN during the study period at both centres was intravenous cyclophosphamide (CYC) in monthly doses of 10 mg/kg [19]. The most common maintenance therapy was azathioprine (AZA). During the last few years of the study period, mycophenolate mofetil (MMF) was introduced for induction therapy in milder cases and for maintenance treatment. Treatment of AAN at both centres was in the beginning of the study period, oral CYC 2 mg/kg for 3 months; and was gradually replaced by intravenous CYC, given according to the CYCLOPS protocol [20], which includes 10 pulses of 15 mg/kg during a 6-month period. Maintenance therapy was regularly given for long periods (>24 months), the most common being AZA. Rituximab was introduced early in Östergötland (Area B), but during the study period it was mainly given to refractory patients and patients with multiple relapses [21].

Statistical analyses

Statistical analysis was performed using the Statistical Package for the Social Sciences, SPSS version 22.0 for Windows (IBM SPSS Statistics). Data are presented as means and ±SD for normally distributed variables and as median and interquartile ranges (IQR) for continuous variables not normally distributed. The differences between groups were compared by means of the non-parametric Mann–Whitney U-test (not normally distributed continuous variable), Student’s t-test (normally distributed continuous variable) and χ²-test (categorical variables). The P value of <0.05 was considered to be significant. The Kaplan–Meier method was employed to estimate survival rates. The 95% confidence interval (95% CI) was calculated assuming a Poisson distribution of the observed cases.

The study protocol was approved by the Regional Ethical Review Board at Lund University (2010/668, 2012/252) and at Linköping University (M75-08/2008) in Sweden.

RESULTS

We identified a total of 82 patients with AAN (44 patients in Area A and 38 patients in Area B) and 27 patients with LN (13 patients in Area A and 14 patients in Area B), all with new-onset biopsy-proven nephritis diagnosed between 1997 and 2008 (Table 1).

Table 1. Clinical and demographic characteristics of incident cases of biopsy-proven AAN and LN in Sweden

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients (n)</th>
<th>Sex F/M</th>
<th>Age at diagnosis, years</th>
<th>Creatinine at diagnosis μmol/L</th>
<th>Time of follow-up, years*</th>
<th>Mortality (n)</th>
<th>ESRD (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAN</td>
<td>82</td>
<td>36/46</td>
<td>65.5 (±13.9)</td>
<td>249 (161–392)</td>
<td>6.5 (±4.1)</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>MPA</td>
<td>60</td>
<td>32/28</td>
<td>66.8 (±12.8)</td>
<td>286 (175–450)</td>
<td>6.4 (±4.1)</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>GPA</td>
<td>21</td>
<td>3/18</td>
<td>61.7 (±16.8)</td>
<td>193 (132–289)</td>
<td>6.9 (±4.3)</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>EGPA</td>
<td>1</td>
<td>1/0</td>
<td>66</td>
<td>44</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LN</td>
<td>27</td>
<td>22/5</td>
<td>38.6 (15.1)</td>
<td>77 (64–100)</td>
<td>8.6 (±3.6)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis (Wegener’s); EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss); ESRD, end-stage renal disease.

*January 2013 or death. Results are given in mean (±SD) for normally distributed variables and median (IQR) for not normally distributed variables.
Comparison between AAN and LN cohorts in a number of demographic, clinical and laboratory characteristics is shown in Table 2.

**Biopsy rate**

In Area B, in addition to the 14 patients included in the study, two more patients with first-time onset of LN according to the SLEDAI criteria were recognized during the study period. Besides the 38 AAN patients included in the study, 18 more patients with AAV and renal involvement according to the BVAS score were recognized during the study period. This gives a biopsy rate of 88% for clinically diagnosed LN compared with 67.9% for AAN.

**Clinical characteristics**

**LN.** Twenty-seven patients (22 women) fulfilled the study criteria (Table 1). In 17 patients (7 in Area A and 10 in B), the diagnosis of SLE was established before the onset of biopsy-proven nephritis, with a median time between the diagnosis of SLE and the diagnosis of biopsy-proven nephritis of 50 months (IQR 16.5–186.5). Kidney biopsy revealed type II glomerulonephritis in 5 patients, type III in 4 patients, type IV in 14 patients and type V in 4 patients. A total of 23 patients (85%) tested positive for anti-ds-DNA and 21 patients (78%) had evidence of complement consumption. Selected clinical and laboratory characteristics of the two LN cohorts from both study areas are shown in Table 3.

