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ORIGINAL ARTICLE

Idiopathic membranous nephropathy in children

Beom Hee Lee · Hee Yeon Cho · Hee Gyung Kang · Il Soo Ha · Hae Il Cheong · Kyung Chul Moon · In Seok Lim · Yong Choi

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Abstract Idiopathic membranous nephropathy (MN) is a rare cause of asymptomatic proteinuria (AP) or nephrotic syndrome (NS) in childhood. To improve our understanding of its clinical course, we retrospectively reviewed 19 cases of idiopathic MN seen in our hospital over a period of 28.5 years, i.e., from January 1977 to July 2005. Eight patients (39%) had AP and 11 (61%) presented with NS. All eight AP patients achieved remission, regardless of treatment modality. Oral corticosteroid was given to all 11 NS patients, but only three of them responded to corticosteroid. Of the eight steroid non-responders, three achieved remissions with the addition of cyclosporine, and the five who were not administered additional immunosuppressive drugs had persistent NS. At the latest evaluation, all six NS patients that achieved remission remained free of proteinuria and had a normal renal function. Moreover, two of the 5 steroid non-responders showed persistent nephrotic-range proteinuria but a stable renal function. The remaining three steroid non-responders progressed into chronic renal insufficiency, and this progression was preceded by renal vein thrombosis (RVT) in two of the three patients. Presentation with NS (P=0.045) and the development of RVT (P=0.010) were identified as poor prognostic factors.

Keywords Membranous nephropathy in children · Asymptomatic proteinuria · Nephrotic syndrome · Corticosteroid · Cyclosporine · Renal vein thrombosis

B. H. Lee · H. Y. Cho · H. G. Kang · I. S. Ha · H. I. Cheong · Y. Choi (✉)
Department of Pediatrics,
Seoul National University Children's Hospital,
28 Yongon-Dong, Chongno-Gu,
Seoul 110-744, South Korea
e-mail: ychoi@snu.ac.kr

K. C. Moon
Department of Pathology,
Seoul National University Hospital,
Seoul, South Korea

I. S. Lim
Department of Pediatrics, Chung Ang University,
Seoul, South Korea

Introduction

Membranous nephropathy (MN) is a renal disease with distinct pathologic features of normocellular glomerular wall thickening and subepithelial electron dense deposits [1]. MN is a common cause of nephrotic syndrome (NS) in adults, but this occurs infrequently in children [2–7]. Idiopathic MN, a form of MN without any associated systemic diseases used to be uncommon in Korean children in whom hepatitis B virus (HBV) infection was endemic and HBV-associated MN (HBV-MN) was the major cause of childhood MN [8, 9]. Moreover, since the introduction of the HBV vaccination in children in 1985, the prevalence of HBV infection [10, 11] and of HBV-MN have been reduced remarkably. Idiopathic MN is still rare, but it now represents the major subset of childhood MN in Korea. However, because of its rarity, its clinical course and appropriate treatment are relatively unknown. In adults, several controlled studies [12–17] have recommended that immunosuppressive agents be administered to patients with NS or persistent nephrotic range proteinuria, although debate remains over the efficacy of the immunosuppressive treatment [18–20]. Moreover in children, the efficacies of immunosuppressive medications have not yet been verified [2–7, 21].

In this study, we reviewed our experiences of idiopathic MN in Korean children to improve our understandings of

clinical course among children with idiopathic MN, and to evaluate the efficacy of immunosuppressive therapy.

Patients and methods

Patients

From January 1977 through to July 2005, 1583 patients younger than 18 years (yr) of age with proteinuria were evaluated by renal biopsy at the Seoul National University Children's Hospital (SNUCH). Seventy two patients (4.5%) were found to show the pathological findings of MN. Among the 72 patients, 49 (68.1%) were associated with HBV infection (HBV-MN) and 4 (5.5%) had systemic lupus erythematosus (SLE-MN). The remaining 19 patients (26.4%) were idiopathic without any identifiable underlying disease. The clinical manifestations, renal pathologic findings and clinical courses of the 19 children with idiopathic MN are reviewed here.

Definitions

Nephrotic-range proteinuria was defined as a 24-hour urinary protein of >40 mg/m^2/hour or a random urine protein/creatinine ratio (Upr/Ucr) >3 [22]. NS was defined as the condition with nephrotic-range proteinuria accompanying hypoalbuminemia less than 2.5 gm/dL, edema and hyperlipidemia. Hematuria was defined as >5 erythrocytes per high-power field on urinalysis. Hypertension was defined as a blood pressure above the 95th percentile for age and sex [23]. Remission of proteinuria was defined as negative or trace urinary protein by dipstick test for 3 consecutive days, Upr/Ucr <0.5 in patients younger than 2 yrs of age and <0.2 in patients of 2 yrs of age or older, or 24 hour urinary protein 4 mg/m^2/hour or less. The remission group was defined as the group of patients that achieved remission of proteinuria for more than 1 month at any time during the clinical course. The non-remission group was defined as the group of patients who showed persistent proteinuria.

