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ORIGINAL ARTICLE

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Prediction of subsequent relapse in children with steroid-sensitive nephrotic syndrome

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Abstract Among nephrotic children with frequent relapses at risk for cumulative steroid toxicity, identification of children who may be at high risk for subsequent relapse is very important in making the decision to introduce cytotoxic drugs. We examined the clinical course of 467 relapses in 121 steroid-sensitive nephrotic children to elucidate the risk factors for subsequent relapse, using the Cox proportional-hazards regression model. Gender, age at onset, duration of illness from onset, prednisolone dosage at the most-recent relapse, and regimens of initial steroid therapy at onset were not associated with risk. Relapse within the 1st year was a powerful independent predictor of subsequent relapse irrespective of the duration of illness. The hazard ratio of patients with more than one relapse within the 1st year increased to 1.72–2.12 compared with those without a relapse within the 1st year. The remission period just before the most-recent relapse was also a significant predictor. The risk for patients with a 1-year or longer remission period decreased to 0.57. Patients treated with cyclophosphamide for 12 weeks had a significantly longer remission than those treated with prednisolone alone. Our results suggest that early relapse after onset and/or a short remission period just before recent relapse are independent risk factors for subsequent relapse. Cytotoxic therapy has serious adverse effects and its effect may be limited. Our results may be helpful in deciding on the suitability of cytotoxic drugs.

Keywords Relapse · Risk factor · Steroid-sensitive · Nephrotic syndrome · Immunosuppressants

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Introduction

Children with steroid-sensitive nephrotic syndrome have a favorable long-term prognosis. Nevertheless, about half the children experience frequent relapses and receive corticosteroid treatment repeatedly, which may induce serious steroid toxicity, such as growth retardation, obesity, and cataracts [1, 2, 3]. Such patients who are given cytotoxic therapy may enjoy a prolonged remission [4, 5, 6, 7, 8, 9, 10, 11, 12, 13], but not without significant side effects [14, 15, 16, 17, 18, 19]. Therefore, it is important to identify children at high risk for subsequent relapse in order to make a decision about the use of cytotoxic drugs.

Previously we reported that the risk factors for relapse in nephrotic children are young age and low concentration of serum protein during the initial episode [20]. However, there are few data available regarding the risk factors for subsequent relapse in nephrotic children with relapse after onset. In order to elucidate these factors, we retrospectively examined the clinical course of nephrosis in a consecutive series of 121 children who were followed from the initial episode during the past 20 years.

Patients and methods

Medical records were reviewed from a consecutive series of 121 children with steroid-sensitive nephrotic syndrome who were admitted to our hospitals during the initial episode between April 1977 and March 1997 and who were followed at our hospitals for at least 2 years from clinical onset. Renal biopsy was performed in 36 children and showed minimal change disease in 35 and focal glomerular sclerosis in 1. During the follow-up period, which ranged from 2.0 to 20.3 years, with a median of 8.2 years, 600 relapses occurred in 93 children, 133 relapses occurred within the 1st year after onset, and the other 467 occurred more than 1 year after onset. The patients who had relapses that occurred after 1 year of illness were entered into the analysis. We examined the influence of the following variables on subsequent relapse: age at onset, gender, frequency of relapse within the 1st year, duration of illness, remission period just before the most-recent relapse (the most-recent remission), prednisolone dosage at the most-recent relapse, regimens of initial steroid therapy at onset, and administration of immunosuppressants.

