Efficacy of school urinary screening for membranoproliferative glomerulonephritis type 1

Y Kawasaki, J Suzuki, R Nozawa, H Suzuki

Aims: In order to evaluate the efficacy of a school urinary screening programme, children with membranoproliferative glomerulonephritis (MPGN) type 1 were studied.

Methods: A total of 52 patients who had been diagnosed with MPGN type 1 from 1970 to 1997 were studied; 35 were identified after 1974 on screening (group S), and 17 were identified by presenting symptoms (group N), mostly before 1989.

Results: Mean blood pressure was 89 mm Hg in group S and 104 mm Hg in group N; urinary protein excretion was 0.9 g/day in group S and 3.0 g/day in group N. Histopathological evidence of chronic changes was found in six group S and 15 group N patients. No patients in group S had renal insufficiency, but five patients in group N required regular haemodialysis.

Conclusions: Results suggest that early identification by school urinary screening may enable early management and so improve prognosis of MPGN.

PATIENTS AND METHODS

Patients
We enrolled 52 patients who had been diagnosed with MPGN type 1 following renal biopsy at the Department of Pediatrics, Fukushima Medical University School of Medicine between January 1970 and December 1997.

These patients were divided into two groups. Group S (screening group) consisted of 35 patients who were asymptomatic and who were identified after 1974 by yearly SUS; group N (symptomatic group) consisted of 17 patients who had been identified by signs and symptoms of acute nephritis (n = 9) or nephrotic syndrome (n = 8). The causative agents, clinical features, laboratory data, and prognosis were determined.

Definitions
Haematuria was defined as present if microscopic examination showed five or more red blood cells per high power field. Proteinuria was evaluated by 24 hour quantitative measurement. Nephrotic syndrome was defined as the presence of proteinuria (≥40 mg/m²/h) and a serum albumin less than 25 g/l, with or without oedema. Hypertension was defined as a systolic or diastolic blood pressure greater than the 95th centile for age, based on the Pediatric Task Force Recommendation. Acute nephritis was defined as haematuria with at least two of hypertension, raised serum urea or creatinine, and oliguria. The clinical status of each patient at the latest observation was classified as follows:

- Stage 0—normal: the patient was normal on physical examination, with normal urine and renal function
- Stage 1—minor urinary abnormalities: the patient was normal on physical examination, with microscopic haematuria or proteinuria less than 40 mg/m²/h
- Stage 2—active renal disease: the patient had proteinuria of 40 mg/m²/h or greater or hypertension, and 24 hour creatinine clearance of 60 ml/min/1.73 m² or greater
- Stage 3—renal insufficiency: the patient had 24 hour creatinine clearance less than 60 ml/min/1.73 m² (including dialysis/transplant or death)

Pathology
All patients had a renal first biopsy; second biopsies were performed in 34. The specimens were assessed by light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). Material for histological study was fixed in 20% neutral formalin, and embedded in paraffin, sliced at 2–3 µm in thickness, and stained with haematoxylin and eosin or periodic acid–Schiff reagent.

To compare the biopsy specimens, a histological scoring system was modified to evaluate acute and chronic changes. Acute changes included capillary wall thickening (grade 0, normal; 1, slight; 2, moderate; 3, severe), mesangial proliferation (grade 0–3), capillary loop patency (0–3, where 0 indicates most loops patent and 3 indicates most loops closed), cellular crescent formation (scored according to the percentage of glomeruli involved: 0% = 0, 1–20% = 1, 20–50% = 2, >50% = 3), and interstitial mononuclear infiltration (grade 0–3). Chronic renal injury was estimated by determining the number of glomeruli showing fibrous crescents and segmental or global sclerosis. Each abnormality was scored 0–3 according to the number of glomeruli involved as for acute crescent formation. In addition, the combination of tubular atrophy and interstitial fibrosis was graded 0–3. Scoring was performed in a blinded fashion.