Steroid responders were defined as patients who had remitted or showed sub-nephrotic proteinuria with a decrease of proteinuria of >50 percent of the pre-treatment level during two months of daily or alternate-day oral corticosteroid treatment. Steroid non-responders were classified as patients with persistent nephrotic-range proteinuria despite two months of full-dose corticosteroid therapy (60 mg/m^2/day).

Chronic renal insufficiency (CRI) was defined as an irreversible reduction in the glomerular filtration rate (GFR) to <75 ml/min/1.73 m^2 for 3 months or longer, and end stage renal disease (ESRD) as a stage of CRI that required long-term renal replacement therapy.

Statistical analysis

Data were analyzed using SPSS for Windows, version 12.0. Results are presented as mean±standard deviation (SD) or as medians and ranges. Differences between two groups were analyzed using the Mann–Whitney U test (for non-parametric continuous variables) or by using the Fisher's exact test and linear-by-linear association (for categorical variables). P values of <0.05 were considered significant.

Results

Changing patterns of the underlying causes of MN in Korean children

Before 1990 (1977–1989), 51 children among the children who had renal biopsy due to proteinuria showed pathological MN. Forty two (82.4%) of these had HBV-MN, 7 (13.7%) idiopathic MN, and 2 (3.9%) SLE-MN. On the other hand, between 1990 to 2005, 21 patients had MN, and 12 (57.2%) of these had idiopathic MN, 7 (33.3%) HBV-MN, and 2 (9.5%) SLE-MN. Therefore, the proportion of idiopathic MN cases in Korean children increased remarkably after 1990 (P=0.000) (Fig. 1).

Interestingly, one case without an extra-renal manifestation of SLE at presentation was initially classified as idiopathic MN; however, malar rash, myopathy, and pancytopenia with positive conversion of anti-dsDNA antibody developed eight years later, and accordingly, she was re-classified as having SLE-MN.

Clinical manifestations at presentation

Of 19 patients with idiopathic MN, 9 (47.4%) were boys and 10 (52.6%) were girls. Median age at onset was 11.0 years with a range of 1.7–14.9 yr (mean±SD, 9.5± 4.2 yr). Eight patients had AP (42.1%) and 11 (57.9%) presented with NS. Hematuria was detected in 16 patients (84.3%), and 8 of these were macroscopic hematuria. Hypertension was noted in 4 patients (21.1%). Seventeen patients (89.5%, including 6 of 8 patients with AP) showed nephrotic-range proteinuria. Serum complement C_3, C_4, creatinine level and creatinine clearance (Ccr) were normal in all the patients at presentation Table 1.