Until February 1980, steroid therapy for the initial nephrotic episode was prednisolone 60 mg/m^2 per day (maximum daily dosage 80 mg) in three divided daily doses for 4 weeks followed by 40 mg/m^2 in a single dose on 3 consecutive days of 7 for 4 weeks. Relapse was treated with 60 mg/m^2 per day in divided doses until response, followed by 40 mg/m^2 in a single dose on 3 consecutive days of 7 for 4 weeks (standard regimen). Since March 1980, although the initial dose and duration of prednisolone were the same as indicated above, a slowly tapering regimen for 8–18 weeks was adopted (long-term tapering regimen). Children with frequent relapses were treated according to each patient's specific regimen, which was determined according to the patient's previous clinical course. Oral prednisolone was given at the lowest possible dose to induce a remission. After complete remission, prednisolone was gradually tapered and maintained for a minimum of 3–6 months at the lowest possible dose to prevent a relapse, and then withdrawn. Maintenance prednisolone was set at the same or somewhat greater dose than that used for previous relapses, and was continued for the same or somewhat longer duration than that of the previous remission. For the patients with recurrent episodes of relapse and serious steroid toxicity, immunosuppressants were introduced after informed parental consent was obtained. Cyclophosphamide was administered for 8–12 weeks at a dose of 2.0–2.5 mg/kg per day. Chlorambucil was administered for 8 weeks at a dose of 0.2 mg/kg per day. Cyclosporin A was started at an initial dose of 5 mg/kg per day and the whole-blood trough levels (measured by monoclonal radio-immunoassay) were maintained between 50 and 150 mg/l. If cyclosporin A maintained a remission for 6 months, it was then reduced to 2.5 mg/kg per day and continued for at least 2 years. Prednisolone was used in addition to immunosuppressants in all but 13 children who were treated with cyclosporin A alone, because of steroid-induced glaucoma, severe growth retardation, or patient's desire. Prednisolone was increased to the dose indicated above and tapered gradually without maintenance.

Patients were considered to have a steroid-sensitive nephrotic syndrome if they achieved a remission during the first 8 weeks of prednisolone treatment. Relapse was defined as a reappearance of proteinuria ≥ 40 mg/m^2 per hour (dipstick reading 2+ or greater) for 3 consecutive days. Complete remission was defined as a reduction in the urinary excretion of protein to <4 mg/m^2 per hour (dipstick reading 0 to trace) for 3 consecutive days [3].

The relapse-free period was calculated by the Kaplan-Meier method. The differences between curves were analyzed by the log rank test. The Cox proportional-hazards regression model was used to examine the adjusted independent effect of variables on relapse. Differences with P values <0.05 were regarded as significant.

Results

Because one of our initial treatments (the long-term tapering regimen) was longer than that of the International Study of Kidney Disease in Children (ISKDC) [3], we evaluated the relapse rate within the 1st year from onset to determine whether the frequency of relapse in the early course predicted the subsequent relapse. The study evaluated a total of 467 relapses that occurred more than 1 year after disease onset. Table 1 summarizes the baseline characteristics of these children. The median age at onset was 4.5 years. During the 1st year of disease, 87 (19%) of patients experienced no relapse, 262 (56%) suffered one or two relapses, and 118 (25%) experienced three or more relapses. The median duration of the most-recent remission was 6.7 months. At the most-recent relapse, 180 (41%) children received no prednisolone, 161 (37%) received less than 0.25 mg/kg of prednisolone, 72 (16%) received less than 0.50 mg/kg, and 28 (6%) received 0.5 mg/kg or more. Of 121 children with an initial episode, 13 received the standard steroid regimen and 108 the long-term tapering regimen. After 1 year from disease onset, the former children experienced 91 (19%) relapses and the latter children 376 (81%) relapses. Nineteen children had received cyclophosphamide, 6 chlorambucil, and 50 cyclosporin A. Because cyclosporin A became available only recently, children treated with cyclosporin A had a longer duration of illness, and previously received immunosuppressants more frequently than those treated with cyclophosphamide or chlorambucil (data not shown).

Table 1 Characteristics of 467 relapses among nephrotic children with a one year or longer history of illness (*ISKDC* International Study of Kidney Disease in Children)

Characteristics	Number (percentage)
Male gender	317 (68%)
Age at onset (years)	4.5 (1.6–16.8)[a]
Frequency of relapse within 1st year	
No relapse	87 (19%)
One or two relapses	262 (56%)
Three or more relapses	118 (25%)
Duration of illness from onset	
1–3 years	231 (49%)
4–6 years	110 (24%)
7 years or more	126 (27%)
Duration of the most-recent remission (months)	6.7 (0.5–128.4)[a]
Prednisolone dosage at the most-recent relapse[b]	
0 mg/kg	180 (41%)
0–0.25 mg/kg	161 (37%)
0.25–0.50 mg/kg	72 (16%)
0.5 mg/kg or more	28 (6%)
Steroid therapy for initial episode	
Standard (ISKDC) regimen	91 (19%)
Long-term tapering regimen	376 (81%)
Administration of immunosuppressants	
Cyclophosphamide for 12 weeks	10
Cyclophosphamide for 8 weeks	9
Chlorambucil	6
Cyclosporin A	50