Abbreviations: BUN, blood urea nitrogen; EM, electron microscopy; IF, immunofluorescence; Ig, immunoglobulin; LM, light microscopy; MD, mesangial deposit; MPGN, membranoproliferative glomerulonephritis; SEND, subendothelial deposit; SEPT, subepithelial deposit; SUS, school urinary screening
Tissue for IF was immediately fixed in OCT compound and frozen at −80°C until use. IF examined the presence of IgG, IgA, IgM, C1q, C3, C4, and fibrinogen. Fluorescein conjugated goat antibody (IgG) towards rabbit IgG, IgA, IgM, C1q, C3, C4, and fibrinogen, respectively was used. The intensity of immunofluorescence was graded on a scale where negative = 0, mild = 1, moderate = 2, severe = 3.

Specimens for EM were fixed in 2.5% glutaraldehyde, postfixed in 1% chromiesmium, and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined and photographed by a Jem-1200EX electron microscope. EM investigated mesangial interposition and electron dense deposits, including mesangial deposit (MD), subendothelial deposit (SEND), and subepithelial deposit (SEPD). The intensity of deposit was graded as follows: MD: (–) no deposit, (+) slight deposit, (2+) moderate deposit, (3+) massive deposit; SEND: (–) no deposit, (+) small deposit in less than 50% of the glomerular capillary loops, (2+) small deposit in more than 50% of the glomerular capillary loops, (3+) massive deposit; SEPD: (–) no deposit, (+) small deposit in less than 50% of the glomerular capillary loops, (2+) massive deposit in less than 50% of the glomerular capillary loops, (3+) massive deposit in more than 50% of the glomerular capillary loops.

Treatment
Following diagnostic renal biopsy, therapy P or therapy P+C was performed. Therapy P was a combination of “pulse” methylprednisolone (30 mg/kg/day intravenous bolus, maximum 1 g) for three consecutive days, followed by four weeks of daily oral prednisolone (1 mg/kg/day) and alternate day prednisolone (1 mg/kg/day) for more than 23 months, together with an antiplatelet agent (dipyridamole 5 mg/kg/day) and anticoagulant (warfarin 1–2 mg). Therapy P+C involved the addition of cyclophosphamide 2.5 mg/kg/day for 8–12 weeks. Corticosteroids were subsequently reduced according to individual improvement in 24 hour creatinine clearance, urinary sediment, urinary protein excretion, and plasma complement.

Statistics
Data are expressed as mean (SEM). Statistical analysis was performed on a Macintosh computer with a software package for statistical analysis (Stat View, Abacus Concepts, Berkeley, California). Several variables, clearly not normal in distribution, were compared using non-parametric statistics such as the Mann–Whitney or Wilcoxon tests; the normally distributed data were compared with parametric tests such as paired or unpaired t tests. Evaluation of correlation was determined with Fisher’s r test. Renal survival rates were calculated using the life table method (Kaplan–Meier); p < 0.05 was considered significant.

RESULTS
Comparison of baseline characteristics between groups
Figure 1 shows the number of patients with MPGN type 1 in the two groups. Age at onset and duration from onset were 13.0 (3.1) and 13.8 (5.2) years in group S, and 9.1 (2.8) and 12.4 (6.3) years in group N; male:female ratio was 11:24 and 7:10, respectively, in the two groups. Baseline characteristics were similar in both groups. Patients in group N were identified between 1970 and 1989 and were less common after 1974. After 1990 all patients were identified by SUS.

Comparison of laboratory data at onset between groups
Table 1 shows laboratory data at onset. Nephrotic syndrome was present in six patients (17%) in group S and eight (47%) in group N (p < 0.05). Serum blood urea nitrogen (BUN), serum creatinine, and mean blood pressure in group N were higher than in group S. Serum albumin and 24 hour creatinine clearance in group N were lower than in group S. The number of patients with MPGN type 1.

