Long-term outcome of adult-onset minimal-change nephropathy

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Abstract
Background. Adult-onset minimal-change nephropathy has been associated with a slower response to corticosteroids and a less benign prognosis when compared to children. However, there are few long-term outcome data reported.

Methods. We have reviewed retrospectively 51 idiopathic adult-onset minimal-change nephropathy patients investigated and treated at a single centre.

Results. Male to female ratio was 1:1.4, mean age at diagnosis was 37 years, and average length of follow-up was 14.1 years. Significant comorbidity was identified in 33%. A raised serum creatinine was found in 55% but returned to normal almost invariably upon remission. At presentation, hypertension was found in 47% of patients, microscopic haematuria in 33%, hypercholesterolaemia and hypertriglyceridaemia in 96%, and hyperuricaemia in 42%. Remission (complete or partial) was achieved by 46, 70 and 92% within 4, 8 and 21 weeks respectively, in patients treated with steroids; steroid resistance was encountered in 8%. The time to remission was positively correlated with age \( (P=0.002) \) and initial albumin level \( (P=0.005) \), and negatively correlated to the number of subsequent relapses \( (P=0.029) \); 33% of patients had a spontaneous remission at some time during the disease course. Patients with multiple relapses were treated with cyclophosphamide and 63% of them had remained in remission after 5 years. Hypertension was present in 25% of patients after an average interval of 11 years. At the time of the final follow-up, only three patients had a raised creatinine and all but three patients were in complete remission.

Conclusions. Adult-onset minimal-change nephropathy shares the same good long-term outcome as the childhood counterpart, with sustained remission and preserved renal function.

Key words: glomerulonephritis; minimal-change nephropathy

Introduction

Minimal-change nephropathy (MCN) is the commonest cause of nephrotic syndrome (NS) in children, accounting for 75–77% of all cases in the International Study of Kidney Disease in Children [1,2]. It responds consistently to corticosteroid therapy. The prompt response within a few weeks is itself an integral part of the clinicopathological description of this disease. Seventy-six to 97% of children suffering from the disorder will relapse after treatment [3,4], and a significant number will relapse frequently. However, overall there is a good long-term prognosis, with an extremely low risk of developing chronic renal failure. In contrast, MCN accounts for less than 25% of adult-onset primary nephrotic syndrome [5,6], the response to corticosteroids is delayed when compared to children [7,8], and prolonged therapy may be necessary to achieve complete remission. A variable proportion of adult patients (31–76% in different series) relapsed during a follow-up period from 2.9 to 7.6 years [5,7–9]. Compared to children, older patients initially tend to have a higher incidence of hypertension and impaired renal function. The adult-onset disease may appear to have a less benign prognosis, and the steroid responsiveness so readily equating with MCN in childhood can be more difficult to define.

There are few long-term outcome data reported for adult patients, in respect of disease course and complications. We therefore reviewed retrospectively 54 adult-onset MCN patients treated in the Manchester Royal Infirmary renal unit presenting between 1950 and 1993.

Subjects and methods

Definitions

Nephrotic syndrome was diagnosed by the presence of oedema, heavy proteinuria (at least 3.5 g/day), together with a serum albumin less than 30 g/l.

Complete remission (CR) was achieved when proteinuria dropped to less than 0.3 g/day, with disappearance of oedema and normalization of serum albumin level.

Partial remission (PR) was defined as loss of oedema, and
proteinuria falling to the range of 0.3–3.5 g/day, with normalization of serum albumin level. Relapse of nephrotic syndrome was defined as reappearance of more than 3.5 g/day proteinuria for at least 2 weeks. Relapse of proteinuria referred to reappearance of proteinuria more than 0.5 g/day for at least 2 weeks. Frequent relapsers were defined as having two relapses within 6 months of the initial response, or four relapses within any 12-month period [10]. Steroid-dependent patients were those who relapsed within 2 weeks of stopping or decreasing the dose of steroid. Hypertension was diagnosed when two sequential diastolic blood pressure readings were 90 mmHg or higher, or when two systolic blood pressure readings were greater than 160 mmHg [11]. Impaired renal function was defined as serum creatinine higher than 130 μmol/l or serum urea higher than 10 mmol/l, or when glomerular filtration rate was less than 50 ml/min. Time to achieve first remission was defined as the time from starting steroid therapy to the first day on which complete/partial remission was observed. For patients with spontaneous remission, the time from onset of disease to the same endpoint was noted. Time to first relapse in those patients who relapsed was defined from (a) remission (prior to successfully weaning off steroid for steroid-dependent patients, i.e. relapse-free period) and (b) from the time of stopping therapy to the onset of the first relapse.