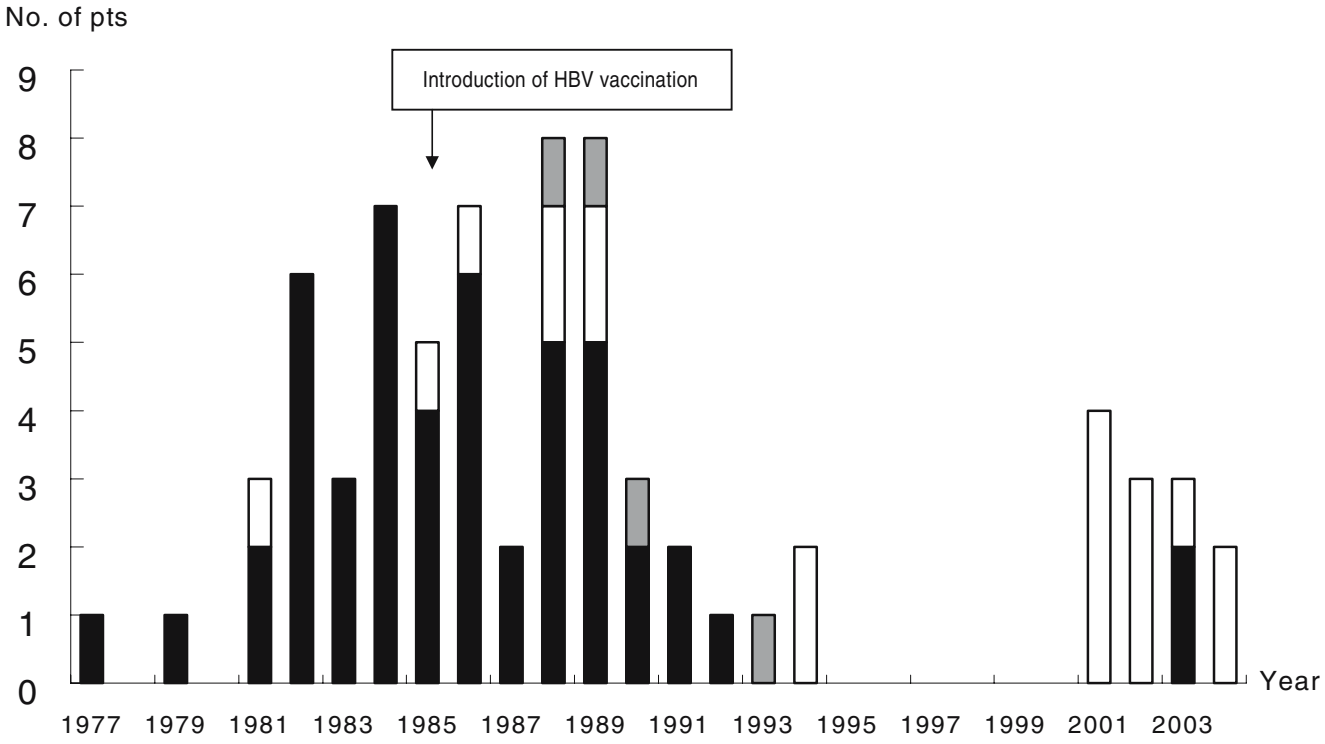

Fig. 1 Chronological changes of membranous nephropathy (MN) in Korean children between 1977 and 2005. The black bar represents the number of patients with MN associated with hepatitis B (HBV-MN), the gray bar the number with systemic lupus erythematosus (SLE-MN), and the white bar the number with idiopathic MN

Pathologic findings

Renal biopsies were performed at a mean 6.4±4.8 months (range 0–20 months) after onset. All the cases showed the typical findings of idiopathic MN with diffuse IgG staining. None of our 19 patients had idiopathic segmental membranous nephropathy. In addition, segmental glomerular hypercellularity, subendothelial-mesangial deposits, and segmental or global glomerular sclerosis were found in some patients (Table 2). One patient showed cellular or fibrocellular crescents in 60% of glomeruli, and 14 patients (73.7%) showed mild or moderate tubular atrophy or interstitial fibrosis. According to the MN staging criteria of Ehrenreich and Churg [1], 11 (57.9%) were in stage II MN and 8 (42.1%) in stage III MN.

Table 1 Clinical features at onset of 19 children with idiopathic membranous nephropathy

Gender, male : female (No. of pts)	9:10
Age (yr)*	9.5±4.2 (1.7–14.9)
Nephrotic syndrome (No. of pts)	11
Hematuria, macroscopic/microscopic (No. of pts)	4/5
Asymptomatic proteinuria (No. of pts)	8
Hematuria, macroscopic/microscopic (No. of pts)	4/3
Hypertension (No. of pts)	4
Urinary protein	
(mg/m^2/day, 15 pts)*	3424.7±2905.6 (1404–11319)
(Upr/Ucr, 4 pts)*	3.48 (0.95–6.85)
Serum albumin (g/dL)*	2.7±0.9 (1.2–3.9)
Serum total cholesterol (mg/dL)*	356.4±172.1 (168–704)
Serum creatinine (mg/dL)*	0.6±0.2 (0.3–1.0)
Creatinine clearance (mL/min/1.73 m^2)*	131.3±29.4 (88.3–195.0)

No. of pts, number of patients
*Values are expressed as mean±standard deviation, (range)

Table 2 Renal pathologic findings of 19 children with idiopathic membranous nephropathy

Renal pathology	Number of patients
Segmental glomerular hypercellularity	5
Segmental glomerular sclerosis (percent of glomerulus with sclerosis)	4 (2–14.3%)
Global glomerular sclerosis (percent of glomerulus with sclerosis)	2 (1–1.35%)
Crescent (percent of glomerulus with crescent)	3 (2.7–60%)
Tubulointerstitial changes	
Mild degree	12
Moderate degree	2
Morphologic stage	
Stage II	11
Stage III	8

Clinical course and treatment

The mean follow-up period for the 19 patients was 48.6± 29.5 (range 17–144) months i.e., 57.9±42.1 (17–144) months for eight children with AP and 41.8±14.4 (18–66) months for 11 children with NS.

Children with asymptomatic proteinuria (AP)

The eight patients with AP (AP 1–8) all achieved remissions at a mean 14.6±13.3 (1–37) months after onset. Three patients (AP 1–3) achieved spontaneous remission at 9–37 months after onset, but one (AP1) experienced relapse of proteinuria at 3 months after remission. The other 5 patients (AP 4–8) were treated with oral prednisolone (60 mg/m^2/day). All four patients who had daily prednisolone (AP 5–8) were steroid responders and achieved remission at 1–7 months after treatment. The condition of one patient with alternate-day prednisolone (AP 4) was not improved by steroid treatment (steroid non-responder); however, spontaneous remission was achieved at 33 months after onset (Figs. 2, 3).

One patient (AP 6) who responded to daily oral corticosteroid initially, showed a relapse at 19 months after remission. Because the renal biopsy of this patient revealed crescentic glomerulonephritis in addition to MN, the patient was treated with methylprednisolone pulses (30 mg/kg for 3 consecutive days) and then with oral prednisolone plus oral cyclophosphamide (2 mg/kg/day for 12 weeks); this patient subsequently achieved a remission. At the latest follow-up visit, renal function was normal in all eight patients that had presented with AP (Fig. 3).