<table>
<thead>
<tr>
<th>Group S</th>
<th>Group N</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/day)</td>
<td>0.9 (0.6)</td>
<td>3.0 (3.4)</td>
</tr>
<tr>
<td>Haematuria (macro)</td>
<td>35/35 (10)</td>
<td>17/17 (9)</td>
</tr>
<tr>
<td>BUN (mg/l)</td>
<td>143 (47)</td>
<td>286 (168)</td>
</tr>
<tr>
<td>Serum creatinine (mg/l)</td>
<td>6.0 (2.0)</td>
<td>10 (5.0)</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>65 (7.0)</td>
<td>57 (10.0)</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>39 (7.0)</td>
<td>29 (8.0)</td>
</tr>
<tr>
<td>24 h creatinine clearance (ml/min/1.73 m²)</td>
<td>105 (33)</td>
<td>65 (22)</td>
</tr>
<tr>
<td>Hypocomplementaemia</td>
<td>28/35 (80%)</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>Hypertension (mm Hg)</td>
<td>89 (15)</td>
<td>104 (15)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>6/35 (17%)</td>
<td>9/17 (53%)</td>
</tr>
</tbody>
</table>

Laboratory data at latest follow up

<table>
<thead>
<tr>
<th>Group S</th>
<th>Group N</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematuria (macro)</td>
<td>3/35 (9%, 0)</td>
<td>6/17 (35%, 0)</td>
</tr>
<tr>
<td>Hypocomplementaemia</td>
<td>6/35 (17%)</td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2/35 (6%)</td>
<td>9/17 (53%)</td>
</tr>
</tbody>
</table>

Prognosis

<table>
<thead>
<tr>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/35 (51%)</td>
<td>2/17 (12%)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>13/35 (37%)</td>
<td>7/17 (41%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>4/35 (11%)</td>
<td>3/17 (18%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>0/35 (0%)</td>
<td>5/17 (29%)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Results expressed as mean (SEM).

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of patients with haematuria or hypocomplementaemia did not differ between groups.

### Comparison of pathological findings between groups

Table 2 lists pathological findings in group S and group N.

#### IF findings at first and second biopsies

At the first biopsy, the degree of deposits of immunoglobulins (such as IgG, IgM, and IgA), complement (C1q, C3, and C4), and fibrinogen did not differ between group S and group N. At the second biopsy, the degree of deposits of immunoglobulins (such as IgG, IgA, and IgM) were more frequent in group N than in group S.

#### Light microscopy findings at first and second biopsies

At first biopsy, pathological findings of acute change did not differ between group S and group N, but chronic changes such as fibrous crescents, glomerular sclerosis, tubular atrophy, and interstitial fibrosis, were more frequent in group N than in group S. Histopathological evidence of chronic changes, including glomerular sclerosis, tubular atrophy, and interstitial fibrosis, were found in six patients (17%) in group S and 15 (88%) in group N (p < 0.05).

At second biopsy, pathological findings of acute change did not differ between groups, but chronic changes such as fibrous crescents and glomerular sclerosis were found in 15 patients in group N (88%) and one in group S (p < 0.05).

#### EM findings at first and second biopsies

At first biopsy, mesangial interposition was found in all patients; the frequencies of electron dense deposits including MD, SEND, and SEPD did not differ between groups. However, the frequencies of SEND and SEPD were lower in group S than in group N at second biopsy.

#### Comparison of therapy between groups

Fourteen patients in group S and seven in group N were treated with therapy P; 21 patients in group S and 10 in group N were treated with therapy P+C. Mean duration of steroid administration was 4.5 (1.9) years in group S and 4.8 (2.5) years in group N. Therapy and mean duration of steroid administration did not differ between groups.

### Comparison of laboratory data after therapy, prognosis, and renal survival rate

There were more patients with hypertension and/or proteinuria in group N than in group S, but the frequency of hypocomplementaemia did not differ between groups. Eighteen patients (51%) in group S and two (12%) in group N did not have proteinuria (p < 0.05). No patients in group S had renal insufficiency, although five (29%) in group N eventually required regular haemodialysis. The renal survival rate in group S was 100% over 15 years, while that in group N was 56% (p < 0.05); the renal survival rate in all patients was 83% (fig 2).

### DISCUSSION

Our study found that school urinary screening identified patients at an earlier stage of MPGN type 1 and that early identification led to improved outcome.