Patients

From the 101 nephrotic patients who had ‘no light-microscopy change’ on renal biopsy, presenting to the renal unit of Manchester Royal Infirmary during the years 1950–1993, 54 were identified as adult-onset minimal change nephropathy (onset after 15 years of age). Patients with no light-microscopy change on renal biopsy were excluded if the presentation was not associated with nephrotic syndrome or if a subsequent biopsy revealed another diagnosis. Three patients were on non-steroidal anti-inflammatory drugs at the time of presentation and were excluded from the analysis. This cohort of 51 patients, then, constitutes a strictly defined series of idiopathic MCN with long-term follow-up. They were all followed-up in the same renal unit, for an average of 14.1 years (range 0.5–38.9).

Renal biopsies were performed on all these patients, usually at the onset of NS, or when referred to our hospital. The light-microscopic changes of segmental sclerosis or hyalinosis, more than mild mesangial proliferative change, any positive immunofluorescence staining, or electron-dense deposits excluded the diagnosis of minimal-change nephropathy (onset after 15 years of age). Patients with no light-microscopy change on renal biopsy were excluded if the presentation was not associated with nephrotic syndrome of apparently abrupt onset, or if a subsequent biopsy revealed another diagnosis. Three patients were on non-steroidal anti-inflammatory drugs at the time of presentation and were excluded from the analysis. This cohort of 51 patients, then, constitutes a strictly defined series of idiopathic MCN with long-term follow-up. They were all followed-up in the same renal unit, for an average of 14.1 years (range 0.5–38.9).

Statistical analysis

The values of parameters are given as mean (± standard deviation) where appropriate. Differences between groups were assessed by non-parametric statistical tests: Fisher’s exact test, Chi-square test, Mann–Whitney U test, or Wilcoxon matched-pairs signed-ranks test where appropriate. Correlation between clinical, pathological and response data were assessed by Spearman correlation coefficients and multiple regression model.

Results

Patient profile at presentation

There were 21 male and 30 female patients (M:F 1:1.4), with a mean age of 37 years (median 36, range: 15–77). Increasing age at presentation was associated with higher serum urea and creatinine levels, systolic and diastolic blood pressure, and lower creatinine clearance (all P<0.0005). Seventeen patients (33%) had history of allergy and 17 (33%) had a documented upper respiratory tract infection preceding onset of either the first episode or a subsequent relapse. Significant comorbidity was identified in a further 17 patients (Table 1).

All patients presented with nephrotic syndrome with mean proteinuria 16.4 g/24 h (range 3.5–51). Mean serum albumin was 17 g/l (range 4–29), and below 10 g/l in four patients (7.4%). Urine protein selectivity (measured by the IgG: transferrin clearance ratio) was measured in 31 episodes of NS in 25 patients. In 13 episodes it was ≤0.1 and in 20 episodes it was ≤0.15.

Renal impairment

A raised serum creatinine (>130 μmol/l) was found in 28 patients (55%) when they first presented, and overall, 31 patients (61%) had a raised creatinine during the active nephrotic phase. GFR below 50 ml/min was found in 29 patients (57%) overall and in 24 patients (47%) at first presentation. One patient developed acute oliguric renal failure requiring temporary peritoneal dialysis (highest serum creatinine 870 μmol/l) during the active phase of NS.

Table 1. Comorbidity of the patients at presentation and subsequently

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Number of patients</th>
<th>Before onset (n)</th>
<th>After onset (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy history</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI preceding NS</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gout</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heart block</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosacea</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*a In the form of hay-fever in seven patients and drug allergy in eight. 
*b Two preceding onset of MCN (7 and 17 years), one after 14 years.
age, hypertension on presentation, and presence of vascular change in histology (presence of arteriolosclerosis or hyaline degenerative change) were found to correlate with a raised serum creatinine or urea level and with the creatinine clearance, while other histological features and the amount of proteinuria did not (Table 2). Proteinuria was negatively correlated with creatinine clearance \( (r = -0.3266, P = 0.035) \) but is an inexact marker if the prevailing plasma albumin level is not taken into account. Multiple regression showed that age was the main factor correlated with impaired renal function \( (P = 0.0002) \). The presence of vascular change did correlate with higher systolic blood pressure \( (165.5 \text{ versus} \ 138.6 \text{ mmHg}, \ P = 0.0044) \), but not with diastolic blood pressure \( (94.1 \text{ versus} \ 87.6 \text{ mmHg}, \ P = 0.1075) \).

Upon achieving remission, serum creatinine values almost invariably returned to normal. A raised serum creatinine occurred much less frequently during subsequent relapses, (14 of 83 episodes in which it was measured, 16.9%). Only one patient developed progressive impairment of renal function, beginning at 45 months from original presentation, and eventually required long-term renal replacement therapy. This patient had severe, diffuse, atheromatous disease of the aorta and is thought to have developed renal failure as a result of this.

**Hypertension**

Hypertension was present in 24 patients (47%) at presentation and 21 of them became normotensive upon remission. However 11 patients (22%) required antihypertensive medication on average 11 years after onset.

**Microscopic haematuria**

Microscopic haematuria was found in 17 patients (33.3%) during active NS, but it disappeared in all on remission. No patient presented with macroscopic haematuria.

