Decreased incidence of lupus nephritis in northern Norway is linked to increased use of antihypertensive and anticoagulant therapy

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Abstract

Background. Lupus nephritis (LN) remains a severe complication in systemic lupus erythematosus (SLE). Over the last decade, antiphospholipid antibodies have become a part of SLE classification criteria, and awareness of cardiovascular morbidity and its risk factors in SLE has increased. This study investigated the potential effect of these alterations on the presentation and severity of LN.

Methods. This is an observational study of two subsequent SLE inception cohorts based on 1982 American College of Rheumatology (acr) classification criteria (82acr; n = 87, enrolled 1978–95) and the updated version in 1997 (97acr: n = 62, enrolled 1996–2006). Annual incidence rates (AIR), point prevalence, clinical and histological features, and outcome of LN (defined as proteinuria with urinary casts and/or haematuria) were compared between both cohorts.

Results. Between 1978 and 2006, the AIR for LN decreased from 0.7 to 0.45/100 000, while LN prevalence rose from 7 to 14/100 000. The relative risk reduction in the 97acr for early- and late-onset LN (>3 months after SLE diagnosis) was 39% and 42%, respectively. Patients developing LN in the 97acr cohort (97LN+; n = 11) had similar demographics, more often low avidity anti-dsDNA antibodies (Ab) and/or anti-cardiolipin Ab at SLE diagnosis, lower proteinuria and diastolic blood pressure, and similar histological findings to those in the 83acr cohort (82LN+; n = 28). Following LN diagnosis, more 97LN+ patients received pulse corticosteroids (55% vs. 7%), anticoagulants (46% vs. 4%) and antihypertensive drugs (46% vs. 11%). Three 82LN+ patients (11%) developed end-stage renal disease versus none in 97LN+ during a 10-year follow-up.

Conclusions. Early detection of low avidity anti-dsDNA and antiphospholipid antibodies, probably in combination with early use of protective cardiovascular measures from SLE diagnosis onwards may contribute to reduced incidence and improved renal survival in LN.

Keywords: antibodies; epidemiology; hypertension; lupus nephritis; survival

Introduction

Renal disease is one of the most serious complications in patients with systemic lupus erythematosus (SLE). The pathogenesis of lupus nephritis (LN) is not fully understood but involves a complex interplay between renal infiltrating leucocytes, cytokines, autoantibodies and complement factors [1], which results in immune complex-mediated glomerulonephritis. In addition, thrombotic and inflammatory vascular lesions may occur that directly affect intrare-
nal or systemic haemodynamics and thus contribute to disease severity [2,3].

Depending on the population studied, nephritis occurs in ~40–70% of SLE patients [2,4] and usually within the first years of disease. As a rule, patients present with asymptomatic abnormalities such as proteinuria, haematuria or hypertension that are detected through regular screening. Renal involvement has been reported to be more frequent and more severe in non-white cohorts and in patients with circulating dsDNA antibodies (Ab) [5]. In the only epidemiological study available, the annual incidence of LN was estimated to 0.4 per 1 000 000 in the UK [6]. As a considerable proportion of SLE patients do not develop LN, studying the mechanisms that protect these patients against LN can provide important insights. A recent report on SLE in this region found that the frequency of LN has decreased over the last decade [7]. The purpose of this investigation was to determine which factors have contributed to this positive development.

Materials and methods

Patients
LN occurrence was studied in two subsequent population-based inception cohorts of SLE patients, which were assembled within the two northern-most counties in Norway [7]. This hospital provides all rheumatology and nephrology services in the area, which otherwise has three local hospitals. Patient inclusion was based on the data from hospital patient registries (in- and outpatients) for all departments in the four hospitals to ensure maximum recruitment. The 97acr cohort was established between 1996 and 2006 using the 1997 update of the American College of Rheumatology classification criteria for SLE [8]. The occurrence and features of LN in adult patients (>15 years) were compared with the 82acr cohort that was established during 1978–95 using the 1982 revised criteria [9]. All patients are followed up on a regular basis at this department in close cooperation with the Department of Nephrology for patients with renal disease, and relevant longitudinal data are periodically stored in the disease registry database [10]. The regional ethics board approved the study protocol, and patients gave written informed consent for the de-identified use of their data.