In 1974, the Japanese Ministry of Education began its mass urine screening programme for school children aimed at early detection of insidious renal diseases.1.
The procedure is as follows: yearly urinary screening tests are performed in first to ninth grade school children (age range 6–15 years). A first morning urine sample is collected at home in a small plastic bottle. The first morning urine is used to exclude a positive result in children with orthostatic proteinuria or floating kidney. The children bring the samples to school which are then transferred to a screening laboratory for testing. Simple dipstick methods are used to detect proteinuria and haematuria. When a urine test is positive, a second test is performed in the same manner. If this is abnormal, urine sediments are checked (a third test) microscopically and diagnostic steps taken to determine a cause for the urinary abnormalities.

Ito and colleagues reported that urinary abnormalities were more frequently detected in junior high school children than in primary school children: the rates in the respective groups were 4.44% and 1.25% at first screening, 0.42% and 0.28% at second screening, and 0.34% and 0.23% at third screening. Murakami and colleagues reviewed the details of children with abnormalities at the third examination. The rate of false positives was 13.5% in children with haematuria, and 0.7% in children with proteinuria. Among these, the prevalence of nephritis was 1%, urinary tract infection 2%, and secondary nephritis 3%.

MPGN is a progressive primary glomerulonephritis characterised morphologically by endocapillary proliferation, increased mesangial matrix, and duplication and/or thickening of the glomerular basement membrane. In many patients it leads to end stage renal failure after several years. MPGN has been diagnosed in an increasing number of asymptomatic school children detected by SUS, and there are several reports that the prognosis of patients with MPGN has improved. In a review by Kitagawa, 65–80% of MPGN patients had been detected on SUS.

Iitaka and colleagues reported on yearly screening performed from 1980 to 1985 in Kanagawa Prefecture, with a total of 370 148 urine specimens evaluated. In five children, serum C3 was below 300 mg/l; four underwent renal biopsy and were diagnosed with MPGN. These results were reported in the multicentre trial, but there are few reports regarding the long term prognosis of MPGN as detected by SUS in one single institution.

We therefore investigated the clinical and pathological findings of patients with MPGN in our hospital who had been followed up long term. In this study, 67% of patients with MPGN had been identified by SUS, 17% presented with nephrotic syndrome, and 15% presented with acute nephritis. Before 1974, all patients were identified by signs and symptoms, but after 1974, this became less common. After 1990, all patients were identified by SUS.

Donadio and colleagues revealed that factors at onset such as renal dysfunction, nephrotic syndrome, and hypertension were associated with poor prognosis of MPGN. In our study, the incidence of renal dysfunction, nephrotic syndrome, and/or hypertension at onset in the screening group was lower than in the symptomatic group. This suggests that patients in the screening group have few factors indicating poor prognosis.

There are some reports of clinical and histological improvement following steroid therapy with immunosuppressive and anti-inflammatory agents, anticoagulants, or antiplatelet agents. In particular, long term corticosteroid therapy, usually given on alternate days, has been shown to improve the outcome of MPGN. McEnery reported a 10 year cumulative renal survival of 75% for 71 patients with MPGN. In Japan, Ito and colleagues described the efficacy of treatment with “pulse” methylprednisolone followed by alternate day prednisolone in children with MPGN type 1. Our treatment regimen was a combination of “pulse” methylprednisolone followed by alternate day prednisolone, antiplatelet agents, immunosuppressive drugs, anticoagulants, and inhibitors of chronic immunological responses, particularly those of B lymphocytes and complement. Our study found a renal survival rate for all patients higher than those described in other reports. Severe side effects attributable to the treatment regime were relatively rare, with the exception of five patients with growth retardation. This “cocktail therapy” including pulse methylprednisolone and immunosuppressive drugs appeared to benefit patients with MPGN type 1.

Schmitt and colleagues found that the prognosis of MPGN can be determined essentially by tubulointerstitial findings in the renal cortex. Donadio and colleagues found a strong correlation between crescent formation and progression of renal damage. We found histopathological evidence of chronic changes, including glomerular sclerosis, tubular atrophy, and interstitial fibrosis, more frequently in the symptomatic group than in the screening group, on both first and second biopsy. On IF examination, deposits of immunoglobulins such as IgG, IgA, and IgM, electron dense deposits of sent, and SEPD at second biopsy were more frequent in the symptomatic group than in the screening group. This suggests that chronic immunoresponses in the kidney and interstitial chronic changes are more common in the symptomatic group than in the screening group.