### Renal histology

An average of 15.7 glomeruli were obtained per renal biopsy (71 biopsies in 51 patients), showing globally sclerosed glomeruli in 16 patients (31%), marginal mesangial proliferation in 7 (14%), and weakly positive immunofluorescence in 12 (24%), regarded as insignificant by the histopathologist. Arteriolosclerosis or hyaline degenerative change of vessels was noted in 11 patients (22%), clustering in the older patients (25 years of age). Tubular degenerative changes or non-specific interstitial infiltrate were observed in 32 patients (63%), including the one who developed acute tubular necrosis upon an ischaemic insult to the kidneys, presumably relating to documented severe atheromatous aortic disease.

### Hyperlipidaemia and hyperfibrinogenaemia

Hypercholesterolaemia (\( > 7 \text{ mmol/l} \)) was detected in all but two patients (96%), while hypertriglyceridaemia (\( > 1.8 \text{ mmol/l} \)) was found in 22 of the 23 patients in whom it was measured. Increased fibrinogen levels (\( > 4 \text{ g/l} \)) were detected in 27 of 32 patients (84%). All these values fell markedly when remission was achieved (Table 3).

### Rheumatoid factor

Rheumatoid factor was found in low titre (SCAT 1 in 64–128) in 3 of 44 patients (6.8%) during the nephrotic phase. All became negative upon remission.

### Uric acid level

Hyperuricaemia (serum urate\( > 0.39 \text{ mmol/l} \) in females and \( > 0.49 \text{ mmol/l} \) in males) was found during the active nephrotic stage in 13 of 31 patients (42%) in whom it was measured. The level dropped significantly on remission. These hyperuricaemic patients had a significantly higher serum creatinine level and were older \( (P<0.03) \). However, there was no correlation with serum albumin or proteinuria (Table 4).

### Serum immunoglobulins

The mean serum IgG level (Table 3) was significantly decreased during nephrotic phase, but returned to normal rapidly with remission. IgA level was in the low normal range initially, but there was a trend to increase on remission. The IgM level was slightly increased in the nephrotic phase, but fell to normal upon remission.

### General management

Most patients received a high-protein diet (1 g protein per kg body weight plus 1 g per g of proteinuria/24 h), fluid restriction, and diuretics as required. Some had

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Impaired renal function</th>
<th>Normal renal function</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.8 ± 18</td>
<td>31.1 ± 13.4</td>
<td>0.0198*</td>
</tr>
<tr>
<td>24-h proteinuria</td>
<td>18.2 ± 9.5</td>
<td>14.8 ± 6.9</td>
<td>0.2327</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>16.6 ± 4.2</td>
<td>18.4 ± 6.4</td>
<td>0.3279</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>153.9 ± 28.2</td>
<td>130.9 ± 24.5</td>
<td>0.0197*</td>
</tr>
<tr>
<td>Diastolic BP(^b)</td>
<td>93.6 ± 14.5</td>
<td>81.9 ± 12.3</td>
<td>0.0118*</td>
</tr>
<tr>
<td>Sclerosed glomerulus(^a)</td>
<td>10/28</td>
<td>6/16</td>
<td>0.9067</td>
</tr>
<tr>
<td>Interstitial change(^a)</td>
<td>20/28</td>
<td>8/16</td>
<td>0.1556</td>
</tr>
<tr>
<td>Vascular change(^b)</td>
<td>11/28</td>
<td>0/16</td>
<td>0.0028*</td>
</tr>
<tr>
<td>Microscopic haematuria</td>
<td>8/28</td>
<td>5/16</td>
<td>0.8529</td>
</tr>
</tbody>
</table>

\(^a\) \text{P value from Mann-Whitney U. Chi-square, and Fisher's exact tests.}

\(^b\) \text{Presence of globally sclerosed glomerulus in renal biopsy.}

\(^c\) \text{Presence of non-specific interstitial infiltrate, hyaline change, or tubular atrophy.}

\(^d\) \text{Presence of arteriolosclerosis, hyaline degenerative change.}
Table 3. Biochemical parameters in nephrotic and remission phases

