Determinants of renal functional outcome in lupus nephritis: a single centre retrospective study

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Summary

Background: Lupus nephritis (LN) is a rare disease but is the strongest predictor of poor outcome in patients with Systemic Lupus Erythematosis (SLE). It is associated with significant morbidity, with 10–20% of patients developing end stage renal failure. As there is a paucity of randomized clinical trial data in LN, and no consistent literature regarding baseline factors that predict renal outcome, we were prompted to analyse our centre’s complete experience of managing LN.

Methods: A retrospective analysis was undertaken of all patients presenting to our renal centre with biopsy proven LN from 1979–2003. Patients were divided into two categories, those with stable or deteriorating renal function over time. Baseline parameters were correlated with renal outcome.

Results: Complete clinical records were available for 45 (40 female) patients. Mean (SD) age of onset of SLE was 32 ± 14 years, and mean age onset of LN was 36 ± 13 years. Patients were followed up for an average of 74 ± 56 months. Four patients (9%) had WHO Class II LN, 11 (24%) WHO Class III and there were 15 (33%) each in Class IV and V, respectively on renal biopsy. Five (11%) patients presented with acute renal failure and all had proliferative changes on biopsy. The chief arbiters of renal functional deterioration over follow up were longer time to development of LN (P = 0.04), a high platelet count and worse baseline renal function (both P = 0.05). There was a trend relating low haemoglobin or membranous histology to poor renal outcome, and Class IV histology to better outcome.

Conclusion: The study has identified that longer time to development of LN, high platelet count and poorer renal function at baseline suggest a worse renal outcome in LN. The study was small but LN is a rare condition. A combination of factors is likely to influence renal outcome in LN and larger prospective trials are required to ascertain consistent baseline prognostic markers.

Introduction

Lupus nephritis (LN) is a rare disease but is the strongest predictor of poor outcome in Systemic Lupus Erythematosis (SLE). Up to 60% of SLE patients develop renal involvement, usually within 5 years of disease onset. Of patients, 10–20% of patients with LN go on to develop end stage renal failure. However, there is a paucity of randomized clinical trial data in LN and the literature lacks a clear description of factors that may determine renal functional outcome in patients with this condition. We decided to review the entire experience of our renal centre in managing patients with LN during an interval spanning a generation.

Methods

We conducted a retrospective epidemiological analysis of all patients presenting to our renal
centre (catchment population of 1.1 million people per year during the study period) with biopsy proven LN from 1979–2003. Our aim was to determine factors at baseline, namely WHO classification, clinical presentation, baseline clinical parameters and treatment and their influence on renal functional outcome. Biopsies were classified according to the 1982 WHO Classification. Patients with the current classification of WHO stage VI LN, representing advanced sclerosing glomerulonephritis or end-stage kidney disease, were excluded. Activity and chronicity indices were not available, and therefore, not included in this study. Glomerular Filtration Rate (eGFR) was estimated by use of the Cockcroft-Gault formula as this was the most widely used estimate of GFR prior to 2006. Deteriorating renal function was defined as a reduction of eGFR of >1 ml/min/yr over the period of follow up. This definition was chosen as previous studies have shown that the ageing process in the general population can be associated with decline in eGFR of 0.5–1 ml/min/year deterioration. The STROBE recommendations for reporting of observational studies were adhered to when preparing this article.

Statistical analyses

All analyses were performed using StatsDirect. Results are given as mean±SD. Chi-square and logistic regression were used to test significance of categorical variables. Independent groups categorized as stable or deteriorating renal function over time were compared with an unpaired t-test. Correlation analyses among quantitative variables in patients with deteriorating renal function were done using the Pearsons correlation test.

Results

By interrogation of the histopathology database, 50 patients were identified as having LN during the study period, providing a crude incidence of 1.9 cases per million population per year. Complete clinical records were available for analysis in 45 patients (40 female). Mean (SD) age of onset of SLE was 32±14 years (range 15–69 years). Mean age onset of LN was 36±13 years (17–69 years). Patients were followed up for an average of 74±56 months (12–300 months). Thirty-four patients were White Caucasian (76%), eight Indo-Asian, two Afro-Caribbean, one Sino-Asian. The initial presentation was with joint and skin manifestations in 36 (80%) and 28 patients (62%), respectively. Renal involvement was present in 16 patients (36%) at presentation. Other baseline characteristics (at the time of LN presentation and biopsy) were creatinine 105±68 μmol/l, creatinine clearance 69±32 ml/min, urinary protein 3.3±2.8 g/day, systolic blood pressure 136±19 mmHg and diastolic blood pressure 82±10 mmHg. Twenty-one patients (48%) had developed LN within 10 years of onset of SLE, the longest latency time to development of LN was 27 years, indicating great variability in onset of LN.