[a] Median (range)
[b] Data from 26 relapses were not available

Figure 1 shows the relapse-free curve for all 467 relapses after 1 year of illness. The percentages of patients with sustained remission at 0.5, 1, 2, 3, 4, and 5 years were 58, 34, 21, 16, 13, and 11%, respectively.

Table 2 shows the results of multivariate analysis of risk factors for subsequent relapse. Gender, age at onset, and duration of illness from onset were not associated with risk. Prednisolone dosage at the most-recent relapse and regimens of initial steroid therapy at onset were also unassociated with subsequent relapse.

Relapse within the 1st year was a powerful independent predictor of subsequent relapse. The hazard ratio for

the patients with one or two relapses and those with three or more relapses during the 1st year increased 1.72 [95% confidence interval (CI) 1.23–2.41] and 2.12 (95%CI 1.42–3.17) respectively, compared with those with no relapse. However, the difference between the groups of patients with relapses during the 1st year was not significant. In further analyses that divided patients into groups by the duration of observation from onset of disease to the most-recent relapse, a similarity was found in the pattern of remission (Fig. 2). Patients with no relapse within the 1st year always had a lower risk of subsequent relapse if relapsed after the 1st year than those who suffered a relapse during the 1st year, irrespective of the duration of illness.

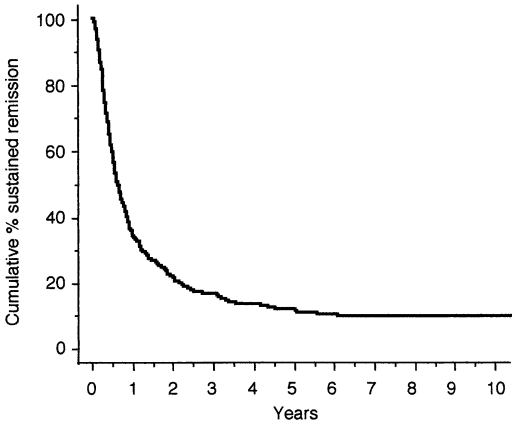

Fig. 1 A relapse-free curve for 467 relapses among patients with a one year or longer history of illness

The duration of the most-recent remission was also a significant predictor of subsequent relapse (Table 2). The risk for patients whose most-recent remission lasted 1 year or longer decreased to 0.57 (95% CI 0.43–0.76) compared with those with a 1-year or shorter remission period.

Smaller dose of prednisolone at the most-recent relapse, in univariate analysis, predicted a lower percentage of subsequent relapse (data not shown). However, there was no significance in multivariate analysis.

There were significant differences in patient characteristics among the groups with immunosuppressants. Therefore, we performed multivariate analysis to compare each immunosuppressant group with the children treated with prednisolone alone. Cyclophosphamide for

Table 2 Risk factors for subsequent relapse in children with relapses 1 year or more after onset. Results of multivariate analysis based on the Cox proportional-hazards regression model (*CI* confidence interval)

