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Original article

Clinical course and outcome of idiopathic membranous nephropathy in Japanese children

Hirokazu Tsukahara[1]*, Yasuo Takahashi[2], Masahiro Yoshimoto[1], Shuhei Hayashi[3], Shinichi Fujisawa[4], Fumihiko Suehiro[5], Kyoji Akaishi[2], Yasuyuki Nomura[6], Kiyoshi Morikawa[7], and Masakatsu Sudo[1]

[1] Department of Paediatrics, Fukui Medical School, Yoshida-gun, Fukui-ken, Japan
[2] Department of Paediatrics, Tenri Hospital, Tenri-shi, Nara-ken, Japan
[3] Department of Paediatrics, Fukui Red Cross Hospital, Fukui-shi, Fukui-ken, Japan
[4] Department of Paediatrics, Kouga Hospital, Kouga-gun, Shiga-ken, Japan
[5] Department of Paediatrics, Amagasaki Prefectural Hospital, Amagasaki-shi, Hyogo-ken, Japan
[6] Department of Paediatrics, Shiga University of Medical Science, Ohtsu-shi, Shiga-ken, Japan
[7] Department of Clinical and Laboratory Medicine, Fukui Medical School, Yoshida-gun, Fukui-ken, Japan

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Abstract. We retrospectively studied 12 Japanese children (8 boys, 4 girls) with idiopathic membranous nephropathy (IMN), aged 2.9–15.8 (mean 7.7) years at onset. All patients were identified through either screening or a routine urinalysis; proteinuria was present in all, haematuria, which was macroscopic in 4, in 11. Three had nephrotic syndrome (NS) at or soon after onset. Stages on electron microscopy, performed in 10 patients, were I in 3, II in 5 and III in 2. Steroids alone or with cyclophosphamide were administered to 5 patients, including the 3 patients showing NS. Complete remission of proteinuria occurred in 8 patients 0.3–1.6 (mean 0.6) years after onset, and proteinuria did not recur. After a follow-up of 1.6–11.6 (mean 5.9) years, these 8 patients were in complete remission and the remaining 4 had only mild proteinuria; none had hypertension or impaired renal function. Thus, we infer that IMN in Japanese children may have a better course and outcome than IMN in non-Japanese children. Based on a comparative study of Japanese (previously reported cases added to ours) and non-Japanese (mostly Caucasian) children with IMN, this was confirmed; it is possible that steroid therapy in Japanese patients is more effective in inducing remission of NS and preserving renal function.

Key words: Idiopathic membranous nephropathy – Japanese children – Clinical course and outcome – Caucasian children – Steroid therapy

Introduction

Idiopathic membranous nephropathy (IMN) is a histologically well-defined immune complex-mediated glomerulopathy [1–3]. It is predominantly a disease of the middle-aged and elderly and rather uncommon in children [2, 3]. In contrast to many reports of IMN in adults [1, 4–12], there is little published information about the disease in children, and the number of patients has been small [3, 13–19]. We report here our experience with 12 Japanese children with IMN, in order to better define its clinical course and outcome.

Patients and methods

Patients. Records of paediatric patients in our hospitals (Fukui Medical School Hospital, Tenri Hospital, Fukui Red Cross Hospital and Hyogo Prefectural Amagasaki Hospital) for the period 1973–1990 were reviewed to identify patients whose renal biopsies satisfied the criteria for membranous nephropathy [1, 2] and who had no clinical or laboratory evidence of underlying systemic disease, such as hepatitis B virus (negative for hepatitis B surface antigen and antibody) and systemic lupus erythematosus (negative for anti-DNA antibodies). Twelve patients, about 3% of those biopsied, fulfilled the criteria for IMN. There were 8 boys and 4 girls; their age at onset of disease ranged from 2.9 to 15.8 (mean 7.7) years. Each patient was treated according to the policy of the attending physician. They were divided into two groups retrospectively. Group 1 comprised 7 patients who had received no immunosuppressive therapy and group 2 5 patients who had received steroid therapy, and in 2 cases cyclophosphamide as well (Table 1).