Methods
LN was defined as persistent new-onset proteinuria (>0.5 g/24 h) and/or presence of >5 red blood cells and/or haeme-granular or red blood cell casts [11]. Arterial hypertension was defined as blood pressure exceeding 140/90 mmHg (135/90 mmHg <40 years) or the use of antihypertensive drugs [diuretics, vasodilators, angiotensin receptor blockers (ARB), and angiotensin-converting enzyme inhibitors (ACE-I)] for more than 3 months [12]. Renal tissue obtained through percutaneous biopsies was re-evaluated by two pathologists for the following features: the Interfeetation was to determine which factors have contribu-

Statistics
Data reported are median values unless indicated otherwise. Continuous data were analysed by Mann–Whitney U-test. Annual incidence rate (AIR) and point prevalence are reported per 100 000. Survival rates were estimated by Kaplan–Meier method and compared by log-rank test and the Gehan statistic. Risk factors for developing LN were analysed by Cox proportional hazards models, and hazard ratios (HR) are reported with 95% confidence interval (CI). All statistical analyses were performed with SPSS version 17.0 and Epi Info version 4.1.

Results

Case ascertainment
From a total of 170 registered SLE patients, 21 were excluded as they were not incident cases. LN developed in 39/149 remaining patients (26%). LN frequency was 28/87 (32%) in 82acr and 11/62 patients (18%) in 97acr (Figure 1). LN patients are further referred to as either 97LN+ or 82LN+, and patients without LN as either 97LN− or 82LN−.

LN incidence
The estimated AIR of LN for the whole study period was 0.6 (CI 0.4–0.8). AIR of LN was higher in females (1.0, CI 0.6–1.4) than in males (0.2, CI 0.1–0.4). The mean AIR for LN decreased from 0.7/100 000 (CI 0.4–1.1) in 82acr to 0.45 (CI 0.3–0.6) in acr97 (P = 0.224).

LN prevalence
Annual prevalence rates increased during the follow-up years and were five times higher for women than men (22.8 vs. 4.4 per 100 000). Including 6 paediatric patients that reached 16 years of age during the observation period and 9 patients diagnosed before 1978 while excluding non-survivors, a total of 48 LN patients (39 women and 9 men) were alive in the region giving a LN point prevalence of 13.8/100 000 as of 1 January 2007.

Risk and predictors of developing LN
Overall, 26 patients (67%) had early-onset LN (≤3 months of SLE diagnosis), and 13 patients (33%) developed later-onset LN. The proportional chance of developing LN was lower, although not significant, in the 97acr cohort during the first 10 years of SLE (Figure 2) with a relative risk reduction in the 97acr cohort of 38% at 1 year, 36% at 5 years and 42% at 10 years compared with the 82acr cohort (P = 0.136).

Baseline risk factors at SLE diagnosis for late-onset LN (manifestation >3 months after SLE diagnosis) were the presence of hypertension (HR 4.6) and anti-SSB antibodies (HR 4.8) at SLE diagnosis. No other treatment, laboratory finding or clinical finding was associated with late-onset LN within 10 years of SLE diagnosis (Table 1). With pre-diagnosis data not available, a comprehensive risk factor analysis for early-onset LN (within 3 months
after SLE diagnosis) was not feasible. However, at SLE diagnosis, patients with early-onset LN were more likely to have diastolic hypertension (OR 2.9), hypocomplementemia (C3; OR 4.4 and C4; OR 3.3), elevated levels of serum creatinine (OR 22.7), increased ESR (OR 7.9) or SLEDAI ≥10 (OR 30.4) compared with LN− patients. A multivariate analysis of potential baseline factors associated with LN development during a 10-year follow-up for all patients with LN (n = 39) indicated that SLEDAI ≥10 (HR 6.3, CI 3.1–12.8), hypertension (HR 3.0, CI 1.5–5.7) and ESR >20 (HR 3.0, CI 1.1–8.6) were significantly and independently associated with LN development (Table 1).