<table>
<thead>
<tr>
<th></th>
<th>First presentation</th>
<th>Nephrotic phase</th>
<th>On remission</th>
<th>ρb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>14.7 ± 10.6 (n = 47)</td>
<td>14.6 ± 10.7 (n = 44)</td>
<td>6.5 ± 2.6</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>186.8 ± 137 (n = 44)</td>
<td>192.7 ± 141.4 (n = 40)</td>
<td>88.8 ± 30.7</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>CrCl (ml/min)</td>
<td>48.3 ± 31.6 (n = 42)</td>
<td>48.4 ± 31.9 (n = 38)</td>
<td>93.6 ± 41.5</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>17.5 ± 5.4 (n = 48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/d)</td>
<td>16.4 ± 8.7 (n = 47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>15.6 ± 5.6 (n = 45)</td>
<td>17.2 ± 5.6 (n = 25)</td>
<td>7.4 ± 2.4</td>
<td>&lt;0.0005*</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>5.6 ± 4.7 (n = 20)</td>
<td>8.9 ± 6.8 (n = 5)</td>
<td>2.6 ± 1.3</td>
<td>0.0431*</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>6.6 ± 2.1 (n = 24)</td>
<td>6.7 ± 1.4 (n = 13)</td>
<td>3.5 ± 1.1</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Urate (mmol/l)</td>
<td>0.4 ± 0.12 (n = 25)</td>
<td>0.51 ± 0.22 (n = 11)</td>
<td>0.32 ± 0.05</td>
<td>0.0076*</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>3.3 ± 1.8 (n = 21)</td>
<td>3.8 ± 2.4 (n = 11)</td>
<td>9.3 ± 2.9</td>
<td>0.0044*</td>
</tr>
<tr>
<td>IgA (g/l)</td>
<td>2.1 ± 0.9 (n = 21)</td>
<td>1.9 ± 1 (n = 8)</td>
<td>2.3 ± 1.1</td>
<td>0.1083</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>2.2 ± 1.4 (n = 21)</td>
<td>2.3 ± 1.6 (n = 12)</td>
<td>1.7 ± 0.8</td>
<td>0.0367*</td>
</tr>
</tbody>
</table>

*Total number of patients for each parameter measured varies depending on available paired data of both nephrotic and remitted phases. ρ: P value calculated using Wilcoxon matched-pairs signed-rank test.

Table 4. Hyperuricaemia during NS

<table>
<thead>
<tr>
<th></th>
<th>Hyperuricaemic patients (n = 13)</th>
<th>Normouricaemic patients (n = 18)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (μmol/l)</td>
<td>234.5 ± 95.9</td>
<td>132.9 ± 81.2</td>
<td>0.0051*</td>
</tr>
<tr>
<td>Age</td>
<td>47 ± 19.1</td>
<td>30.5 ± 15.9</td>
<td>0.0029*</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>18.2 ± 4.4</td>
<td>19.1 ± 4.9</td>
<td>0.7148</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>15.3 ± 5.9</td>
<td>19.1 ± 5.1</td>
<td>0.0655</td>
</tr>
</tbody>
</table>

*P value from Mann-Whitney U test.

Effect of albumin infusion

Twelve of the 51 patients received i.v. albumin infusion during the nephrotic stage. This did not affect the response time to corticosteroid therapy (5.9 versus 6.1 weeks, P = NS), nor the overall relapse frequency (1.5 versus 2, P = NS).

Initial corticosteroid treatment and response (Figure 1)

Dosage and duration of corticosteroid used varied considerably but the most frequent regimen employed was prednisolone 1.5 mg/kg/day or 2 mg/kg/alternate days until remission (mean 4.3 weeks), followed by tailing off at a rate of 10 mg/day/week. Thirty-eight percent of patients received from 2 to 6 months therapy, the longer courses being given mainly because of evidence of steroid dependence or because of a low starting dose. One patient was given ACTH before short-term enteral tube feeding when the oral high protein intake was not tolerated initially, and some had intravenous albumin infusion when there was severe hypoproteinaemia and gross fluid retention and a diuresis was difficult to establish. Prophylactic heparin was used in seven patients during their nephrotic phase, when prolonged bedrest was unavoidable. Antihypertensive therapy was given as required. Acute dialysis was given for one patient with acute renal failure.

![Fig. 1. Rate of first remission with corticosteroid treatment.](image-url)

referral to the Manchester Royal Infirmary, but was given standard oral prednisolone therapy for subsequent relapses, and was included in the analysis of response to corticosteroids. Two patients were given pulse methylprednisolone followed by standard oral prednisolone therapy: one in association with grossly impaired renal function at the onset of disease (but requiring the addition of a cytotoxic agent), and the other (receiving multiple pulses of methylprednisolone) for a concomitant exacerbation of multiple sclerosis.

Of the 51 patients, 37 were given a full course of oral prednisolone on presentation, and 12 patients were untreated. One patient received pulse methylprednisolone (multiple sclerosis), one developed steroid psychosis, necessitating a switch to cyclophosphamide after 3 weeks treatment. By the 4th week, 18 patients (50%) achieved remission (17 CR, 1 PR), 26 by the 8th week (70%, 21 CR, 5 PR), 33 by the 16th week (89%, 27 CR, 6 PR) and 34 by the 21st week (92%, 28 CR, 6 PR). Three patients (8%) were steroid resistant with an average duration of steroid therapy given for 16.3 weeks. Their average age was 41, proteinuria 17.4 g/24 h, and serum albumin 17.3 g/l, similar to the rest of the group. Only one of them had weak staining of IgM and C3 in the biopsy, while electron-microscopy showed only features of MCN.
Only age and presenting albumin level were positively correlated with the time to achieve first remission with corticosteroid ($r=0.5118$, $P=0.002$, and $r=0.4884$, $P=0.005$ respectively). Patients over 30 years old required a mean of 7.9 weeks to achieve complete remission while those younger required 4.1 weeks on average ($P=0.0195$). The response time was negatively correlated with the number of subsequent relapses ($r=-0.3742$, $P=0.029$). No patient who responded after the 12th week of treatment relapsed. Pathological factors (presence of sclerosed glomerulus, mild mesangial proliferation, immunofluorescence staining and vascular or interstitial changes), and clinical parameters (presenting creatinine, microscopic haematuria) did not affect the response time to corticosteroid treatment.