Angiotensin-converting enzyme (ACE) inhibitor was also administered to seven patients (AP 1, 2, 4–8) for 9.7±9.4 (2–30) months.

Children with nephrotic syndrome (NS 1–11)

Six of 11 children with NS (NS 2–7) achieved remission at 12.3±4.7 (8–19) months after onset. All 11 children received oral prednisolone (60 mg/m^2/day) daily (NS 2–11) or every other day (NS 1); three on daily prednisolone (NS 2,3,4) were steroid responders and became free of proteinuria at 6, 16, 2 months after therapy, respectively, and did not experience a relapse (Figs. 4, 5).

Another three children (NS 5–7) who did not respond to two-month prednisolone treatment (steroid non-responders) achieved remission on adding cyclosporine (3–5 mg/kg/day, two divided doses, trough blood level of 20–92 ng/ml) after 2, 6 and 2 months of combined therapy. Although proteinuria

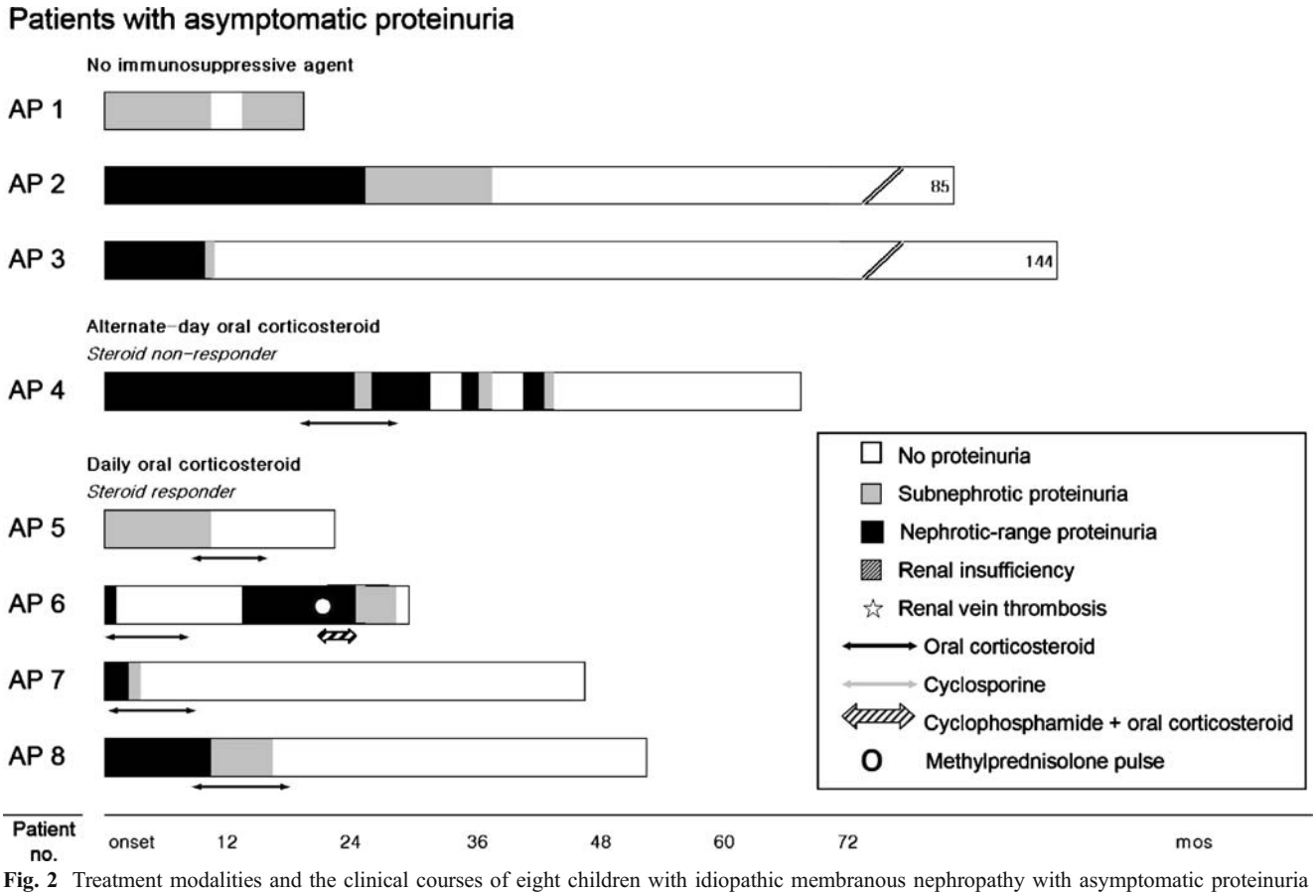

Fig. 2 Treatment modalities and the clinical courses of eight children with idiopathic membranous nephropathy with asymptomatic proteinuria

