Outcome of idiopathic membranoproliferative glomerulonephritis in children

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The aim of this multicentre study was to analyse the long-term outcome of idiopathic membranoproliferative glomerulonephritis (MPGN) according to histological type and to the presence of C3 nephritic factor. Fifty patients aged 2–14 years at the onset of the study were followed over 2–20 years; 26 patients had MPGN type I, 17 had type II and 7 had type III. Treatment was variable. At the last observation, 30 patients had reached terminal and four pre-terminal renal failure. The median survival probability until renal death was 15.3, 8.7 and 15.9 years for disease types I, II and III respectively (difference between MPGN types I–III versus type II: \( p = 0.013 \)). The presence of an initial nephrotic syndrome was associated with a more rapid progression \( (p = 0.018) \). C3 nephritic factor was of no prognostic value. We conclude that the outcome of MPGN mainly depends on the histological type observed.

C3 nephritic factor, membranoproliferative glomerulonephritis, renal failure

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Idiopathic membranoproliferative glomerulonephritis (MPGN) is a primary glomerular disease that is a major cause of renal failure in adolescents and young adults (1, 2). Studies of glomerular fine structure and of the mechanisms of complement activation have led to a distinction between three types of MPGN (3–5). The presence of the C3 nephritic factor (C3 NeF) has been reported to be more or less specific for MPGN, and appears to influence its outcome (6, 7). Controversial issues exist on the pathogenesis and treatment of MPGN (8).

In 1978, the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN) started a multicentre study on children with biopsy-proven MPGN (9). The aim of the study was to describe the clinical course in relation to histological findings in kidney biopsies and changes in serum complement, particularly with regard to the presence of C3 NeF. A short interim report on the clinical outcome and complement profiles of the same patients reported here has been published previously (9). In the present paper we give an account of the long-term prognosis of MPGN.

Patients and methods

From 1978 to 1982, 50 children with idiopathic MPGN (27F, 23M) were recruited in 17 paediatric nephrology centres. Twenty-nine patients had initial symptoms before 1978 for a median time of 3.0 years. The age range was 2.2–13.7 (median 9.8) years at the apparent onset of MPGN. The patients were followed regularly one to two times a year over a period of 1.9–20.5 (median 11.4) years. All living patients were re-examined in 1992–1994 except five patients who were earlier lost to follow-up. At the last observation or at renal death the median age of the patients was 21.2 (range 5.4–29.1) years.

The diagnosis of idiopathic MPGN was made according to the clinical presentation (proteinuria, nephrotic syndrome (NS), haematuria, hypertension) and to the findings of renal biopsies obtained by light microscopy.
electron microscopy (including silver impregnation of ultra-thin sections) and immunofluorescent studies. Biopsy material was reviewed centrally (H Thoenes, Department of Pathology, University of Mainz). Criteria for the classification of MPGN have been reported previously (3, 4). Secondary forms of MPGN (8) were excluded. The median time from apparent onset of the disease to renal biopsy was 0.4 (range 0.1–4.1) years, with 11 patients undergoing a biopsy procedure more than 1 year after onset.

Proteinuria in the range 150–1000 mg m⁻²/24 h (P +) was regarded as mild, and proteinuria > 1000 mg m⁻²/24 h was regarded as severe (nephrotic range) (P + +). NS was defined as the presence of severe proteinuria accompanied by serum albumin levels of < 25 g l⁻¹. Hypertension was defined as an arterial blood pressure > 140/90 mmHg or the application of antihypertensive agents. Chronic renal failure (CRF) corresponded to the presence of serum creatinine (SCR) levels that were regularly above 106 μmol l⁻¹ (1.2 mg dl⁻¹), and end-stage renal disease (ESRD) corresponded to the start of regular dialysis therapy, except in one patient who had undergone a primary kidney transplant.

Patients' sera were regularly screened centrally for the presence of C3 NeF using a cell-bound alternative C3-convertase (10).

The treatment was left to the discretion of each centre. Fifteen patients received prednisone for less than 6 months and four patients received it for longer periods (usually on alternate days). Eight patients received cyclophosphamide and seven received various other immunosuppressive agents. Dipyridamole was given in 18 patients (four with NS at onset), usually over several years after diagnosis, in combination with acetylsalicylic acid (14 patients) and/or dicoumarol (four patients). Diuretics and/or various antihypertensive agents were given to 32 patients. Eight patients received symptomatic therapy alone either in the form of diuretics and/or antihypertensive drugs. Four patients received no drugs at all.

Statistics

For data evaluation the Statistical Analysis System (SAS Institute, Cary, NC, USA) was used. The following procedures were applied: PROC FREQ (Fisher's exact test for 2 × 2 or larger tables) (11), PROC PLOT (graphical presentation of percentages) (12) and PROC LIFETEST (survival analysis) (13).