**AAN.** Eighty-two patients (36 women) fulfilled the study criteria: 21 classified as granulomatosis with polyangiitis (Wegener’s, GPA), 60 as microscopic polyangiitis (MPA) and 1 as eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA; Table 1). All patients in the study had renal involvement already at diagnosis; the median time of diagnosis delay was 1.8 months (IQR 1.0–3.0). At the time of biopsy, the most common extra-renal manifestations were as follows: general (n = 56, 68%), chest (n = 23, 28%), ear–nose–throat (n = 18, 22%), nervous (12, 15%), cutaneous (n = 8, 10%) and abdominal (n = 7, 9%). Seventy-nine (96%) patients tested positive for ANCA by direct enzyme linked immunosorbent assay (31 PR3-ANCA and 48 MPO-ANCA). Selected clinical and laboratory characteristics of the two AAN cohorts from both study areas are shown in Table 4. When comparing patients with biopsy-proven AAN in area A (n = 44) with patients with renal disease according to BVAS but not confirmed by biopsy (n = 15), no statistically significant differences were found in demographic, clinical, laboratory or outcome parameters (for detailed list of parameters, see Table 4, data not shown).

**The annual incidence rates**

The annual incidence rate per million adults aged ≥18 years in Area A was estimated to be 19.5 (95% CI 13.7–25.2) for AAN compared with 5.7 (95% CI 2.6–8.9) for LN (P < 0.001), the corresponding figures for Area B were 9.6 (95% CI 6.6–12.7) for AAN and 3.5 (95% CI 1.7–5.4) for LN (P < 0.001). When combining the results from both areas, the annual incidence rate per million adults aged ≥18 years was 13.2 (95% CI 10.4–16.1) for AAN and 4.3 (95% CI 2.7–6.0) for LN (P < 0.001). Comparing the two areas, the incidence of...
AAN was significantly higher in Area A (P = 0.001), stemming mainly from a difference in MPA, while there was no statistically significant difference in incidence of LN between Areas A and B. The gender-specific incidence rates for all disease phenotypes included in this study in both study areas are shown in Table 5.

### Renal outcome

The patients were followed from diagnosis to development of ESRD, death or January 2013 (mean 6.4 years ± 4.3). No patient was lost to follow up. Renal survival was significantly better among patients with LN than with AAN. During the follow-up period, 20 patients (12 women) went into ESRD, 19 with AAN and 1 patient with LN (Table 1 and Figure 2A; P = 0.020). For the patients with AAN, the median time from diagnosis to the development of ESRD was 4 months (IQR 0–61). The only patient with LN who developed ESRD did so 3 months after the LN diagnosis.

### Patient survival

During follow-up, 38 patients died: AAN 36 and LN 2 (P = 0.001). The 1-, 5- and 10-year survival for patients with AAN was 85.4, 71.8 and 48.3%, respectively. For LN the corresponding figure was 100, 96.3 and 96.3% (Figure 2B). The mean follow-up time from diagnosis to death or January 2013 was 6.5 years (± 4.1) for patients with AAN and 8.6 years (± 3.6) for patients with LN (P = 0.019). Compared to patients who were alive at the end of follow-up, AAN patients who died were older at time of biopsy (73.5 ± 9.4 vs. 59.2 ± 13.7, P < 0.001). Similarly, at time of biopsy, the age of patients who developed