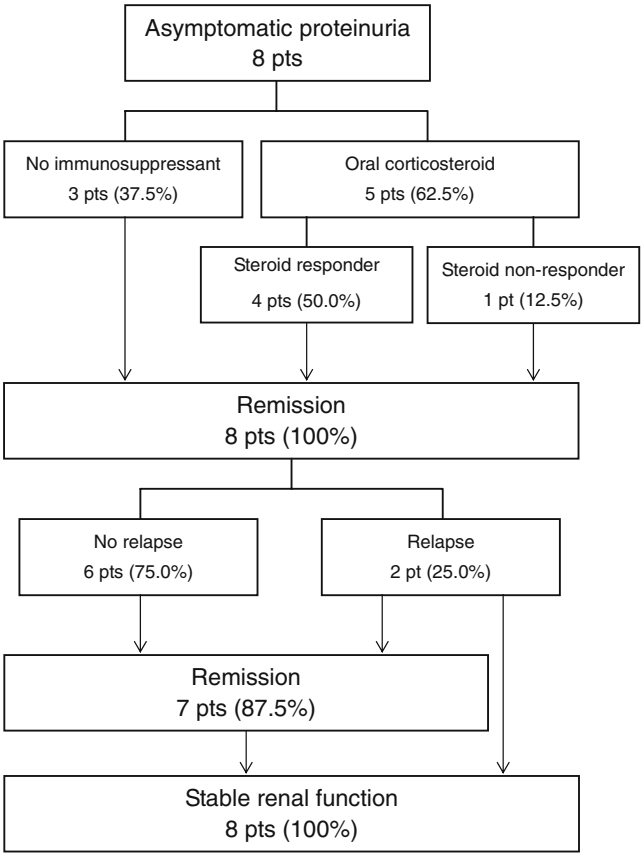

Fig. 3 The outcomes of eight children with idiopathic membranous nephropathy with asymptomatic proteinuria

relapsed at 6–8 months after the discontinuance of cyclosporine, all three patients (NS 5–7) responded again to oral prednisolone plus cyclosporine. During the 12–19 months of cyclosporine treatment, no remarkable complication occurred except a transient increase in serum creatinine in one patient (NS 7), though this recovered spontaneously after cessation and did not increase with the re-use of cyclosporine.

The remaining five steroid non-responders with persistent nephrotic range proteinuria (NS 1, 8–11) did not receive additional immunosuppressive drugs, and did not achieve remission through the follow-up period. Three of these five patients (NS 1, 10, 11) progressed into CRI at 46, 26 and 33 months after onset, respectively, and two of them (NS 10, 11) required long-term renal replacement therapy at 33 and 63 months after onset. Three of the patients with persistent NS (NS 1, 9, 10) were complicated by renal vein thromboses (RVT) at 43, 10 and 23 months after onset and only one (NS 9) responded to anticoagulation therapy. The other two patients (NS 1, 10) progressed into CRI; one (NS 10) progressed to ESRD at 10 months after RVT detection.

At the latest follow-up of NS patients, six patients were in remission, and two had persistent proteinuria but a stable renal function. The remaining three patients were in a CRI state, 2 of these were in ESRD (Fig. 5).

Angiotensin-converting enzyme (ACE) inhibitor was also given to 6 patients (NS 3-7, 10) for 24.7±11.0 (12–45) months.

Comparative studies on clinicopathological findings

The clinicopathological findings of AP and NS patients were compared (Table 3). The degree of urinary protein (P=0.000) was lower, and the proportions of patients with glomerular sclerosis (P=0.045) or tubulointerstitial changes (P=0.035) were smaller in children with AP. The remission rate was higher in the children with AP (P=0.045), and RVT and CRI were only observed in patients with NS.

When we compared the clinicopathological findings of the remission and the non-remission groups (Table 4), NS (P=0.045) was more common in the non-remission group, and RVT (P=0.010) and CRI (P=0.010) were found only in the non-remission group. Other variables were not significantly different in these two groups. Further analysis of the 11 patients who presented with NS revealed no clinicopathological variables that differentiated between the six patients and five patients that experienced or did not experience remission (data not shown).

Discussion

MN is an uncommon cause of AP or NS in children. Previous studies have reported the prevalences of MN in children of 3.7 to 6.8% based on renal biopsies conducted to evaluate proteinuria or NS [2–4, 7, 24], which is similar to the prevalence found in the present study i.e., in 5% of biopsies for proteinuria. In Korea, HBV-MN used to be the predominant subgroup of childhood MN [8, 9], but the prevalence of HBV-MN has reduced markedly since the early 1990s as shown by the present study. This decrease is attributable to a nation-wide HBV-vaccination program, which commenced in 1985 [10, 11]. As a result, idiopathic MN has become the more important MN subset in Korea.