**Duration of remission with corticosteroid therapy** (Figure 2)

Of the 34 patients who achieved remission with corticosteroid therapy, 17 patients relapsed during the first year of follow-up. Another three patients relapsed in the second year. Only two patients had their first relapse after 4 years of remission. For those with relapses, the duration of remission was not correlated with serum creatinine and albumin levels, or the total number of relapses experienced. Those who relapsed within 6 months or 12 months from onset had similar mean total number of relapses when compared with those who relapsed later (3.5 versus 3.1, $P=NS$; and 3.5 versus 2.9, $P=NS$ respectively). The only factors to affect the timing of the relapse was age, with younger patients tending to relapse earlier ($r=0.4205$, $P=0.041$), and duration of corticosteroid treatment, those receiving shorter courses relapsed earlier ($r=0.6242$, $P=0.013$).

**Relapses after corticosteroid-induced remission**

In total, 32 of the 51 patients experienced relapses on from one to eight occasions during follow-up, and 26 were from the group of 34 who responded to initial corticosteroid treatment (76%). These 26 patients had an average of 3.3 relapses. Among them, 13 were steroid dependent, none was a frequent relaper, five had just one relapse, and eight had two or more relapses. The number of relapses was negatively correlated with the response time to corticosteroid, as stated above, with serum albumin level ($r=-0.4552$, $P=0.009$), and the duration of corticosteroid therapy ($r=-0.4156$, $P=0.049$). There was no correlation with age ($P=0.071$), serum creatinine level, or the timing of the first relapse.

Eight patients (24%) had not relapsed after a mean follow-up of 12.9 years. They had a similar sex ratio and mean age to those who had relapsed, but had required a longer response time to corticosteroid (9 versus 5.3 weeks, $P=0.088$), and had received longer courses of corticosteroid therapy (46.6 versus 26.3 weeks, $P=0.0522$). None of the pathological parameters were different between the two groups, nor were the incidence of microscopic haematuria and positive allergy history.

**Cyclophosphamide therapy**

Cyclophosphamide was used in 22 patients, given in a dose of 2–2.5 mg/kg/day for 8 weeks. For most of the steroid-dependent patients, and those with multiple relapses, it was given after steroid-induced remission, and the corticosteroid was then gradually tailed off. A second course of cyclophosphamide, again given at 2–2.5 mg/kg/day for 8 weeks, was given to six patients, mainly because of continued relapses including one with steroid-dependent relapse. Three patients had further relapses despite the second course of treatment.

For the 22 patients given cyclophosphamide, two were given for steroid resistance, nine for steroid dependence, five for multiple relapses ($\geq 2$), and one because of steroid psychosis. The other five patients were given cyclophosphamide after their first relapse. The two steroid-resistant patients remitted in 6–14 weeks, and one had further relapses which were steroid sensitive.

For the nine steroid-dependent patients, they were all weaned off steroid after cyclophosphamide treatment. However, five had further relapses, including two with steroid-dependent relapses. There were four other steroid-dependent patients who were given corticosteroid only, but not cyclophosphamide, as they were of reproductive age. The mean total number of relapses, as well as the proportion of time off corticosteroid treatment, were similar in the cyclophosphamide group and the prednisolone only group. None of the factors including age at onset, age at cyclophosphamide treatment, sex, duration of disease or number of relapses before cyclophosphamide treatment were different between the groups with and without relapse after cyclophosphamide. The mean time to relapse was 18 months (range 6–27).

For the five patients given cyclophosphamide for multiple relapses, 4 (80%) had sustained remission (mean follow-up after treatment 9.1 years).
Minimal change nephropathy in adults

Considering all the 22 cyclophosphamide-treated patients together, 86% maintained remission at 1 year (50% for corticosteroid therapy), 74% at 3 years (35% for corticosteroid therapy), and 63% at 5 years (26% for corticosteroid therapy, Figure 2). Relapse after the 4th year was unusual.

Leukopenia developed during six of the 29 courses of cyclophosphamide given for the whole group. They all recovered with adjustment of dosage and no serious complication was encountered. Two patients developed carcinoma of caecum and carcinoma of clitoris after two and one courses of cyclophosphamide respectively.

Other immunosuppressive therapies

Cyclosporin A was given to one patient when she relapsed again after two courses of cyclophosphamide given for her steroid dependence, and maintains remission. Another patient was given cyclosporin A for her multiple sclerosis relapses, when she was in stable partial remission from her nephrotic syndrome. Prolonged azathioprine treatment was given in two patients in an attempt to prevent further relapse but was unsuccessful in one of them.