### Table 4. Comparison between the AAN cohorts from two study areas in Lund (Area A) and Linköping (Area B)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Area A (n = 44)</th>
<th>Area B (n = 38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n (%)</td>
<td>19 (43)</td>
<td>17 (45)</td>
<td>0.887</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>65.9 ± 15.7</td>
<td>65.1 ± 11.7</td>
<td>0.798</td>
</tr>
<tr>
<td>Patients with ≥3 organ systems involved, n (%)</td>
<td>28 (64)</td>
<td>15 (40)</td>
<td>0.029</td>
</tr>
<tr>
<td>Deaths during follow-up, n (%)</td>
<td>22 (50)</td>
<td>14 (37)</td>
<td>0.231</td>
</tr>
<tr>
<td>ESRD, n (%)</td>
<td>13 (30)</td>
<td>6 (16)</td>
<td>0.141</td>
</tr>
<tr>
<td>Organ systems involved at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General, n (%)</td>
<td>37 (84)</td>
<td>19 (50)</td>
<td>0.001</td>
</tr>
<tr>
<td>ENT, n (%)</td>
<td>10 (23)</td>
<td>8 (21)</td>
<td>0.855</td>
</tr>
<tr>
<td>Chest, n (%)</td>
<td>16 (36)</td>
<td>7 (18)</td>
<td>0.071</td>
</tr>
<tr>
<td>Nervous, n (%)</td>
<td>2 (4.5)</td>
<td>10 (26)</td>
<td>0.010</td>
</tr>
<tr>
<td>Cutaneous, n (%)</td>
<td>5 (11)</td>
<td>3 (8)</td>
<td>0.719</td>
</tr>
<tr>
<td>Mucocutaneous and eyes, n (%)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>0.212</td>
</tr>
<tr>
<td>Cardiovascular, n (%)</td>
<td>3 (7)</td>
<td>0 (0)</td>
<td>0.245</td>
</tr>
<tr>
<td>Abdominal, n (%)</td>
<td>7 (16)</td>
<td>0 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Laboratory results at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>100 (21–157)</td>
<td>88 (13–139)</td>
<td>0.903</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>52 ± 28.3</td>
<td>73 ± 35</td>
<td>0.050</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>105 ± 18.3</td>
<td>105 ± 15</td>
<td>0.871</td>
</tr>
<tr>
<td>Platelets count, ×10^9/L</td>
<td>323 (±122)</td>
<td>345 (±123)</td>
<td>0.437</td>
</tr>
<tr>
<td>White blood cell count, ×10^9/L</td>
<td>11.6 (±5.3)</td>
<td>10.6 (±3.4)</td>
<td>0.331</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>280 (142–463)</td>
<td>205 (173–326)</td>
<td>0.146</td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease; ENT, ear, nose and throat.

Results are given in mean (±SD) for normally distributed variables and median (IQR) for not normally distributed variables.

### Table 5. The annual incidence rate of biopsy-proven AAN and LN in two defined populations in Sweden (population ≥18 years)

<table>
<thead>
<tr>
<th></th>
<th>AAN, n/incidence (95% CI)</th>
<th>GPA, n/incidence (95% CI)</th>
<th>MPA, n/incidence (95% CI)</th>
<th>EGPA, n/incidence (95% CI)</th>
<th>LN, n/incidence, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Area A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>44/19.5 (13.7, 25.2)</td>
<td>9/4.0 (1.4, 6.6)</td>
<td>34/15.0 (10.0, 20.1)</td>
<td>1/0.4 (0, 1.3)</td>
<td>13/5.7 (2.6, 8.9)</td>
</tr>
<tr>
<td>Women</td>
<td>19/16.6 (9.1, 24.0)</td>
<td>1/0.9 (0, 2.6)</td>
<td>17/14.8 (7.8, 21.9)</td>
<td>1/0.9 (0, 2.6)</td>
<td>10/8.7 (3.3, 14.1)</td>
</tr>
<tr>
<td>Men</td>
<td>25/22.4 (13.6, 31.2)</td>
<td>8/7.2 (2.2, 12.2)</td>
<td>17/15.3 (8.0, 22.5)</td>
<td>0/0 (0, 0)</td>
<td>3/2.7 (0, 5.7)</td>
</tr>
<tr>
<td><strong>Area B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>38/9.6 (6.6, 12.7)</td>
<td>12/3.0 (1.3, 4.8)</td>
<td>26/6.6 (4.1, 9.1)</td>
<td>0/0 (0, 0)</td>
<td>14/3.5 (1.7, 5.4)</td>
</tr>
<tr>
<td>Women</td>
<td>17/8.5 (4.5, 12.6)</td>
<td>2/1.0 (0, 2.4)</td>
<td>15/7.5 (3.7, 11.3)</td>
<td>12/6.0 (2.6, 9.4)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>21/10.7 (6.1, 15.3)</td>
<td>10/5.1 (1.9, 8.3)</td>
<td>11/5.6 (2.3, 9.0)</td>
<td>2/1.0 (0, 2.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Both areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>82/13.2 (10.4, 16.1)</td>
<td>21/3.4 (1.9, 4.8)</td>
<td>60/9.7 (7.2, 12.1)</td>
<td>1/0.2 (0, 0.5)</td>
<td>27/4.3 (2.7, 6.0)</td>
</tr>
<tr>
<td>Women</td>
<td>36/11.5 (7.7, 15.2)</td>
<td>3/1.0 (0, 2.0)</td>
<td>32/10.2 (6.7, 13.7)</td>
<td>1/0.3 (0, 0.9)</td>
<td>22/7.0 (4.1, 9.9)</td>
</tr>
<tr>
<td>Men</td>
<td>46/15.0 (10.7, 19.3)</td>
<td>18/5.9 (3.2, 8.6)</td>
<td>28/9.1 (5.7, 12.5)</td>
<td>0/0 (0, 0)</td>
<td>5/1.6 (0.2, 3.1)</td>
</tr>
</tbody>
</table>