As found in other studies (48–83%) [2–7], 58% of our patients with idiopathic MN presented with NS. Macroscopic hematuria was found in 40% of patients, which was an unexpected, because previous studies found that hematuria in idiopathic MN is predominantly microscopic [2–7], However, one study from Japan showed that 33% of patients with idiopathic MN showed macroscopic hematuria [21]. Hypertension at onset was uncommon (21.1%) in the present study, as in previous studies (6–50%) [2–7]. Renal insufficiency at onset, a rare presentation in childhood MN [3, 4, 6], was not detected in our patients. In two

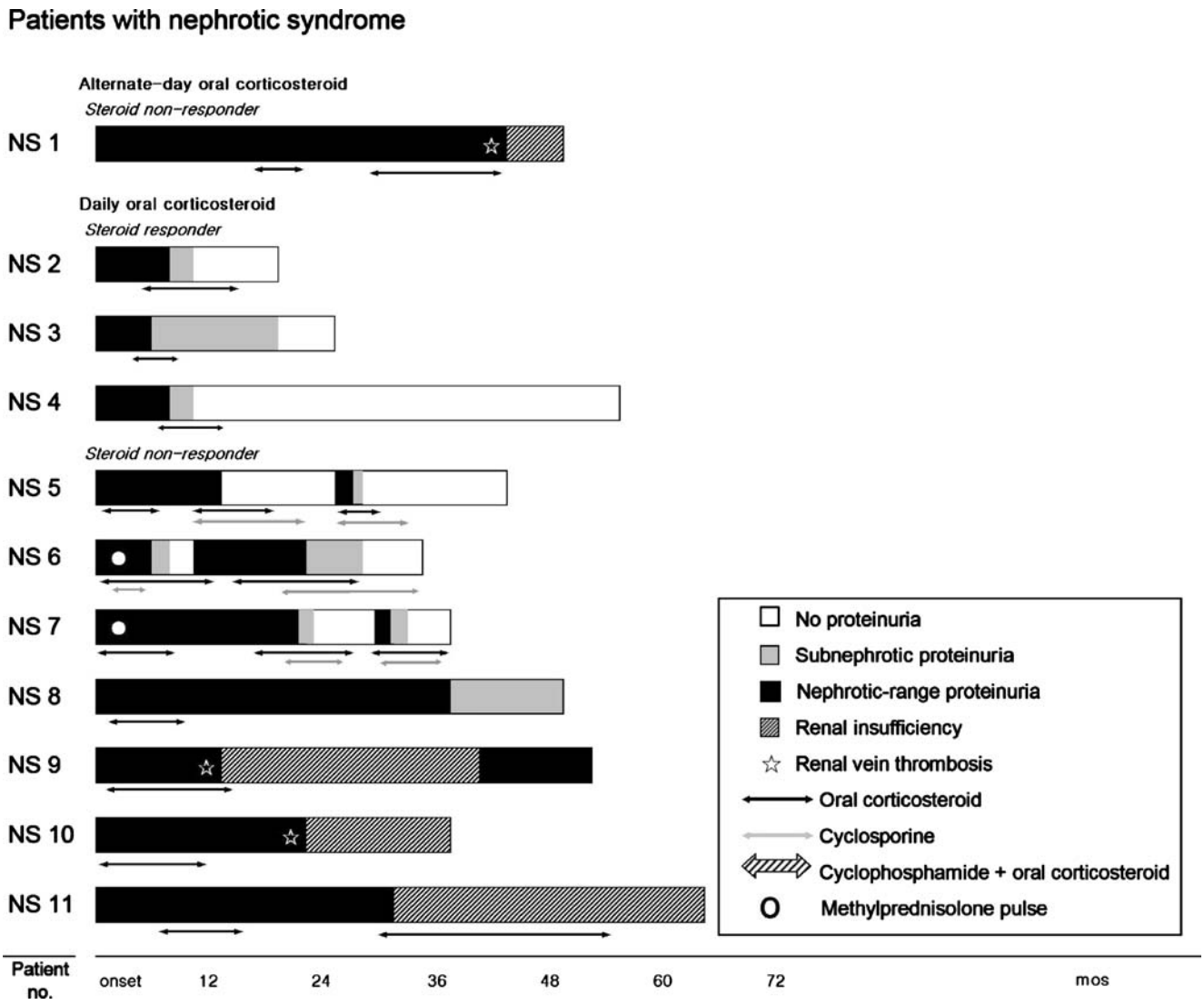

Fig. 4 The treatment modalities and clinical courses of 11 children with idiopathic membranous nephropathy with nephrotic syndrome

of our patients (AP 7, NS 6), renal pathology showed subendothelial and mesangial deposits, in addition to subepithelial deposits, which are characteristic findings of systemic lupus erythematosus (SLE-MN) [7, 25, 26]; but we found no clinical or laboratory manifestations of SLE in either of these patients throughout the follow-up period (45 and 34 months, respectively). On the other hand, one patient with typical pathologic features of idiopathic MN turned out to have SLE-MN at 8 years after onset, which suggests that all patients with idiopathic MN should be monitored carefully for covert underlying systemic diseases.