Spontaneous remission

Besides the 12 patients who were untreated following initial presentation (8 of whom achieved CR in 80 weeks, 4 PR in 77 weeks), five other patients had a spontaneous remission following a relapse. Overall 33% of patients experienced a spontaneous remission at some time. They required significantly longer time to achieve remission (79 versus 6 weeks, \( P = 0.03 \)), compared to those who had corticosteroid-induced remission. Fewer patients with initial spontaneous remission had a relapse \( (P = 0.0269) \), but there was no difference in the timing of the first relapse.

Pregnancies

There were eight normal pregnancies in five female patients during the follow-up period. They were all uneventful and the patients were all in remission at the time of conception. Four pregnancies were after cyclophosphamide courses. No exacerbation of the nephrotic syndrome occurred. However, one patient who became pregnant only 1 month after her first remission had premature labour at 24 weeks gestation, and the baby died soon after delivery. She then experienced a relapse of the NS, but had two normal pregnancies subsequently.

Non-nephrotic proteinuria

A total of seven patients had 1 or 2 episodes of ‘asymptomatic’ non-nephrotic proteinuria during follow-up. They were not associated with other reasons to account for the proteinuria, and in all proteinuria subsided rapidly and spontaneously.

Complications

Six patients experienced steroid-related side-effects other than cushingoid appearance: one had steroid myopathy, one suffered bilateral avascular necrosis of hips, two exhibited a steroid psychosis (one with past history of schizophrenia), one experienced recurrent bleeding gastric ulcer, and one developed diabetes mellitus. Apart from the patient with AVN of the hips, requiring bilateral hip replacement, all other complications settled when the steroid was stopped or substituted with cytotoxic therapy. A total of four patients developed symptomatic peripheral vascular disease or ischaemic heart disease during the long follow-up period—all 51 patients had been asymptomatic prior to the onset of MCN.

Pulmonary embolism occurred in three patients (5.9%) with one fatality (before complete remission was achieved); seven other patients were put on prophylactic subcutaneous heparin with no venous thrombosis noted. One patient, presenting with severe right iliac fossa pain together with gross fluid retention, underwent laparotomy, with ascites as the only finding. It was postulated that this may have been due to a ‘pseudo-intussusception’ of oedematous bowel.

Three patients developed malignancies after onset of disease. Patient FF was found to have carcinoma of caecum 11 years after onset of MCN, 5 years after his second course of cyclophosphamide for multiple relapses. Patient ES developed carcinoma of clitoris after receiving methotrexate for her psoriatic arthropathy and a single course of cyclophosphamide. Patient LP, who developed chronic lymphocytic leukaemia 20 years after onset of MCN, had received no cytotoxic therapy.

Last follow-up status

The mean serum creatinine and creatinine clearance at the last follow-up (mean 14.1 years, range 0.5–38.9) were 98 \( \mu \text{mol/1} \) and 84 \( \text{ml/min} \) respectively. Apart from one patient on chronic haemodialysis because of end-stage renal failure from severe atheromatous aortic disease, only two patients had a raised creatinine (237 and 256 \( \mu \text{mol/1} \)). The first had impaired renal function ever since onset of the disease, and the second was on cyclosporin A to maintain remission after failing to respond to two courses of cyclophosphamide therapy. Overall, a residual raised serum creatinine was observed in three patients (5.9%), and a decreased serum creatinine clearance in 4 (7.8%), all above 60 years of age.

Apart from the patient on chronic haemodialysis, and the one who died of pulmonary embolism during NS, all except three patients were in complete remission without therapy. Excluding eight of them having a follow-up less than 2 years, the mean follow-up after the last relapse in these patients was 11.6 years (median 9.6). There were two patients with persistent asymptomatic proteinuria of 1–2 g/day after partial remission. One other patient had, at this last follow-up, a relapse.
with heavy proteinuria and hypoalbuminaemia, but no oedema.

Hypertension was found in 13 patients (25%) after an average interval of 11 years. Except for three (one was on long-term cyclosporin A therapy), all had a history of transient hypertension at presentation.

Discussion

Minimal-change nephropathy is the commonest cause of nephrotic syndrome in children, and has the unique characteristic of prompt response to corticosteroid therapy, but with a high incidence of relapses, which tend to be frequent in about half the childhood patients. The response rate to corticosteroid in adults with MCN is quoted as 81–97% [7–9,13]. However, data on the long-term outcome in terms of response to corticosteroid and cyclophosphamide, renal function impairment, hypertension, and possible long-term complications are scarce. It is probable that adult cases diagnosed as MCN purely on the basis of no light-microscopy change will have undetected glomerular pathology to account for their steroid resistance [14]. Therefore in the present series we have excluded all patients who had subsequent renal biopsies showing another glomerular histology when steroid resistance was encountered, so as to define in strict clinical and histological terms an adult series of MCN, followed exclusively at a single centre for many years, which might give a clear picture of its behaviour.

