Nephrotic Syndrome in Thai Children: Nakornping Hospital Experience

Surachai Laopornpichayanuwat, M.D.
Division of Pediatrics, Nakornping Hospital, Chiang Mai 50180, Thailand.

ABSTRACT

Objective: The purposes of this study are to determine the incidence, age of onset, gender, initial presentations, predictive parameters of frequent relapsers/steroid dependence and steroid resistance, results of disease course, growth retardation and complications of long term prednisolone therapy.

Methods: A retrospective descriptive study was done in 37 pediatric patients with their first episode of primary nephrotic syndrome admitted at Nakornping Hospital during 1 October 2002 to 30 September 2005. The data in medical records were analyzed by using descriptive statistics. This study used percentage, mean, median and standard deviation for basic data. Statistical analyses were done by Student's t - test, Fisher's exact test and Chi-square test for testing of statistically significant differences.

Results: The average age of patients was 7.7 years (male 7.7 years, female 7.7 years). The estimated annual incidence of nephrotic syndrome in healthy children in Chiang Mai was at least 3.48 new cases per 100,000 children younger than 15 years of age with the average of treatment period 19.2 months (2-36 months). Initial presentations consisted of generalized edema (86.4%), renal insufficiency (48.6%), fever (37.8%), hypertension (32.4%), gross hematuria (21.65%), and microscopic hematuria (21.6%). Initial therapy consisted of 60 mg/m^2/day prednisolone daily for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks, thereafter decreasing alternate-day therapy every month by 25% over the next 4 months. Thirty-one patients (83.8%) were steroid-responsive, 6 patients (16.2%) were steroid-resistant. Of the 31 initial responders, 4 patients were excluded because of short follow-up period. Of the remaining 27 patients, 16 patients (59.2%) were nonrelapsers, 4 patients (14.85%) were infrequent relapsers, 6 patients (22.2%) were frequent relapsers/steroid dependence and one (3.7%) subsequently became steroid-resistant. The average of initial remission time (protein-free urine) was 16.4 days (15.2 days in nonrelapsers and infrequent relapsers, 21 days in frequent relapsers/steroid-dependent patients). The study for predictive parameters predicting the response of steroid therapy found that a group of the frequent relapsers/steroid-dependent and steroid-resistant patients had ascites, pulmonary edema/plural effusion, moderate renal insufficiency (GFR <60 ml/min/1.73m^2), and gross hematuria more frequent than a group of the nonrelapsers and infrequent relapsers. But mild renal insufficiency (GFR 60-89 ml/min/1.73m^2) was found less than the latter group. Only moderate renal insufficiency was statistically different in both groups. Six frequent relapsers/steroid-dependent patients had average occurrence of 2.83 relapses. All had complete remission. Three patients who used cyclophosphamide had longer complete remission than nonuser group (17 months versus 3.6 months). Seven steroid-resistant patients were treated with cyclophosphamide, 2 patients (28.56%) had complete remission for 25 months, the other two patients had complete remission for 1.5 and 3 months, respectively. Three patients were still depended on steroid. BMI and height for age in all patients were normal except one patient with BMI> 25.

Conclusion: The increasing average age of first diagnosis of primary NS may indicate that there are more frequent relapsers/steroid-dependent and steroid-resistant patients than the past. The frequent initial presentations are generalized edema, renal insufficiency, hematuria, fever, and hypertension. The initial parameters that can predict the frequent relapsers/steroid dependence and steroid resistance are moderate renal insufficiency, gross hematuria, pulmonary edema/pleural effusion, and ascites. The frequent relapsers/steroid dependence and steroid resistance had more severe degree of renal insufficiency. The longer duration of treatment until the patient's urine became protein-free may be a predictor of frequent relapsers/steroid dependence. The long regimen of steroid therapy for the initial episode may result in sustained complete remission and reduce frequency of relapses with few complications and growth retardation. The treatment of frequent relapsers/steroid dependence with cyclophosphamide may result in longer complete remission. Failure of cyclophosphamide therapy in steroid resistance indicates a consideration of other drugs. Therefore, this study indicates the benefits of completed information collection which may improve the outcome of treatment and encourage the physicians to study further for more completed outcomes.

Keywords: Nephrotic syndrome(NS); Initial responder; Nonrelapser; Infrequent relapser; Frequent relapser; Steroid-dependent; Nonresponder/steroid-resistant