**Clinical findings at LN diagnosis**

Both LN+ cohorts were comparable with regard to age at SLE diagnosis (32.5 vs. 30.0 years, P = 0.8), gender distribution (85.7% vs. 72.7% female, P = 0.3), disease duration at LN diagnosis (0 month in both, P = 0.6), non-renal SLEDAI (4 vs. 6, P = 0.9) and total SLEDAI score (16 vs. 14.5, P = 0.8) (Table 2). Proteinuria levels were higher in 82LN+ (3.0 g/L vs. 0.9; P = 0.3), as was nephrotic presentation (hypoaalbuminemia <30 g/L and proteinuria >3 g/L) (44% vs. 25%). While systolic blood pressure was also lower, only diastolic pressure was significantly lower (80 vs. 90 mmHg, P = 0.026) in the 97LN+ cohort. In addition, anti-dsDNA Ab and aCL Ab were significantly more frequent at baseline in the 97LN+ cohort (Table 2).

**Histological findings at LN diagnosis**

Biopsy slides were available for review in 82% (9/11) of the 97LN+ cohort and 54% (15/28) of the 82LN+ cohort. The proportion of patients with proliferative lesions (ISN/RPS 2003, Class III–VI) was similar (93.3% vs. 88.9%). Also, NIH Activity Index (median score 8) and Chronicity

![Fig. 1. Flow chart illustrating the assembling of two subsequent inception cohorts of SLE patients in northern Norway with subdivision in LN cohorts (82LN+ and 97LN+ cohorts) and cohorts without LN (82LN− and 97LN− cohorts). Outcomes reflect events during a 10-year follow-up from SLE diagnosis. LN, lupus nephritis; SDSC, sustained doubling of serum creatinine; ESRD, end-stage renal disease; CVD, cardiovascular disease.](https://academic.oup.com/ndt/article-abstract/26/2/620/1891939)

![Fig. 2. Kaplan–Meier curves showing the risk of developing LN in two subsequent inception cohorts of SLE patients. The relative risk reduction in 97acr cohort compared with the 82acr cohort was 38%, 36% and 42% at 1, 5 and 10 years, respectively (P = 0.1 by log-rank test).](https://academic.oup.com/ndt/article-abstract/26/2/620/1891939)
The first column includes all patients with LN and shows the multivariate analysis of significant variables first examined in univariate analysis (drug treatment excluded, P < 0.1). The last column includes only late-onset LN (≥3 months after SLE diagnosis) in a univariate analysis. Drug treatment refers to use during the three first months after SLE diagnosis. Significant values are presented in bold. CI, confidence interval.

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Discussion

This study shows a nearly 50% reduction of the incidence of LN in this region over the last decade. In addition, ESRD development was not seen during that time even though demographics, histological severity, cytotoxic drug treatment and overall mortality in LN patients had not changed. These findings were paralleled by an increased use of sensitive autoantibody detection assays and pulse steroid therapy as well as anticoagulant and antihypertensive treatment.

The reported AIR in the last decade (0.45/100 000) is in line with the data on LN incidence in the north-west of the UK, where in 2001, the AIR of biopsy-proven LN was 0.4/100 000 [6]. In addition, our data document and quantify a decrease in AIR over time, which confirms the Swedish data that renal involvement in SLE is becoming less frequent in this region [18]. The only other quantitative data available are from Okinawa, Japan where AIR for ESRD due to LN increased from 1.6 to 4.6/100 000 between 1972 and 1991. This dramatic increase was possibly related to more severe renal involvement in Asian SLE patients at the time, but no comparative data after 1991 are available [19].