Definitions. Proteinuria was expressed semiquantitatively as negative, trace (10–29 mg/dl), 1+ (30–99 mg/dl), 2+ (100–299 mg/dl), 3+ (300–999 mg/dl) or 4+ ($\geq$1,000 mg/dl) by dipstick testing of the early-morning urine specimen. Nephrotic syndrome (NS) was defined as 3+ or 4+ proteinuria associated with hypoalbuminaemia ($\leq$3 g/dl), complete remission as negative or trace urinary protein. Haematuria was defined as five erythrocytes or more per high-power field in the sediment of a 10-ml centrifuged urine sample. Renal impairment was defined as serum concentrations of creatinine higher than 1.2 mg/dl and/or urea nitrogen higher than 20 mg/dl. Hypertension was defined as blood pressure above the 95th percentile of children matched for age and sex [20].

* *Present address:* Division of Nephrology and Hypertension, Department of Medicine, Health Sciences Center, State University of New York at Stony Brook, NY 11794-8152, USA

Correspondence to: H. Tsukahara, Division of Nephrology and Hypertension, Department of Medicine, Health Sciences Center, State University of New York at Stony Brook, NY 11794-8152, USA

Table 1. Clinical data at onset and renal histological findings in 12 Japanese children with idiopathic membranous nephropathy (IMN)

Patient no.	Sex	Age at onset (years)	Urinalysis at onset		Serum albumin at onset (g/dl)	Age at biopsy (years)	Electron microscopic staging
			P	H			
Group 1							
1	M	2.9	(1+)	(M)	3.2	3.1	Not done
2	M	4.0	(2+)	(M)	3.0	9.1	Stage III
3	M	4.1	(2+)	(M)	3.3	4.5	Not done
4	F	6.9	(3+)	(m)	3.7	7.8	Stage II
5	M	11.8	(2+)	(m)	4.0	12.3	Stage III
6	M	11.9	(3+)	(m)	4.0	12.1	Stage I
7	M	15.8	(3+)	(–)	3.2	16.0	Stage I
Group 2							
8	F	3.1	(3+)	(M)	2.5	3.1	Stage II
9	M	3.4	(3+)	(m)	2.9	3.6	Stage II
10	M	7.6	(2+)	(m)	3.7	7.9	Stage I
11	F	8.6	(2+)	(m)	4.4	9.3	Stage II
12	F	12.0	(2+)	(m)	3.6	12.1	Stage II

P, Proteinuria; H, haematuria; M, macroscopic haematuria; m, microscopic haematuria

Renal histology. Percutaneous renal biopsies were performed within 0.9 years of onset in all but 1 patient (no. 2, Table 1). Repeated biopsy was not performed. The tissue obtained was examined by light microscopy using haematoxylin and eosin, periodic acid-Schiff, periodic acid-silver methenamine (in all patients) and Masson trichrome stains (in 10 patients), and in 5 patients by immunofluorescence using labelled antisera to IgG, IgA, IgM, C1q, C3c, C3d, C4, C5 and fibrinogen. In 10 patients, sections were also viewed under the electron microscope. The biopsy findings were staged into grades I–IV according to Ehrenreich and Churg [1]: initial subepithelial dense deposits (stage I), subsequent spike response of the basement membrane (stage II), eventual incorporation of the deposits within the basement membrane material (stage III) and finally the formation of a thickened basement membrane with disappearing deposits (stage IV).

Results

Clinical status at onset (Table 1)

Urinary abnormalities were detected in all patients either through mass screening (8 patients) or on routine urinalysis (4 patients) when they attended a clinic because of upper respiratory tract infection. Proteinuria occurred in all, with 2 (nos. 8 and 9) fulfilling the criteria of NS and having facial and peripheral oedema. Haematuria was also present in all but 1 and was macroscopic in 4. No patients had hypertension, renal insufficiency (their serum concentrations of creatinine and urea nitrogen were 0.3–1.0 mg/dl and 8–18 mg/dl, respectively) or hypocomplementaemia.