The clinical course of childhood idiopathic MN has been reported to be variable with a reported overall remission rate of children of 26–52%, and a progression to chronic renal insufficiency rate of 10–28% [2–7]; the overall remission rate among our patients was 73.7%, and the rate of progression to CRI was 17.6%. The overall remission rate was higher in our study, but the remission rate of NS patients was 54.5%, which is similar to the previous reports [2–7]. Notably, all of our AP patients, who are generally considered to have a favorable outcome [4, 21, 27], did achieve remission, regardless of the immunosuppressive treatment. However, there remains a risk of unexpected disease progression even among those who have achieved remission [5, 28]. We also experienced one case (AP 6) who relapsed and the renal biopsy showed MN associated with crescentic glomerulonephritis. Therefore, the achievement of remission should not be considered as a cure in idiopathic MN and long-term follow-up is required. Unresolved RVT, a rare complication of childhood idiopathic MN [6, 7, 29], preceded chronic renal insufficiency in the present study. Thus, it appears to be important to screen RVT during the follow up of childhood as well as adult MN.

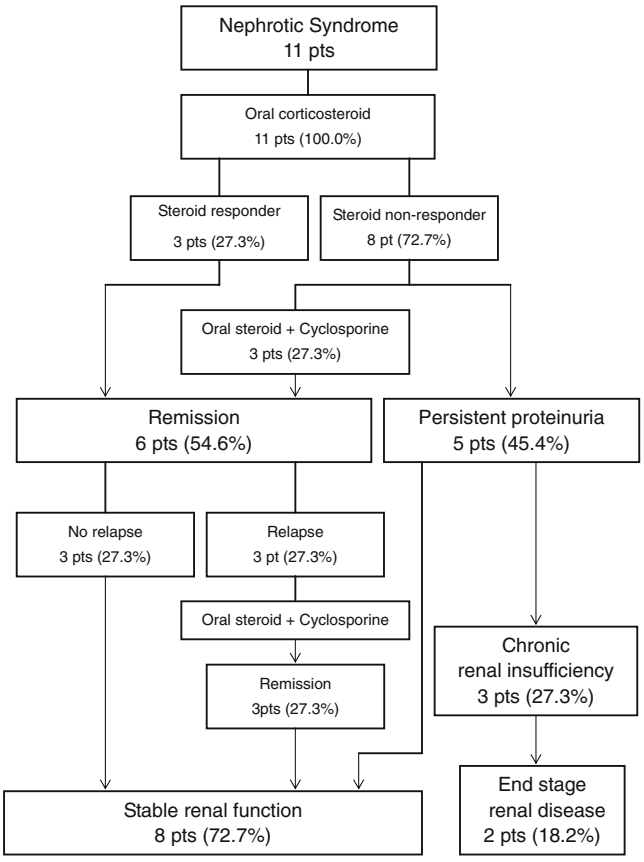

Fig. 5 The outcomes of 11 children with idiopathic membranous nephropathy with nephrotic syndrome

For adults with idiopathic MN, oral corticosteroid single therapy has been reported to be ineffective [18, 19]; so combined immunosuppressive therapies, such as oral corticosteroid with chlorambucil or cyclophosphamide [12, 15–17] or oral corticosteroid with cyclosporine [12–14], are recommended. On the other hand, the effects of immunosuppressive agents, such as oral corticosteroids or cytotoxic drugs, have not been yet proven in children [2–7, 27]. A small number of uncontrolled studies have reported that single oral corticosteroid treatment appears to be ineffective in childhood MN, but none of these studies mentioned the efficacy of combined immunosuppressive therapy [4, 5, 7]. In our study, alternate-day steroid was ineffective in one AP patient (AP 4) and another patient with NS (NS 1). However, all the patients with AP (AP 5–8) and three patients with NS (NS 2–4) given daily oral corticosteroids achieved remission. Remission of these patients could have been spontaneous; however, it may also be attributable to the effect of daily oral corticosteroids, considering that all these patients were steroid responders. And most of them (AP 5–8, NS 4) achieved remission within 2 months of therapy. Therefore, daily oral corticosteroid can be attempted for children with idiopathic MN; a two month observation period seems sufficient to evaluate the efficacy of the therapy.

Interestingly, the three steroid non-responders (NS 5–7) who were treated with additional cyclosporine achieved remissions within 6 months of therapy, which suggests that combined daily oral corticosteroid plus cyclosporine is effective in patients with steroid-resistant idiopathic MN with NS. It is noteworthy that the relapses of NS after discontinuance of cyclosporine were also treated successfully by reintroducing prednisolone and cyclosporine. These findings strongly suggest that cyclosporine may be effective at inducing remission in steroid-resistant idiopathic MN.

Unfortunately, the effect of ACE inhibitors could not be evaluated in the present study because most of our patients who received ACE inhibitors were also given oral corticosteroids.