AAN, ANCA-associated nephritis; GPA, granulomatosis with polyangiitis (Wegener’s); MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis (Churg–Strauss); LN, lupus nephritis. The incidence rates of disease phenotypes (GPA, MPA and EGPA) indicate patients with biopsy-proven nephritis.

Area A: Lund, Area B: Linköping.

Incidence is presented per 1,000,000 inhabitants and year. Values between parentheses are 95% CI.
ESRD was higher than patients with native kidney function at last follow-up (68.8 ± 11.3 vs. 64.5 ± 14.6, P = 0.233).

DISCUSSION

The major finding in this study is a greater incidence of biopsy-proven AAN compared with LN. The relative incidence was 3.4 in the area around the University Hospital in Lund and the finding was reproduced in the county of Östergötland (the Linköping University Hospital area) with a relative incidence of 2.7. We also found biopsy-proven nephritis to be more severe in patients with AAV, with a higher creatinine value at time of biopsy and a higher incidence of ESRD at the last follow-up. As severity of renal disease is a major prognostic factor for survival in both diseases, together with the fact that AAN patients are older, it is not surprising that we also found a substantially higher mortality among the AAN patients. The relative contribution of age and renal function to the difference in survival is difficult to distinguish due to the low number of deaths among the LN patients.

We limited our analysis to biopsy-proven nephritis. The reason for performing a renal biopsy in SLE and AAV is somewhat different. In AAV, a renal biopsy is in most cases performed to establish and/or confirm the diagnosis of vasculitis, while in SLE the biopsy is most often done to classify the type of renal involvement to guide treatment. In this study, all AAV patients had renal involvement already at diagnosis, while this was the case for only 44% of the SLE cases. These differences might have bearing on the tendency to do biopsies. Nevertheless, in Area B, only 2/16 SLE patients with clinical signs of renal disease had not undergone a biopsy. Among the AAV patients in Area B with renal involvement according to the BVAS scoring system, 67.9% were confirmed by biopsy as compared with 88% for LN. Reasons for not performing biopsy were severe disease, bleeding tendency and diagnosis already established through biopsy of other organ system (i.e. skin or nose). The higher incidence of AAN as compared with LN is thus not explained by differences in biopsy rates between the two diseases. Differences in age distribution between areas could also induce changes in incidence rates; however, in this study (as indicated in the method section) no such differences were found.

This study is limited to adult cases, which tend to underestimate LN as SLE is more common in children as compared with AAV. However, this has no major impact on our finding and do not change our conclusions. The SLE registry in Area B covers all adult SLE patients and in that registry only 8% of the biopsy-proven LN cases had their biopsy performed before the age of 18.