The renal biopsy results are shown in Table 1. Four patients (9%) had WHO Class II (mesangial proliferative nephritis), 11 (24%) WHO Class III (focal proliferative), and there were 15 (33%) each in Class IV (diffuse proliferative) and V (membranous), respectively. Five (11%) patients presented with acute renal failure and all had proliferative changes, four had WHO IV and one had WHO III. Fifteen (33%) patients presented with nephrotic syndrome of which 27% had WHO IV, 53% WHO V and 20% WHO III. The remaining 25 (56%) patients had asymptomatic proteinuria and the histology revealed 28% in each class WHO III, IV, and V, and 16% were WHO II. Five patients were rebiopsied. Transformation was noted in all of these cases (one from Class II–IV, one from Class III–IV, one Class III–V and two from Class IV–V). All patients with WHO IV were diagnosed with LN within 5 years of diagnosis with SLE.

For the primary analysis we separated patients into two groups, those who deteriorated or maintained stable renal function over time. The results are shown in Table 2. Four patients (9%) required dialysis; three of these subjects had membranous histology (WHO V) and one had diffuse proliferative glomerulonephritis. A strong association was shown between haemoglobin level and rate of change of GFR (r = –0.94, P = 0.05), supported by results from previous studies that identify anaemia as a risk for progression of renal function decline in LN, as well as in all forms of CKD. One of the dialysis patients (LN for 15 years) died as a result of end-stage kidney disease.

As can be seen, the chief arbiters of renal functional deterioration were longer time to

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Histological description</th>
<th>Number</th>
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<tbody>
<tr>
<td>WHO II</td>
<td>Mesangial proliferative</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>WHO III</td>
<td>Focal proliferative</td>
<td>11 (24%)</td>
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<tr>
<td>WHO IV</td>
<td>Diffuse proliferative</td>
<td>15 (33%)</td>
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<tr>
<td>WHO V</td>
<td>Membranous</td>
<td>15 (33%)</td>
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development of LN, a high platelet count and worse baseline renal function. All patients with a deterioration of GFR had proteinuria >0.5 g/day at baseline. There was a trend relating membranous histology to poor outcome, and Class IV to better outcome. There were various treatment regimes used, all of which included steroids. Thirty-four patients received cyclophosphamide either alone or in various combinations as described earlier. No particular treatment regime was predictive of renal functional outcome.

Discussion

Historically, there has been uncertainty in identifying consistent factors, which predict a worse renal prognosis in LN. The revised WHO classification divides pathology into six classes, which have prognostic value and may determine which treatments are used. In our single centre experience, which spanned a long period of follow up, patients with lower baseline haemoglobin, higher creatinine values, higher platelet count and WHO Class V had a worse renal functional outcome. Membranous GN was most common in the minority of patients who eventually required dialysis. Previous reports have shown that LN is more common and also more severe in men with SLE, as opposed to women, but this was not borne out in our study, presumably because the numbers were too small (five men) to show a difference. It is well recognized that LN has a higher incidence in Black and Asian populations and this was supported by our study as 24% of LN patients were in these ethnic groups, whereas our catchment population for renal services is predominantly (95%) White Caucasian. One quarter of patients with SLE usually display thrombocytopenia. Thrombocytosis, as shown in our study, is an unusual finding. Thrombocytosis may be an indication of disease activity and reactivity, and in some patients with SLE, it has been shown to be a clue to autosplenectomy. Previous studies show that renal survival is mainly determined by the severity of renal involvement. For example, WHO Class IV confers a worse renal survival than other histological
classes of LN.\(^1,7,8\) Interestingly, patients with WHO Class IV had a better renal functional outcome in our study, however, this may be due to more aggressive treatment. We did not take clinical flares, histological transformation and treatment regimes into account. Howie et al. found that histological chronicity index was more predictive of renal functional outcome than WHO Classification,\(^9\) and this may be more useful as a clinical marker of eventual renal functional decline. Due to the retrospective biopsy results, the old WHO Classification was used in this study in order to maintain consistency. A recent study has shown that lower baseline GFR and filtration fraction (a measure representing GFR to effective renal plasma flow using \(^{125}\)iodotlamate and \(^{131}\)hippuran, respectively) correlated with worse renal outcome, though this was not consistent on an individual basis.\(^10\) Our results support this finding, patients with deteriorating renal function had higher baseline creatinine values. Despite LN being an aggressive condition it was pleasing to see that the likelihood of developing end-stage renal disease was low with four (11%) patients requiring renal replacement therapy, which is in keeping with renal survival data published by others.\(^1,11\) The finding that longer time to development of LN confers a worse renal outcome is somewhat counter-intuitive. However, it may be that these patients had been undiagnosed for longer, and so presented with more advanced renal disease. Due to lack of clinical trial evidence treatment regimes are varied. Newer drugs such as MMF show encouraging results,\(^12\) however, optimum medical management is still undecided.

The course of LN is dependent on a large number of factors.\(^13\) As it may run a potentially severe course, negative prognostic baseline measurements would greatly assist treatment decisions and ensure closer monitoring to prevent renal decline. Our study was small but LN is a rare condition and the majority of published studies do not contain larger numbers,\(^12\) and so we believe this observational study is a valid enrichment of the literature. Although retrospective, our study spans a long period of follow up and trends in baseline factors, which may be predictive of renal outcome are evident. Larger prospective trials are still required to ascertain consistent baseline prognostic markers.

**Conflict of interest:** None declared.

**References**