Despite the declining incidence, the prevalence of LN in this region increased to nearly 14/100 000 in 2007; the

![Fig. 3. Histological classifications of renal biopsy findings in patients with lupus nephritis in two subsequent inception cohorts. Bars indicate percentage of patients in each category. (a) Histologic classification follows the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis [13,14]. (b) The National Institutes of Health Renal pathology scoring system [15]. AI, Activity Index (maximum score 24); CI, Chronicity Index (maximum score 12).]

![Table 3. Treatment regimens used in the two different cohorts of patients with lupus nephritis after establishing LN diagnosis]

<table>
<thead>
<tr>
<th></th>
<th>97LN+, n (%)</th>
<th>82LN+, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 (18)</td>
<td>3 (27)</td>
<td>4 (15)</td>
<td>0.390</td>
</tr>
<tr>
<td>NSAID</td>
<td>9 (82)</td>
<td>9 (33)</td>
<td>0.011</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>6 (55)</td>
<td>2 (7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>9 (82)</td>
<td>17 (63)</td>
<td>0.444</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>2 (18)</td>
<td>7 (25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>5 (46)</td>
<td>1 (4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>5 (46)</td>
<td>3 (11)</td>
<td>0.030</td>
</tr>
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Cytotoxic drugs include the use of azathioprine, cyclophosphamide, mycophenolate mofetil or methotrexate. Methylprednisolone was usually instituted in combination with i.v. cyclophosphamide. Significant values are presented in bold.
prevalence in females reached 22/100,000, compatible with the rates reported from the UK in white (5.6/100,000), Indo-Asian (21/100,000) and Afro-Caribbean patients (99/100,000) [6], and patients from Japan (68/100,000) [19]. The relative risk reduction for LN (36% for early onset and 40% for late onset) over time indicates that some form of LN prevention has occurred in the latest cohort. Given the prolonged follow-up, it seems unlikely that this risk reduction is a spurious observation. More likely, certain features in the 97acr SLE cohort have convened to prevent LN in a number of patients. Due to the lack of dependable data prior to fulfillment of SLE criteria, we can but speculate about the causes of the observed primary LN prevention (less renal involvement at SLE diagnosis). The landmark US military study showed a mean onset of anti-DNA Ab production 2.2 years before SLE diagnosis [20], and the increased frequency of anti-dsDNA Ab detection in our dataset suggests that increased availability and utilization of serologic testing have facilitated an earlier case recognition in SLE [7]. The snake poison ancrod decreases fibrin deposition and crescent formation, and improves renal function in LN through decreasing factor VIII and von Willebrand factor levels, normalizing platelet hyperaggregation, and increasing prostaglandin I2 [28,29]. Others have shown that renal impairment in LN is partly due to an exaggerated synthesis of renal thromboxane A2 by infiltrating monocytes, which can be reversed by a thromboxane antagonist [30,31]. Aspirin also improves endothelial dysfunction through acetylcholine-induced peripheral vasodilatation [32]. Finally, treatment with low-molecular-weight heparin delays LN development by preventing immune complex binding to the glomerular basement membrane [33,34]. These experimental data thus support, although through various mechanisms, our idea that early institution of anticoagulant therapy may have a preventive effect on LN development.

LN characteristically appears within the first years after diagnosis of SLE, and in our study, 67% of the patients were diagnosed during the three first months. In a multivariate analysis, SLEDAI ≥10 and ESR >20 as baseline predictors of the chronic renal disease [2,25]. The 1997 update of ACR classification [8] reinforced screening for aPL Ab which likely contributed to an earlier case recognition in the cohort 97acr. aPL Ab represent a risk factor for thrombotic events including renal and glomerular capillary thrombosis [3,22,25]. The aPL-associated renal thrombotic microangiopathy that may occur in SLE is not well delineated but may be initiated by intraluminal accumulation of fibrin [26], together with aPL-dependent upregulation of endothelium-derived vessel contraction factor (pre-pro-endothelin-1) mRNA expression [27]. The snake poison ancrod decreases fibrin deposition and crescent formation, and improves renal function in LN through decreasing factor VIII and von Willebrand factor levels, normalizing platelet hyperaggregation, and increasing prostaglandin I2 [28,29]. Others have shown that renal impairment in LN is partly due to an exaggerated synthesis of renal thromboxane A2 by infiltrating monocytes, which can be reversed by a thromboxane antagonist [30,31]. Aspirin also improves endothelial dysfunction through acetylcholine-induced peripheral vasodilatation [32]. Finally, treatment with low-molecular-weight heparin delays LN development by preventing immune complex binding to the glomerular basement membrane [33,34]. These experimental data thus support, although through various mechanisms, our idea that early institution of anticoagulant therapy may have a preventive effect on LN development.