Variable	Hazard ratio	CI (95%)	*P* value
Gender			
Female	1.00		
Male	1.07	0.83–1.38	0.60
Age at onset			
Under 5 years	1.00		
Over 5 years	0.93	0.74–1.18	0.56
Frequency of relapse within 1st year			
No relapse	1.00		
One or two relapses	1.72	1.23–2.41	0.002
Three or more relapses	2.12	1.42–3.17	0.0003
Duration of illness from onset			
1–3 years	1.00		
4–6 years	1.12	0.86–1.46	0.41
7 years or more	1.06	0.79–1.42	0.72
Duration of the most-recent remission			
Under 1 year	1.00		
1 year or more	0.57	0.43–0.76	0.0001
Prednisolone dosage at the most-recent relapse			
0 mg/kg	1.00		
0–0.25 mg/kg	0.94	0.71–1.23	0.63
0.25–0.50 mg/kg	0.86	0.61–1.23	0.41
0.5 mg/kg or more	1.35	0.79–2.33	0.28
Steroid therapy for initial episode			
Standard (ISKDC) regimen	1.00		
Long-term tapering regimen	0.86	0.65–1.13	0.27
Administration of immunosuppressants			
Prednisolone	1.00		
Cyclophosphamide for 12 weeks	0.34	0.15–0.77	0.01
Cyclophosphamide for 8 weeks	0.57	0.28–1.15	0.12
Chlorambucil	0.45	0.18–1.11	0.08
Cyclosporin A	0.89	0.61–1.28	0.52

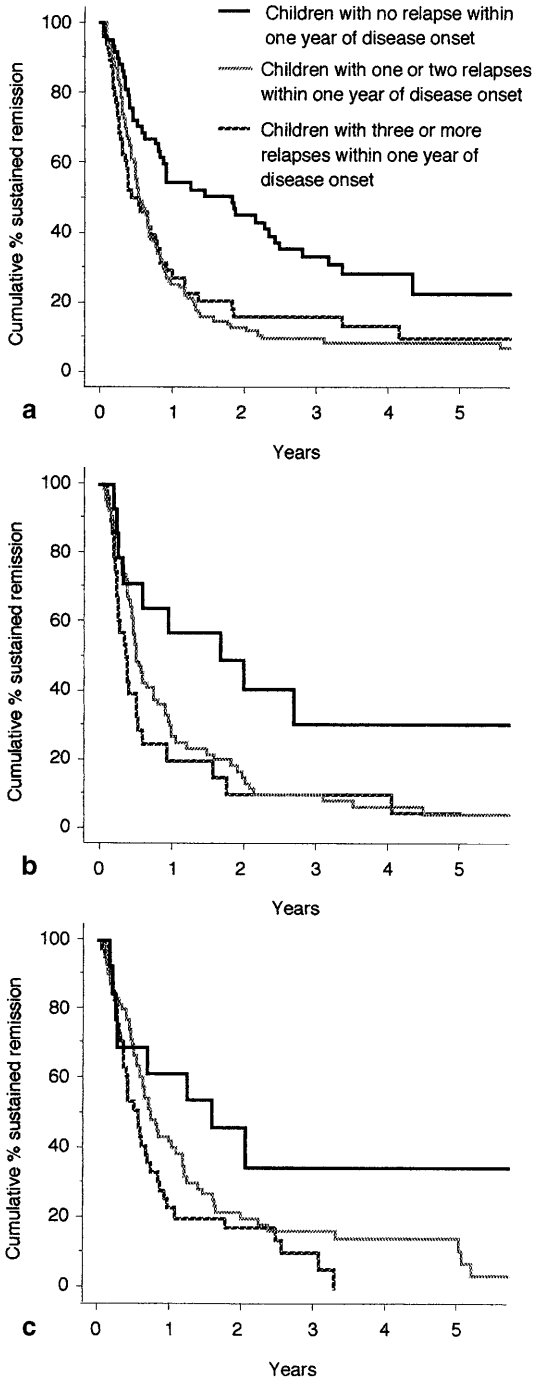

Fig. 2a–c Relapse-free curves of nephrotic children after the most-recent relapse, grouped by the frequency of relapse within 1 year of disease onset. Patients are divided further into three groups by the duration of observation from onset of disease to recent relapse: patients with a history of 1–3 years (**a**), 4–6 years (**b**), and 7 years or more from onset to recent relapse (**c**). Patients with no relapse within the 1st year always had a lower risk of subsequent relapse if relapsing after the 1st year than those who suffered a relapse during the 1st year, irrespective of the duration of illness. **a** P=0.0002, **b** P=0.03, and **c** P=0.03 by log rank test

12 weeks had a significant effect in preventing subsequent relapse and its hazard ratio was 0.34 (95% CI 0.15–0.77). Cyclophosphamide for 8 weeks, chlorambucil, and cyclosporin A also decreased the risk for subsequent relapse. However, their hazard ratios were 0.57 (95% CI 0.28–1.15), 0.45 (95% CI 0.18–1.11), and 0.89 (95% CI 0.61–1.28), respectively, which were not significant (Table 2).