Results

At apparent onset 27 patients had clinical and laboratory signs of NS which was persistent in 7 and transient in 20 patients; 23 patients had mild proteinuria. Six patients with mild proteinuria later developed NS. Macroscopic haematuria initially occurred in 10 patients and hypertension was present in 15 cases. Urinary findings are summarized in Table 1 according to the histological type of MPGN. The distribution was similar in the different types of MPGN, except for macro-haematuria which was more frequent in type II (6/17) than in type I (3/26) (ns; Fisher's exact test, p = 0.069). C3 NeF activity was detected at various times during the follow-up in 30 patients (Table 2); it was more frequent in MPGN type II than in types I or III (88% vs 42%; Fisher's exact test, p = 0.003). Two C3-NeF-positive patients had partial lipodystrophy (both type II) and one had hemihypertrophy (type I).

The outcome of the disease at the last observation is summarized in Table 3. Thirty patients reached ESRD.

Table 1. Clinical presentation at apparent onset of MPGN.

<table>
<thead>
<tr>
<th>MPGN type</th>
<th>I (n = 26)</th>
<th>II (n = 17)</th>
<th>III (n = 7)</th>
<th>Total (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotic syndrome (NS)</td>
<td>13</td>
<td>10</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Mild proteinuria (P)</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>Macrohaematuria (HM)</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Microscopic haematuria (Hm)</td>
<td>16</td>
<td>9</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension (Hy)</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2. Distribution of C3 nephritic factor in serum according to the different histological types of MPGN.

<table>
<thead>
<tr>
<th>C3 nephritic factor</th>
<th>MPGN type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Positive</td>
<td>11</td>
</tr>
<tr>
<td>Negative</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 3. Outcome of MPGN at the last observation.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MPGN type</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-stage-renal disease (ESRD)</td>
<td>14</td>
</tr>
<tr>
<td>(dialysis or transplantation)</td>
<td>15.3</td>
</tr>
<tr>
<td>Time from onset to ESRD (median in years)</td>
<td>2</td>
</tr>
<tr>
<td>Pre-terminal renal failure (CRF)</td>
<td>6</td>
</tr>
<tr>
<td>Proteinuria &gt; 1 g m⁻²/24 h without CRF</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria &lt; 1 g m⁻²/24 h without CRF</td>
<td>2</td>
</tr>
<tr>
<td>Cured</td>
<td>26</td>
</tr>
</tbody>
</table>

* Two patients died in each group.

95% confidence interval, 9.3–15.9 years.
At the last observation four patients had CRF at 16–19 years after apparent onset and 14 had proteinuria in the presence of normal SCR levels. Proteinuria was severe in 7 cases followed for 2–20 years, and mild in 7 followed for 8–20 years. Two patients (both type I) were in complete remission. Four patients died after they had reached ESRD.

The probability of renal survival was analysed according to sex, initial presentation with or without NS, macrohaematuria, hypertension, histological type, presence of C3 NeF and the use of dipyridamole for treatment. By the Wilcoxon test, a significant association of renal survival was found with the covariates initial proteinuria or NS \((p = 0.016)\) and histological types I + III versus type II \((p = 0.021)\), but not with sex \((p = 0.607)\), macrohaematuria \((p = 0.356)\), hypertension \((p = 0.637)\), C3 NeF \((p = 0.856)\) or use of dipyridamole \((p = 0.117)\). Of 27 patients with an initial NS, 20 reached ESRD; two had CRF and five had proteinuria (one P++) at the last observation. In contrast, of 23 patients with mild proteinuria at onset only ten developed ESRD, two CRF, and 11 ended up with persistent proteinuria (six P++) or were cured. ESRD occurred in 13 of 20 patients with a transient NS and in all with persistent NS (ns). In the six patients with initial proteinuria who later developed NS, ESRD was obligatory, whilst it occurred only in four of 17 patients with initial proteinuria without a change in NS (Fisher's exact test, \(p = 0.002)\). Only two out of 11 patients with macrohaematuria did not reach CRF or ESRD (ns).

In the survival analysis the median time to reach ESRD after apparent onset of MPGN was 8.7 years in type II compared to 15.3 years in type I and 15.9 years in type III (Fig. 1). Ten years after onset renal survival was 47% in type II compared to 64% in type I and 83% in type III. There was a statistically significant difference in renal survival between types I + III versus type II \((p = 0.013)\). However, the interval from the first SCR above 106 \(\mu\)mol\(^{-1}\) (1.2 mg\(\text{dl}^{-1}\)) to ESRD was not significantly different \((p = 0.087)\), although after 3 years there was a trend that patients with type II deteriorated more rapidly than those with type I or III disease (Fig. 2). The difference in renal survival from onset of the disease to ESRD in patients starting with NS against those with mild proteinuria was significant \((p = 0.018, \text{Fig. 3})\). However, when patients with NS at onset were analysed separately according to histological type, no

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**Fig. 1.** Renal survival probability from apparent onset of idiopathic MPGN to ESRD. (—) MPGN type I; (•••) MPGN type II; (— - —) MPGN type III.