Lupus nephritis, and antihypertensive and anticoagulant therapy

Fig. 4. Cumulative survival following SLE diagnosis in two subsequent inception cohorts of SLE patients during 1978–2006 in Northern Norway. (a) Survival in patients in the acr97 and acr82 cohort with lupus nephritis (LN+) (P = 0.3). (b) Survival in patients in the acr97 and acr82 cohort without lupus nephritis (LN−) (P = 0.2). P-values reflect the Gehan statistics.
variables were associated with the occurrence of LN (Table 1). These variables are found in other studies as well and reflect the general and renal inflammatory state seen early in the disease course of SLE patients with multiorgan affection. The observation that no patient in the 97LN+ developed ESRD in the initial 10 years of disease is likely related to anti-inflammatory treatment. The therapeutic approach at this centre has been relatively uniform with initial i.v. pulse steroid treatment and cyclophosphamide pulses for 3–6 months reserved for patients at increased risk for irreversible organ damage (raised serum creatinine, LN WHO Class III/IV). While our data are not randomized, intravenous pulse therapy is effective in rapidly reducing inflammatory changes and also lessens the need for long-term, high-dose oral corticosteroid therapy and its side effects [35,36].

Baseline SLEDAI scores and initial immunosuppressive treatment for non-renal manifestations were not found to influence the risk of late-onset LN, but hypertension at SLE diagnosis was not only a marker for LN in general but especially a risk factor for the development of late-onset LN. Arterial hypertension has a major impact on the progression of end-organ damage in general, and the additional observation that lower diastolic blood pressure and increased use of antihypertensive drugs were associated with the absence of progression to ESRD in 97LN+ cohort supports a strategy of strict blood pressure in all SLE patients. We did not consistently register the class of antihypertensive drugs, but ACE-I over the last decade has become the drug of choice in arterial hypertension in SLE in our department [12]. Mesangial cell (MC) proliferation is a prominent feature of human and experimental LN, and precedes the increase of extracellular matrix in the mesangium and subsequent glomerulosclerosis. Treatment with ACE-I but also with heparin and/or low-protein diet and statins reduces experimental MC proliferation [37,38]. ACE-I or ARB enhance the capacity of mesangial cells to phagocytes and remove renal immune complexes in lupus mice [39,40].

Antimalarial drugs were prescribed more often in the acr97, but we did not detect a protective effect on the development of late-onset LN. Antimalarials are not thought to have any short-term benefits in LN due to the slowness of its effects, but multiple other long-term benefits (improvement in overall disease activity, lipid profiles and thrombotic risk) may have contributed to the improved renal outcome in the acr97.

The limitations of this study need to be recognized. With low numbers, the study has limited statistical power which increases the risk of not detecting a real difference (type II errors). The study cohort was overwhelmingly Caucasian, increasing the risk of not detecting a real difference (type II errors). The study has limited statistical power which needs to be validated a possible renoprotective effect of the indicated non-immunological treatment options in SLE. Finally, while our data indicate potential new ways to improve renal disease in SLE, it is important to realize that the effect on patient survival was limited.

In summary, our results argue for the monitoring of SLE patients at a very early stage of the disease, even before fulfilling scientific classification criteria, with regard to the presence of low avidity anti-dsDNA, aPL Ab and arterial hypertension as risk factors for LN. When combined with early treatment that includes immunosuppressive and vasoactive drugs, this may reduce LN severity and perhaps even help prevent LN development.

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Conflict of interest statement. None declared.

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