Discussion

ISKDC reported that the number of relapses that occurred during the first 6 months after 8 weeks of initial therapy was highly predictive of the subsequent course [3, 21]. Because our initial treatment, the long-term tapering regimen, was longer by 4–14 weeks than that of ISKDC, we examined the relationship between the relapse rate within 1 year of disease onset and the tendency for subsequent relapse. Therefore, we analyzed 467 episodes that occurred 1 year or longer after onset. The remission-free rate fell rapidly to 21% within 2 years, but thereafter changed little, which is in agreement with the observation of Habib and Kleinknecht [22] and ISKDC [3].

Although gender, age at onset, duration of illness from onset, and regimens of initial steroid therapy were not associated with the risk of subsequent relapse, relapse within 1 year of disease onset was a powerful risk factor. This trend persisted even with a long follow-up. However, the number of relapses within the 1st year did not influence the subsequent clinical course. ISKDC reported in 1982 [21] that the number of relapses within the first 6 months was associated with the frequency of subsequent relapsing course. However in 1997 ISKDC [3] added that whether or not the relapse occurred within the early period, not the number of relapses, predicted the long-term clinical course. Our results are similar to those recently reported by ISKDC, and suggest that children with relapse early in their illness continue to have a stronger tendency to relapse throughout their illness than those without an early relapse.

A longer period of remission has been thought to indicate a lesser risk for relapse. In the reports of ISKDC [3] and Habib and Kleinknecht [22], a non-relapsing course for 2 consecutive years predicted an excellent prognosis. Lewis et al. [23] revealed that there was an inverse linear relationship between the length of remission and the proportion of patients relapsing in the subsequent course. Our study showed for the first time by multivariate analysis that the remission period just before the most-recent relapse was an independent predictor for the subsequent relapse. We also revealed that the prednisolone dosage at the most-recent relapse did not predict the subsequent relapse. These results suggest that relapse after a short-term remission, irrespective of prednisolone dosage if the patient is on preventative prednisolone maintenance therapy, strongly predicts subsequent relapse.

Most nephrotic children have fewer relapses as they grow older [2, 3, 23]. We could not show that the duration of illness was an independent predictor for relapse, but this does not mean frequency did not decrease with time. In fact, as we have previously reported, the relapse rate in the patients decreases as the clinical course becomes longer [24]. Our results were apparently contradictory, because there were more episodes in patients who continued to have relapses than in those who were showing improvement.

There are some reports that suggest that prolongation of the initial steroid therapy beyond 8 weeks may reduce the rate of subsequent relapse and the proportion of frequent relapsers [25, 26, 27]. However, we found no preferable effect of a long-term tapering regimen at onset on children with relapses after the 1st year.

Immunosuppressants have been reported to have beneficial effects in preventing relapse, but these were not enough to satisfy the relapsing children and their parents [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. Among the immunosuppressants, we showed the independent effect only with cyclophosphamide for 12 weeks. Other immunosuppressants also showed beneficial effects in preventing relapse but were not significantly strong. Moreover, their effects did not continue for a long time. Most patients had relapse soon after cessation of cyclosporin A [10, 11, 12, 13]. We previously revealed that neither cyclosporin A nor chlorambucil had a long-term effect in preventing a relapse, although cyclophosphamide did [28]. Serious adverse effects, such as gonadal toxicity [14, 15, 16], leukemogenesis [17], and nephrotoxicity [18, 19], are other troublesome problems of these drugs. Therefore, the decision to introduce immunosuppressants is sometimes difficult; for example, in children who have frequent relapses and steroid toxicity but who hesitate to receive them, or in children who have relapse after one or two courses of immunosuppressants. Our results, i.e., early relapse after onset and/or a short remission period just before the most-recent relapse are independent risk factors for subsequent relapse, may be helpful in making the decision about the use of such potentially toxic drugs. We can not answer the question as to which children will respond better to the immunosuppressants from this study. Konrad et al. [29] reported that the absence of HLA-DR7 in children with frequent relapses indicated a higher remission rate after cyclophosphamide or chlorambucil treatment. Further studies on reliable predictors of the response to immunosuppressants will make our results more useful for the treatment of nephrotic children suffering from frequent relapses.