A male gender, old age, persistent high-grade proteinuria, decreased renal function at presentation, and renal pathologic findings, such as, segmental glomerular sclerosis and tubulointerstitial change have been suggested to be poor prognostic factors in adult idiopathic MN [12, 30–34]. In children, age, presentation with NS, hypertension at onset, and high-grade pathological stages were considered as poor prognostic factors in several uncontrolled studies [2, 4–7]. In the present study, presentation with NS and the development of RVT were found to be significantly more frequent in patients with persistent nephrotic range proteinuria. A comparison between the patients older and younger than 10 years old revealed no significant differences (data not shown) in prognosis. Gender and hypertension at onset were also not significant prognostic factors. Although the pathological stage of MN (Stage I, II vs. III, IV) was not a significant prognostic factor, it should be noted that none of our patients had stage-IV MN. However, tubulointerstitial changes and glomerular sclerosis, the poor prognostic factors reported in adults with MN [12, 32, 33], were found in a smaller proportion of AP than NS patients.

In conclusion, the clinical course of the children with AP was found to be favorable regardless of immunosuppressive treatment. Of the children with NS, steroid responders achieved remission. Moreover, addition of cyclosporine in patients with steroid-resistant NS also resulted in remission. During long-term follow-ups of children with idiopathic MN, careful consideration should be given to unexpected disease progression, delayed manifestations of underlying diseases such as SLE, and the development of RVT, a devastating complication of idiopathic MN.

Table 3 Comparison of the clinicopathological findings of patients with asymptomatic proteinuria and nephrotic syndrome

	Patients with asymptomatic proteinuria	Patients with nephrotic syndrome	*P* value
Gender (male:female)	8 (4:4)	11 (5:6)	NS
Onset Age (yr)*	10.1±3.4 (4.8–13.3)	9.1±4.9 (1.7–14.9)	NS
Clinical findings at the onset			
Urinary protein (mg/m^2/day)*	2470.8±1975.2 (1390–6470)	4060.7±3346.5 (1203–11319)	0.000
Hypertension (No. of pts)	0	4	NS
Creatinine clearance (mL/min/1.73 m^2)*	133.9±32.9 (88.3–195.0)	128.7±27.4 (92.5–164.2)	NS
Pathologic findings			
Glomerular sclerosis/segmental/global (No of pts)	0/0	4/2	0.045
Tubulointerstitial change, mild /moderate (No. of pts)	4/0	8/2	0.035
Stage, II / III (No. of pts)	5/3	6/5	NS
Treatment			
Oral corticosteroid (No. of pts)	5	11	NS
Interval between onset and steroid therapy (mos)*	7.0±6.9 (0–17)	3.5±5.0 (0–17)	NS
Combined immunotherapy (No. of pts)	1	3	NS
Responder to daily corticosteroid (No. of pts)	4 out of 4	3 out of 10	NS
ACE inhibitor (No. of pts) used	7	6	NS
Clinical course			
Remission (No. of pts)	8	6	0.045
Interval between onset and remission (mos)*	14.6±13.3 (1–37)	12.3±4.7 (8–19)	NS
Renal vein thrombosis (No. of pts)	0	3	NS
Chronic renal insufficiency (No. of pts)	0	3	NS
Total follow-up duration (mos)*	57.9±42.1 (17–144)	41.8±14.4 (18–66)	NS

No. of pts, number of patients; mos, months; NS, not significant
* Values are expressed as mean±standard deviation, (range)

Table 4 Comparison of the clinicopathological findings between the remission and the non-remission group

	Remission group	Non-remission group	*P* value
No. of pts (male:female)	14 (7:7)	5 (2:3)	NS
Onset Age (yr)*	8.7±4.5 (1.7–14.9)	7.0±3.0 (7.4–14.2)	NS
Clinical findings at the onset			
Nephrotic syndrome (No. of pts)	6	5	0.045
Urinary protein (mg/m^2/day)*	2914.5±1956.9 (1390–6470)	4445.2±4356.6 (1203–11319)	NS
Serum albumin (g/dL)*	2.9±0.8 (1.7–3.9)	2.0±0.7 (1.2–2.7)	0.046
Serum total cholesterol (mg/dL)*	306.4±153.2 (168–674)	496.5±153.7 (312–704)	0.026
Hypertension (No. of pts)	3	1	NS
Creatinine clearance (mL/min/1.73 m^2)*	131.4±30.1 (88.3–195.0)	130.9±31.5 (94.5–164.2)	NS
Pathologic findings			
Glomerular sclerosis/segmental/global (No. of pts)	1/1	3/1	NS
Tubulointerstitial change, mild/moderate (No. of pts)	7/2	5/0	NS
Stage, II / III (No. of pts)	8/6	3/2	NS
Treatment			
Oral corticosteroid (No. of pts)	11	5	NS
Interval between onset and steroid therapy (mos)*	4.4±5.3 (0–17)	5.0±7.1 (0–17)	NS
Combined immunotherapy (No. of pts)	4	0	NS
ACE inhibitor (No. of pts)	10	3	NS
Clinical course			
Renal vein thrombosis (No. of pts)	0	3	0.010
Chronic renal insufficiency (No. of pts)	0	3	0.010
Total follow-up duration (mos)*	48.2±34.1 (17–144)	49.6±11.5 (34–66)	NS

No. of pts, number of patients; mos, months; NS, not significant
* Values are expressed as mean±standard deviation, (range)

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