As our findings were similar in two areas in Sweden 250 miles apart, they are most likely true also for the rest of our country. The question is, however, to what extent they are representative for other Caucasian populations in Europe and overseas. The incidence of AAN in this study of 13.4 per million is in the same range as reported from Miyazaki in Japan 14.8 [22] and Norfolk in the UK 12.2 [23]. We found, however, a statistically significant difference in AAN incidence between the two areas in this study, driven by differences in MPA. We have previously done capture–recapture analysis of our case finding strategy in the Lund area, and case retrieval completeness was found to be 96% in that study [11]. A similar analysis has not been done in Östergötland and as there are nephrology units at referring hospitals, completeness might be lower here, especially among renal limited cases. Of course we cannot exclude a true lower incidence in area B. We also would like to point out that in the Malmö area, which is adjacent to Area A, we found a lower incidence as compared with the Lund area (=Area A) in an earlier publication [12].

Our finding of a LN incidence of 4.3, with no major differences between the two study areas, is compatible with results from other Caucasian populations. The incidence of LN has previously been reported to be 4 per million in the UK [24], 4.5 per million in Norway and 8 per million in MN, USA [25]. From this we conclude that our finding that AAN is more common than LN is most probably not restricted to Sweden.
In previous reports from our group, the SLE incidence has been reported to be 48 per million [5] compared with 21 per million for AAV [12]. Consequently, a low incidence of nephritis among SLE patients is the main explanation for our findings of lower incidence of LN than AAN. Earlier studies have shown that the frequency of renal involvement fell from 41% during the period 1981–86 to 19% during the period 1987–91 [5]. Similarly, the incidence of LN has decreased in Norway from 7 per million during 1978–95 to 4.5 per million during 1996–2006 [6]. This declining frequency of nephritis in SLE patients can be explained by the use of drugs to treat other SLE manifestations. This includes a widespread use of hydroxychloroquine also during remission, a drug known to interfere with toll receptor activation in plasmacytoid dendritic cells. Among patients with SLE, whose diagnosis preceded onset of LN, we found that the median time from SLE diagnosis to the development of LN was 50 months. The latency between onset of SLE and LN allows longer time for treatment of non-renal SLE and has been reported by others as well [26]. Thus, socioeconomic factors including access to health care seems to be important for our results. To what extent such factors influence the findings of the higher LN incidence among ethnic groups such as Hispanics and Afro-Americans remains to be determined [27]. There are reports showing differences in duration between onset of SLE and development of LN among such ethnic groups compared with Caucasians [28, 29]. Therefore, drawing conclusions that are applicable to other ethnic groups should take into consideration such differences.

The outcome of AAN in our study is comparable with other reports. The frequency of patients who went into ESRD is around 30%, similar to that reported by Rihova et al. [30]. In agreement with these figures, N. Hedger et al. reported that 36% of their patients with pauci-immune rapidly progressive glomerulonephritis needed long-term dialysis [31]. In addition a newly published study from Japan including patients with MPO-ANCA-associated nephritis reported results similar to ours with ESRD in 36% and with an age distribution comparable to our study [32].

In this study, only 1/27 (3.7%) patients with LN developed ESRD during a mean follow-up time of 6.4 years. This is in line with other recent studies showing a favourable outcome in LN in Caucasians. In the Norwegian study, 11% developed ESRD in the 1987–95 cohort compared with none in the 1996–2006 cohort [6]. In contrast, the incidence of ESRD due to LN in the USA was stable, estimated to 4.4 per million in 1996 and 4.9 per million in 2004 [33], but in this study 48% of the patients were Afro-Americans. Recently, the follow-up study of the Euro-Lupus trial has shown that there was no decrease in the incidence of ESRD developed in 9% of patients with LN [34]. Furthermore, the incidence of LN in the Olmsted County in the USA was stable over a nearly 30-year period [25].

Our findings of a higher relative abundance of AAN as compared with LN is of interest for health care officials organizing the care of patients with glomerular disease as well as for pharmaceutical companies developing drugs and planning intervention studies. Even more importantly, if our assumption that the key to the favourable results in LN is early diagnosis and preventive therapy is correct, lessons could be learned of how to improve outcome also in AAN.

In conclusion, we find in two separate areas in Sweden that AAN patients outnume LN by around three to one and that the outcome is considerably worse. We welcome other researchers to elucidate to what extent our findings are representative for other parts of the World. We also suggest that early recognition and effective treatment of non-renal disease is the key to success in LN, which emphasizes the importance of greater awareness in the medical community of AAV and vigilance in the care of these patients.

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CONFLICT OF INTEREST STATEMENT
None declared.

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