The mean age of our adult-onset MCN patients was 37, and the male to female ratio 1:1.4. The absence of the male predominance seen in childhood disease (M:F ratio 1.7–2:1) [2,15,16] has also been observed in other adult series [7,17,18]. Thirty-three percent of patients had a history of allergy and in 33% an upper respiratory tract infection had preceded the onset of NS. This is similar to the childhood population [19]. The allergy history did not affect the relapse tendency, which is different from the findings in childhood patients [20]. There were a significant number of patients with a coexisting inflammatory or autoimmune disease. This therefore constitutes a unique characteristic of the adult patients.

In contrast with childhood patients, where non-selective proteinuria was found in 15–25% only [2,21], urine protein selectivity in this series was more variable, with 36 and 52% having a ratio ≤ 0.1 and ≤ 0.15 respectively.

A raised serum creatinine (≥ 130 µmol/l) was found in 55% of patients on presentation. The incidence is much higher than in childhood patients (10–32.5%) [2,21,22], but is consistent with findings in other adult series (40–70%) [7,17,23]. Increasing age, hypertension and presence of vascular change in histology were associated with a higher creatinine level during the nephrotic phase. The degree of proteinuria had a negative correlation with the creatinine clearance, as found by others [24–26]. Besides the proposed mechanism of tubular obstruction secondary to interstitial oedema [27], underlying impairment of renal reserve may be associated with the vascular degenerative process seen on histology.

Hypertension, detected in 24 (47%) patients on presentation, was more common in older patients, and usually disappeared after the nephrotic phase. The incidence is higher than in children with PKN (6–20%) [2,21,22]. A raised systolic blood pressure at presentation was related to the presence of vascular changes on renal histology, and raised systolic and diastolic blood pressure were associated with a higher initial serum creatinine. Eleven of these 24 patients required antihypertensive therapy many years later but the final incidence of hypertension, 25% of the patients in the study, is not different from that of the general population of similar age [28].

Transient microscopic haematuria was present in 33% of our patients, and it was not correlated with any parameters of outcome of the disease. The incidence is similar to that in childhood patients (13–36%) [2,21,22].

Hypertriglyceridaemia was found in 96% of patients in whom it was measured. The levels of both cholesterol and fasting triglyceride fell significantly upon achieving remission, the mean values of these within 4 weeks after remission were still abnormal (7.3 and 2.5 mmol/l respectively), and there was a time lag before they returned normal. There was an apparently low incidence of atherosclerotic vascular disease (only 4 patients in the long-term follow-up) despite the universal, albeit transient, presence of a specific dyslipidaemiac state. This is worth further consideration since it is possible that the altered high-density lipoprotein pattern in MCN [29] has an intrinsic protective effect on the atherosclerosis process.

Only three patients (6.8%) had a transiently positive rheumatoid factor (RF) during the nephrotic phase, in low titre. This contrasts with the high incidence of IgM RF in adults with MCN reported by Endoh et al. [30]. A link with polyclonal B cell hyperactivation in MCN patients as suggested by those authors is therefore not supported by our results.

The hyperuricaemia found in 42% of patients during nephrotic phase was transient and was not associated with any clinical manifestation. This mirrors the findings in both IgA and membranous nephropathy patients reported by Hosaya et al. [31]. They also reported a lowered uric acid urinary excretion in the majority of their patients. Our finding of the correlation of hyperuricaemia with higher serum creatinine and increasing age is not unexpected.

The serum immunoglobulin levels we found in relapse were in accord with those in MCN children (significant decrease in IgG, modest decrease in IgA, and increase in IgM) [32]. The raised IgM level fell back to normal right upon remission of NS, unlike the persistent elevation in remission noted in Giangiacomo’s series [32].

Intravenous albumin infusion in minimal-change nephrotic syndrome has been related to (a) a prolonged time to achieve complete remission, (b) further
increases in proteinuria before remission was achieved, and (c) a higher relapse rate in the first 2 years of follow-up [33]; we have found no such correlation.

Of the 37 patients given corticosteroid therapy, the overall response rate was 92%. This is comparable to the few reported adult series (81–97%) [7–9,13], despite the variation in dosage and regimen. There was a slower response when compared to childhood patients in whom 82–92% went into remission in 4 weeks, and 90–95% in 8 weeks [34]. In adult patients the reported response rates have been 37–48% in 4 weeks, 59–76% in 8 weeks, and 76–93% in 16 weeks. Comparable rates for our series were 50% of patients in 4 weeks, 70% in 8 weeks and 89% by 16 weeks. This consistent trend of a slower response in adult patients indicates that a longer trial of corticosteroid therapy should be given in adults. Increasing age was associated with a longer time to respond, supporting the finding of Korbet et al. [8], but not that of Nolasco et al. [7]. We have found a highly significant positive correlation between serum albumin level and response time, the more severely hypoalbuminaemic patients responding faster. The response time to corticosteroid therapy was negatively correlated with the number of subsequent relapses. Those patients responding after 12 weeks of treatment did not relapse. None of the pathological or clinical parameters (presenting creatinine, microscopic haematuria) affected the response time.