**Fig. 2.** Renal survival probability from first SCR above 106 \(\mu\)mol\(^{-1}\) (1.2 mg\(\text{dl}^{-1}\)) to ESRD in patients with idiopathic MPGN. (—) MPGN types I and III; (•••) MPGN type II.

**Fig. 3.** Renal survival probability from apparent onset of disease to ESRD in patients with idiopathic MPGN. (—) Patients with NS at apparent onset of the disease; (•••) patients without NS at apparent onset.
characteristic findings were found in renal survival. ESRD developed in nine of the ten initial NS patients with type II compared with 11 of 17 NS patients with type I or type III disease (Fisher's exact test, \( p = 0.161 \)).

Our analysis of the outcome in patients with and without detectable C3 NeF activity at any time revealed no significant difference. When C3-NeF-positive patients were analysed separately the difference between the outcome in type II versus types I + III remained significant; ESRD developed in 12 of 15 positive patients with type II against 6 of 15 positive patients with type I or III (Fisher's exact test, \( p = 0.03 \)).

The outcome was also analysed according to treatment with or without dipyridamole, combined or not with acetylsalicylic acid or dicoumarol. There was no significant difference in renal survival between these two groups. However, in patients with mild proteinuria at onset the progression to CRF or ESRD was less frequent (2/12) when receiving dipyridamole than when the drug was not given (8/11) (Fisher's exact test, \( p = 0.01 \)).

Discussion

In earlier reports an overall renal survival of 50% at 10 years was calculated for children with MPGN (14, 15). Our results are slightly better. The long observation period of our patients and the statistical analysis used in this study enabled us to investigate more closely some factors influencing the prognosis. It was shown previously that patients who never develop NS survive longer than those with severe degrees of proteinuria (14–16). This observation was confirmed for our population who in presence of initial NS reached ESRD 6.6 years earlier than patients with mild proteinuria (Fig. 3). It seems that, with regard to the prognosis, initial clinical manifestation is more important than the histological type of MPGN. The presence of NS seems also to be detrimental if it occurs during the later stage of the disease. In contrast to other studies we could not prove an influence of initial macrohaematuria (17) or initial hypertension (16).

We found a higher probability of renal survival in MPGN types I and III compared to type II, irrespective of the initial presence of a NS. For statistical reasons types I and III were combined in our analysis because their clinical and histological presentation is similar compared to type II. From Fig. 1 it seems that type III has a slightly better prognosis than type I.

Controversial opinions have been expressed regarding the renal survival with different morphological types of MPGN. Cameron et al. (15) could not detect significant differences, although remissions occurred less frequently in patients with type II disease. Habib et al. (17) found a 50% renal survival at 18 years for type I and at 9 years for type II, values which, despite considerable advances in the symptomatic treatment of CRF in the last 20 years, are similar to our data.

We confirmed that the C3 NeF in serum is more frequently found in type-II than in type-I patients (6, 15). We failed, however, to detect any significant difference in renal survival according to the presence of C3 NeF activity. This suggests that the C3 NeF status per se is of no prognostic value. This result is in contrast to a report (6) in which adult patients with C3 NeF activity deteriorated more rapidly. The discrepant results might be due to analytical differences in C3 NeF screening which is poorly standardized.

Many drugs have been proposed for the treatment of MPGN, including corticosteroids (2, 16, 18–20), various immunosuppressive agents (8, 15, 20–23) and anticoagulants with platelet inhibitors (22–25). Most studies were uncontrolled. A randomized, double-blind trial showed only a marginal effect of alternate-day prednisone treatment on the rate of deterioration of the glomerular filtration rate in children (19). Our study was not controlled and only a few patients were treated with steroids or immunosuppressive agents over longer periods. Eighteen children received anticoagulants and platelet inhibitors (24). We got the impression that in the presence of mild proteinuria this regimen delayed the progression to CRF or ESRD. However, recent data reported in the literature would deny any benefit of anticoagulants (24, 25).

In conclusion, the results of the study suggest that children suffering from MPGN continue to have an unfavourable late prognosis. The outcome is determined mainly by the initial presentation and by the histological type of the disease, while the presence of C3 NeF appears to play no role. There is a continuing need for new therapeutic options for MPGN.

References


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