In conclusion, we demonstrated that early relapse after onset and/or a short remission period just before the most-recent relapse are independent risk factors for subsequent relapse in children with steroid-sensitive nephrotic syndrome. Cytotoxic therapy has serious adverse effects and its effect may be limited. Our results may be helpful in deciding on the use of such potentially toxic drugs.

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LITERATURE ABSTRACTS

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Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment

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Cystatin C is a nonglycosylated basic protein produced at a constant rate by all investigated nucleated cells. It is freely filtered by the renal glomeruli and primarily catabolized in the tubuli (not secreted or reabsorbed as an intact molecule). Because serum cystatin C concentration is independent of age, sex, and muscle mass, it has been postulated to be an improved marker of glomerular filtration rate (GFR) compared with serum creatinine level. We compared serum cystatin C level with other markers of GFR, such as serum creatinine level and creatinine clearance, and analyzed their variations based on iothalamate labeled with iodine 125 ((125)I-iothalamate) clearance ((125)I-ICl), used as the gold standard for GFR. The concentrations of the two different markers of GFR in patients with impaired renal function were classified according to (125)I-ICl. Twenty individuals with normal renal function ((125)I-ICl, 128±23 mL/min/1.73 m(2)) were used as the control group. Serum cystatin C level showed a greater sensitivity (93.4%) than serum creatinine level (86.8%). Also, serum cystatin C showed the greatest proportion of increased values in patients with impaired renal function (100%) compared with serum creatinine level (92.15%). Serum cystatin C levels started to increase to greater than normal values when GFR was 88 mL/min/1.73 m(2), whereas serum creatinine level began to increase when GFR was 75 mL/min/1.73 m(2). These data suggest that measurement of serum cystatin C may be useful to estimate GFR, especially to detect mild reductions in GFR, and therefore may be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.

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Regulation of potassium channel Kir 1.1 (ROMK) abundance in the thick ascending limb of Henle's loop

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The renal outer medullary potassium channel (ROMK) of the thick ascending limb (TAL) is a critical component of the countercurrent multiplication mechanism. In this study, two new antibodies raised to ROMK were used to investigate changes in the renal abundance of ROMK with treatments known to strongly promote TAL function. These antibodies specifically recognized protein of the predicted size of 45 kD in immunoblots of rat kidney or COS cells transfected with ROMK cDNA. Infusion of 1-deamino-(8-D-arginine)-vasopressin (dDAVP), a vasopressin V2 receptor-selective agonist, for 7 d into Brattleboro rats resulted in dramatic increases in apical membrane labeling of ROMK in the TAL of dDAVP-treated rats, as assessed by immunocytochemical analyses. Using immunoblotting, a more than threefold increase in immunoreactive ROMK levels was observed in the outer medulla after dDAVP infusion. Restriction of water intake to increase vasopressin levels also significantly increased TAL ROMK immunolabeling and abundance in immunoblots. In addition, dietary Na(+) levels were varied to determine whether ROMK abundance was also affected under other conditions known to alter TAL transport. Rats fed higher levels of sodium, as either NaCl or NaHCO(3) (8 mEq/250 g body wt per d), exhibited significantly increased density of the 45-kD band, compared with the respective control animals. Moreover, in rats fed a low-NaCl diet (0.25 mEq/250 g body wt per d), a 50% decrease in band density for the 45-kD band was observed (relative to control rats fed 2.75 mEq/250 g body wt per d of NaCl). These results demonstrate that long-term adaptive changes in ROMK abundance occur in the TAL with stimuli that enhance transport by this segment.