Renal histology (Table 1)

Light microscopy showed virtually continuous subepithelial spikes along the glomerular capillary basement membrane after periodic acid-silver methenamine staining (in 10 of the 12 patients) and subepithelial red deposits after Masson trichrome staining (in all 10 patients studied). Thickening of the glomerular capillary wall was present in 10 of the 12 patients; it was mild in 9 (nos. 1, 3–6, 8–10 and 12) and marked in 1 (no. 11). Focal and segmental mild mesangial cell proliferation was present in all, but crescent formation was not found. Global or segmental sclerosis was noted in a few glomeruli in 2 patients (nos. 2 and 10) and very small foci of tubular atrophy in another 2 (nos. 4 and 8). Immunofluorescence microscopy showed diffuse and global granular deposits of IgG, C3c and C3d of 1+–3+ intensity (on a scale of 1+–3+) along the glomerular capillary walls in all patients studied (nos. 1, 3, 8, 10 and 12), with no positive staining for IgA, C1q, C4 or C5. On electron microscopy, 3 biopsies showed stage I, 5 stage II, and 2 stage III membranous nephropathy.

Follow-up and outcome (Table 2)

The mean duration of follow-up was 5.9 years; 7.3 years in group 1 and 4.0 years in group 2. One patient (no. 10) became nephrotic and 2 (nos. 4 and 10) had macroscopic haematuria transiently soon after onset. Complete remission of proteinuria occurred in 4 from group 1 and 4 from group 2, 0.3–1.6 (0.9) and 0.3–0.9 (0.4) years after onset, respectively. In the remaining 4 patients, proteinuria decreased to 1+ finally. Haematuria disappeared in 5 of the 6 of group 1 and in 4 of group 2, 0.9–3.1 (mean 1.7) and 0.2–1.2 (mean 0.6) years after onset, respectively. Hypertension, deterioration of renal function (their serum creatinine was 0.4–1.0 mg/dl and urea nitrogen 10–18 mg/dl, finally) or recurrence of proteinuria was not observed in any patient.

Discussion

Our study confirmed [13–19] that IMN is an infrequent renal disease of childhood. We found a male predominance for the disease as have most [1, 2, 4, 6–13, 17, 18], but not all [3, 5, 15, 16], published reports of both adult and paediatric cases. The onset of the disease was insidious in our patients and identified either during screening or a routine urinalysis. We found proteinuria to be a consistent finding

Table 2. Clinical data on follow-up

Patient no.	Age at last investigation (years)	Nephrotic syndrome duration (months)	Macroscopic haematuria duration (months)	Specific treatment		Final urinalysis	
				drugs	duration (years)	P	H
Group 1							
1	4.5	(–)	1	D	0.2	(–)	(m)
2	15.6	(–)	1	(–)		(1+)	(–)
3	8.5	(–)	1	D	2.8	(–)	(–)
4	17.3	(–)	2[b]	(–)		(–)	(–)
5	18.2	(–)	(–)	D	2.1	(1+)	(–)
6	18.2	(–)	(–)	D	5.0	(1+)	(–)
7	26.1	(–)	(–)	(–)		(–)	(–)
Group 2							
8	6.6	1	0.4	SC[c]	0.3	(–)	(–)
9	9.9	0.2	(–)	SD[d]	0.5	(–)	(–)
10	10.4	2[a]	0.3[b]	SD[e]	0.3	(–)	(m)
11	11.2	(–)	(–)	S[e]	0.6	(1+)	(–)
12	16.5	(–)	(–)	SCDW[F]	0.9	(–)	(–)

D, Dipyridamole; S, corticosteroids; C, cyclophosphamide; W, warfarin

[a] Nephrosis was present from 2 months after onset in patient no. 10

[b] Macroscopic haematuria was present from 6 months and 1 month after onset in patients 4 and 10, respectively