Seventy-six percent of patients achieving remission with corticosteroid therapy relapsed, and among them 50% were steroid dependent. The overall rate of steroid dependence was therefore 35% of all steroid-treated patients. The relapse rate in children is reported as 76–97% [3,4], slightly higher than our adult patients. The lower relapse rate of 31% at 3-year follow-up by Nair et al. [9] was not reproduced in our data. They attributed the better result to a tapering steroid regimen, but this was used in the majority of our patients as well. We have not found any relationship between the timing of the first relapse with the total number of relapses. However, younger patients tended to relapse earlier ($P=0.041$).

The incidence of steroid dependence is higher in our study than in that reported by Nolasco (14%) [7]. We have not identified any clinical or pathological factors associated with this group of patients. We have found that the serum albumin level was negatively correlated with the number of relapses. Therefore the more hypoalbuminaemic patients responded to corticosteroid faster, but also had more relapses. The group without relapses (24%) had a significantly longer response time as well as a longer course of corticosteroid therapy, but none of the pathological parameters considered were different.

Of the nine steroid-dependent patients given cyclophosphamide therapy, all were weaned off corticosteroid after treatment. However, only 44% had sustained remission, while 22% had further steroid-dependent relapses. The simple comparison with those steroid-dependent patients not given cyclophosphamide showed no benefit in terms of total number of relapses or the time off corticosteroid treatment. We have found no factors which will predict relapse after cyclophosphamide. Although there are studies in children showing that a 12 week course of cyclophosphamide (when compared with an 8 week course for steroid-dependent nephrotic syndrome), reduced the relapse rate from 78% to 33% at 2 years [35], others have found no benefit from the longer courses, after prolonged follow-up (75–76% relapsed by 5 years) [36,37]. This issue should be addressed by controlled studies in adults, since such a course of cyclophosphamide is usually safe even in long-term follow-up [38]. We found, like Jones et al. [39], that a second course of therapy, though not always preventing further relapse, tended to further prolong remission.

Cyclophosphamide was found to have benefited steroid-resistant patients and those with multiple relapses. Eighty percent of the multiple relapers had a sustained remission averaging 9.1 years. Considering all cyclophosphamide-treated patients together, 74% and 63% had sustained remission at 3 and 5 years respectively. Ponticelli et al. [40] found a 63% sustained remission at 2 years after 8-week cyclophosphamide course for steroid-dependent and frequently relapsing nephrotic syndrome, but their series included children.

For the six patients receiving a second course of cyclophosphamide, three had further relapses (with 2 having a longer duration of remission when compared with that after their first course).

A number of patients, particularly those presenting before 1960, were managed conservatively without corticosteroid therapy. They required a much longer time to achieve remission (mean 79 weeks), two-thirds of which were complete and one-third partial. However, they also tended to have a lower incidence of relapse ($P=0.0269$). The overall rate of 33% of our patients experiencing a spontaneous remission was comparable to that after relapses of steroid-sensitive nephrotic syndrome in children (31%) [41]. Unfortunately, none of these spontaneously remitting adult patients developed complications related to prolonged proteinuria. It has been suggested that by allowing 10–14 days for spontaneous remission in frequently relapsing or steroid-dependent MCN children, a reduced total corticosteroid usage and hence toxicity might be achieved [42]. There was no suggestion that the same strategy applies to adults, since the time to achieve remission was so much more prolonged.

Most of the pregnancies of our MCN patients were uneventful and without exacerbation of the disease. We witnessed one premature labour at 24 weeks gestation followed by a relapse of the NS, in a woman who became pregnant soon after achieving her remission.

Pulmonary embolism was documented in only 5.9% of patients. One patient who had a severe nephrotic syndrome, died of massive pulmonary embolism after 6 weeks corticosteroid therapy, having by then only achieved partial remission. She had not received prophylactic heparin, the value of which is now recognized. Sepsis, including peritonitis and pneumococcal sepsis,
has been a major complication in children [43–45] but was not encountered in our patients.

Transient leukopenia occurred, however, during six of the 29 courses of cyclophosphamide given to the whole group, without any serious complication. Two patients developed carcinoma (citrinosis and caecum). It is not possible to establish whether these represented potential long-term side-effects of the cytotoxic therapy or were incidental findings.

MCN in adults does not seem to be identical with the childhood counterpart. A different sex ratio, a different urine protein selectivity, a slower response time to corticosteroid therapy, a lower incidence of frequent relapses, and a different spectrum of complications of the nephrotic syndrome would support this contention. Adult patients also tend to have a higher incidence of transient hypertension and impaired renal function. However, we have shown that they have a similar association with allergy and upper respiratory tract infection, a similar problem with steroid dependence and spontaneous remission rate, and most importantly, they shared the same good long-term outcome, in terms of having sustained remission and preserved normal renal function. The pathogenesis remains to be determined and may be similar; there are differences in immunological responses, at least as these are represented by the response to treatment.

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