The renal survival rate of group S was higher than that of the group N. No patient in group S had renal insufficiency, but five patients in the symptomatic group eventually required regular haemodialysis treatment. The renal survival rate and prognosis in group S were superior to those of the British children studied by Cameron and colleagues, and French children studied by Habib and colleagues. We attribute the higher renal survival rate and good prognosis in our study to earlier detection of asymptomatic patients by SUS or to the prompt administration of cocktail therapy including pulse methylprednisolone.

We conclude that early identification by yearly SUS may enable early management and improve prognosis for MPGN type 1 in children.

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REFERENCES
Examinations

One of the earliest tasks of professional development in a career in paediatrics is to pass some exams. The FRACP—Fellowship of the Royal Australasian College of Physicians—is entered by paediatric registrars here at a comparable stage to their UK counterparts. FRACP is harder than MRCPCH; well that is what my FRACP colleagues tell me, and who am I to doubt them? To compare the two:

There is no equivalent to MRCPCH part I. Access to the exam is limited by a requirement to have completed 3 years of approved training, with permission from the college, granted by the Director of Physician Training. This honorary (but high maintenance) college position held at each tertiary teaching centre acts as an effective filter to entry.

The written paper in March is multiple choice. A two hour morning paper covers medical sciences; the three hour afternoon paper examines clinical applications including investigations, practice, and therapeutics. Two thirds of candidates pass; you don’t “fail” this exam, but you may be “not successful”.

The clinical part is four months later, in July. This is a long run up, with huge training commitments generated by the registrars.

Examination centres are widely scattered, and candidates are not examined locally. This may mean a 4000 km, £400 round trip—fortunately tax deductible. Examiners combine local co-opted consultants and a college appointed group who move around the country during the exam week. Examiners attend calibration sessions to assess their style of marking. There are long cases and short cases, but no viva. On exam day, each candidate sees two long cases—an hour with the patient, 20 minutes with the examiners for each—and four short cases, each 15 minutes. They start at about 9 am, and finish at about 4 pm, during which time they are examined by four different examining teams.

Long case patients are chosen with multiple different issues. Before the exam, the examiners spend forty minutes with the patients, and are asked to use the supplied notes as little as possible. A mature attitude to the assessment, differentiation of problems and plans for management of the complex patient is expected. Each long case is marked out of seven and are weighted threefold compared with the short cases.

Short cases, with 15 minutes per patient, are markedly different from the 5 or 6 minutes in MRCPCCH. This format deliberately avoids spot diagnosis, making the point that this is a show-off skill, good in medical company but of relatively little value in real medical life. The focus is on methodical examination of the patient, eliciting subtle signs, and careful discussion. The examiners use just one short case for the morning, and one for the afternoon, four candidates each session. They’ve had 20 minutes with the patient before the examination starting, and prefer to examine on their own findings rather than the supplied notes. They will “reject” unsuitable short cases too—something an organising registrar needs to be ready for!

Each short case is marked out of seven. The clinical exam is marked out of 70; candidates need 40 or more to pass. Unsuccessful candidates are granted one further attempt at the clinical a year later. Overall, about two thirds pass, and each year a medal is awarded to the highest achiever.

Exams occur once a year; a significant stress to everyone involved. For candidates, failure means a setback to career plans for a whole year. For centres training registrars it means chunks of the year when many junior staff are utterly focused on the exam, and points when large numbers of people are away from work, being examined.

What would I take from FRACP and MRCPCCH? I would:

• remove MRCPCCH part I, and put in its place a human filter to say “you are ready, you are not”. Of course, the revenue would go, which in an ideal world would not be a factor
• Have 10 weeks between the written and clinical exam
• Have one long case only, lasting an hour and weighted appropriately
• Have four short cases, but they would each last 15 minutes
• Have a 20 minute viva.
• Hold exams twice a year, with the results a month before a national application date for jobs.

And I’d negotiate worldwide peace while I was at it.

I D Wacogne,
Chief Resident, Royal Children’s Hospital, Brisbane

Postcard from Down Under

Postcard from Down Under 25

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