[c] Patient no. 8 received a 4-month course of alternating monthly cycles of prednisolone (2 mg/kg per day initially then tapered) and cyclophosphamide (2 mg/kg per day). Three intravenous pulses of methylprednisolone (30 mg/kg per day) (pulse therapy) were given at the beginning of the 3rd month; treatment commenced 0.6 month after onset

[d] Patient no. 9 received pulse therapy followed by a 6-month course of prednisolone (1 mg/kg per day initially then tapered); treatment commenced 2 months after onset

[e] Patients 10 and 11 received prednisolone in one (for 3 months, 1.5 mg/kg per day initially then tapered) and two (for 7 months in total, 2 mg/kg per day initially then tapered in each course) courses, respectively; treatment commenced 4 and 7 months after onset, respectively

[f] Patient no. 12 received pulse therapy followed by two courses of prednisolone (for 10 months in total, 2 mg/kg per day initially then tapered in each course) and cyclophosphamide between each course (for 1 month, 2 mg/kg per day); treatment commenced 2 months after onset

at presentation as it has been in other series [13–19]. Haematuria, either microscopic or macroscopic, occurred more frequently in our patients than in other reported series [13–17, 19]. Conversely, few (17%) of our patients presented with NS. Other reports indicate a much higher prevalence of NS (62%–85%) in non-Japanese (mostly Caucasian) subjects [13–17, 19] than in Japanese patients (42%) [18].

The clinical course and outcome of IMN appear to be more favourable in children than in adults, of whom 20%–50% demonstrate deterioration of renal function within 5 years [1, 2, 4–12]. It has been proposed that the prognosis may be favourable for Japanese adult patients [8, 9]. In our series, after a mean follow-up of 5.9 years, two-thirds of our patients were in complete remission with respect to proteinuria and one-third had only mild proteinuria; none had NS, hypertension or impaired renal function. Thus, our experience suggests that the prognosis of IMN may be especially benign in Japanese children.

To determine whether there are differences in IMN between Japanese patients and those from other countries, we combined our observations with those in children from other Japanese centers [18, 21–28] and compared the results with those in children from other countries [13–17, 19] (Table 3). The age at onset of disease was slightly lower in Japanese patients than in non-Japanese patients. The incidence of NS at onset was remarkably low in the Japanese. Furthermore, no Japanese patients were hypertensive at onset or during the observation period. After a mean follow-up of 4.2 years, complete remission of proteinuria was found in about 75% of Japanese patients and none had NS or impaired renal function. These data indicate that IMN has a better clinical course and outcome in Japanese than in non-Japanese children.

However, several points need to be discussed. First, the difference in prognosis may be due to bias in selection of the patients. Most Japanese children with IMN were detected through either screening or a routine urinalysis (92%, 44/48 for whom data were available [22–28]). Widespread screening tests were probably the reason for early detection of IMN and could identify a clinically silent form of IMN which is not seen in other countries that do not have such a screening system. However, the Japanese patients described in Table 3 were from referral centres likely to see patients who have relatively severe disease. In addition, the glomerular capillary wall changes determined by electron microscopy were comparable between Japanese and non-Japanese patients [13, 16, 17]. Therefore, it seems unlikely that patients with severe disease were preferentially excluded in the Japanese series.

Second, the benign course in the Japanese might be attributed to the therapeutic regimens. In the 66 Japanese IMN patients, 41 (62%) received immunosuppressive therapy (mostly steroids), while the remaining 25 (38%) did not. Twenty (49%) of the former patients had NS at or soon after onset, in contrast to only 2 (8%) of the latter patients.

Table 3. Comparison of clinical course and outcome of childhood IMN in Japanese and non-Japanese patients

	Japanese patients[a] ($n = 66$)	Non-Japanese patients[b] ($n = 154$)	P value[c]
Age at onset (years) (mean)	2–16 (7)	0.7– 19.9 (10)	–
Boys/girls	39/27	92/62	NS
Presentation:			
proteinuria	64	152	NS
nephrosis	19	116	<0.001
hypertension	0	36 (of 152)[d]	<0.001
Electron microscopic staging[e]			
early/late stages[f]	42/17 (of 59)	39/18 (of 57)	NS
Treatment with steroids and/or alkylating agents	41[g]	113	NS
Duration of follow-up (years) (mean)	0.3–12 (4.2)	<1–16 (4.6)	–
Outcome:			
complete remission	50	38 (of 100)	<0.001
proteinuria (no nephrosis)	16	27 (of 100)	NS
nephrosis	0	25 (of 100)	<0.001
impaired renal function	0	23	<0.001
death	0	3[h] (of 100)	NS

NS, Not significant
[a] Present study and previous reports [18, 21–28]
[b] Studies from France [13], the United States [14–16, 19] and Canada [17]
[c] Chi-squared test
[d] Values in parentheses refer to numbers of patients for whom data were available
[e] Data on initial biopsy shown for patients undergoing repeated biopsies
[f] Early stage indicating combined I and II stages and late stage combined III and IV stages
[g] Twenty-five patients (38%) receiving steroids, 1 cyclophosphamide and 15 (23%) both
[h] Non-renal cause for 1 patient

Thus, there was a bias towards the treatment of patients with heavier proteinuria, one of the possible indicators of a poor prognosis [3, 13, 15, 16], in Japanese patients including ours. For the non-Japanese, similar or higher percentages (59%–93% in each series [13–17, 19]) of the patients received such treatment. No appreciable effect of immunosuppressive therapy on remission of NS was observed in any series, although a beneficial effect of steroids in preserving renal function was suggested in one series from the United States [19]. It is possible, therefore, that steroid therapy can bring about remission of NS and help to preserve renal function in Japanese children with IMN.

Genetic and/or environmental factors should also be discussed when considering the course of IMN in different countries [2, 5, 8–10]. As previously reported [29, 30], there is a strong association between HLA-DR2 and MT1 and the development of IMN in Japanese adult patients, while an association in Caucasian patients is found with HLA-DR3 and MT2. Further studies are needed in this field focusing on childhood IMN.

Many reports supporting [4, 6, 11] or refuting [1, 8–10, 12] the effectiveness of steroids and/or alkylating agents in adult IMN have been published. At present it can be stated that Japanese children with IMN not showing NS usually do not require such immunosuppressive therapy. If the patients become nephrotic, then a trial of steroids may be worthwhile, because, as stated above, steroid therapy may then be beneficial.

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Literature abstract

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Growth hormone treatment in children with preterminal chronic renal failure: no adverse effect on glomerular filtration rate

B. Tönshoff, C. Tönshoff, O. Mehls, J. Pinkowski, W. F. Blum, U. Heinrich, B. Stöver, and N. Gretz

Impaired growth and stunting remains a major therapeutic problem in children with chronic renal failure (CRF). Recombinant human growth hormone (rhGH) treatment may be beneficial, but concern has been raised about possible side-effects, i. e. deterioration of renal function and glucose intolerance. We have treated 10 prepubertal children with CRF (median age 7.5 [1.7–10.0] years) with 4 IU rhGH/m^2 per day s. c. over a period of 1 year. Height velocity increased significantly (P <0.03) from basal 4.6 (2.0–14.0) cm/year to 9.7 (6.8–17.6) cm/year. Height velocity SDS for chronological age and for bone age increased in all children from basal median –2.3 to +3.8 (P <0.005). Median glomerular filtration rate (GFR) measured by single injection inulin clearance at onset was 18 (11–66) ml/min per 1.73 m^2 and did not change significantly during the treatment year. The loss of GFR as estimated by creatinine clearance was similar during the treatment year (median loss 1.3 ml/min per 1.73 m^2) compared to the year before treatment (median loss 3.7 ml/min per 1.73 m^2). Serum glucose levels during an oral glucose tolerance test did not change, but fasting as well as stimulated insulin levels increased significantly with time during the study period. It is concluded that the rhGH regimen employed was remarkably effective in improving growth velocity in children with CRF without adversely affecting GFR. Glucose homeostasis remained stable, but at the expense of increased serum insulin levels.