Siriraj Med J 2006;58: 648-653
E-journal: http://www.sirirajmedj.com

Correspondence to: Surachai Laopornpichayanuwat
E-mail: surachailao@hotmail.com

Nephrotic syndrome (NS) of childhood is a frequent chronic disease, characterized by massive proteinuria and hypoproteinemia leading to edema and hypercholesterolemia. NS is caused by many kidney diseases. But in children, most cases are primary NS without other systemic diseases. The annual incidence of NS in healthy children is 2-7 new cases per 100,000 children younger than 15 years old.[1,7] The age of onset is between 18 months to 6 years (average 4.37 years). The average age of onset is 2.5 years in minimal change nephrotic syndrome (MCNS) and 6 years in focal segmental glomerulosclerosis (FSGS). Male: female ratio is found in 1.5-2:1. Various histopathologic findings have been found in children with NS and about 75% of the cases have minimal change disease. Recently, the prevalence of FSGS has been reported to be increasing in children.[1] Approximately, 90-93% of children[2,3] with MCNS will initially respond to daily prednisolone and most responders have MCNS (91.8-94%).[4,5] It is clinically important to differentiate NS as early as possible in the course of disease, between patients with MCNS and those with other glomerular lesions. Based on the results of ISKDC, a common practice in patient presenting with feature of idiopathic NS is the initiation of steroid treatment without performing kidney biopsy[4] by prednisolone 60 mg/m^2/day for 4 weeks, followed by 40 mg/m^2 alternate days for another 4 weeks. Unfortunately, the rate of relapses is high (60-75%),[2] with a significant proportion of patients (39%) becoming frequent relapsers or steroid-dependent. Thus, the study for predictive parameters predicting the steroid response is important. The steroid response is the best indicator for the prognosis. The majority of children with idiopathic NS (85%) are steroid-sensitive. Also, the majority (80.5-94.4%) of those who are steroid-resistant have FSGS or mesangioproliferative glomerulonephritis.[5] The aim of management of NS is to induce and maintain complete remission with resolution of proteinuria and edema without encountering serious adverse effects of the therapy.[6] The purposes of this study are established to find the incidence, age of onset, gender, initial presentations, predictive parameters for frequent relapsers /steroid dependence and steroid resistance, the results of disease course, growth retardation, and complications of long-term prednisolone therapy.

MATERIALS AND METHODS

The study was conducted as a retrospective chart review of all pediatric patients with first episode of NS admitted at Nakornping Hospital during 1 October 2002 to 30 September 2005. All patients satisfied the following criteria, namely: 1) heavy proteinuria> 50 mg/kg/day; 2) hypoalbuminemia <2.5 gm/dl; 3) edema; 4) hypercholesterolemia; 5) no prior treatment with steroids or other cytotoxic agents; and, 6) no evidence of underlying systemic diseases.

Definition and treatment regimen

Initial responder: a patient who responds (protein-free urine) during 8 weeks of initial treatment. Nonrelapser: a responder who has no relapse. Infrequent relapser: a responder who relapses but has less than 2 relapses within 6 months of the initial response. Frequent relapsers: a responder who has 2 or more relapses within 6 months of the initial response. Steroid dependent: a responder who relapses frequently while receiving or within 2 weeks after discontinuing steroid treatment. Nonresponder: a patient who has no response during the initial 8 weeks of treatment. Initial therapy consisted of prednisolone 60 mg/m^2/day (maximum dosage, 80 mg/day) 4 weeks, followed by 40 mg/m^2 (maximum dosage, 60 mg/day) on alternate days for 4 weeks; thereafter, decreasing alternate-day therapy every month by 25% over the next 4 months. Standard relapse therapy consisted of 60 mg/m^2/day prednisolone until urine was protein-free for at least 3 days, followed by 40 mg/m^2 on alternate days for 4 weeks; thereafter, decreasing the dosage by 15-20 mg /m^2 (maintenance alternate-day steroid therapy just above steroid threshold (0.1-0.5 mg/kg/48 hr) for 6-12 months).[3,5] The child should start oral prednisolone therapy after negative tuberculosis skin test, normal stool examination and normal chest x-ray results has been determined. The nonresponder and frequent relapser/steroid dependence were considered oral cyclophosphamide (dosage, 1-2 mg/kg/day) for 1-3 months with CBC monitoring (WBC count >4,000/mm^3). Variable: the medical records of patients with NS were analyzed and the following information was noted: gender, age, weight, height, initial presentations, treatment regimen, remission days, duration of therapy, duration of follow-up, frequency of relapses, the pattern of relapses, duration of complete remission, height for age, body mass index. Data analysis: this study used percentage, mean, median and SD, for basic data. Statistical analyses were done by Student's t-test, Fisher's exact test and Chi-square test for testing of statistically significant differences.

RESULTS

Of the 42 patients diagnosed as first episode of NS from October 1, 2002 to September 30, 2005, 5 patients were excluded (3 patients due to their prior treatment with steroids, and 2 patients based on their insufficiency information). Of the remaining 37 patients: 27 patients (73%) were male and 10 patients (27%) were female, giving a male: female ratio of 2.7:1. The mean age at presentation was 7.7 years (male: mean 7.7 years; median 7 years; female: mean 7.7 years; median 8.5 years) with a range of 2 to 14 years. The estimated annual incidence of NS in healthy children was at least 3.48 new cases per 100,000 children younger than 15 years of age (34 of 37 patients lived in Chiang Mai per 325,213 children younger than 15 years old in Chiang Mai). The average of follow-up time was 19.2 months with a range of 2 to 36 months. Of the initial presentation of 37 patients with

TABLE 1. Initial presentations of initial diagnosis of nephrotic syndrome (N = 37)

Initial presentation	Number of patients (Case)	Number of patients (%)
Generalized edema	32	86.4
Renal insufficiency (GFR <90 ml/min/1.73m^2)	18	48.6
Fever	14	37.8
Hypertension	12	32.4
Ascites	9	24.3
Gross hematuria	8	21.6
Microscopic hematuria	8	21.6
Pulmonary edema/pleural effusion	8	21.6
Scrotal / labial swelling	6	16.2
Only facial swelling	5	13.5
Non-pitting edema	2	5.4

TABLE 2. Outcomes of long term follow up in the initial responders (N = 27)

Outcome	Number of patients (Case)	Number of patients (%)
Nonrelapses	16	59.2
Infrequent relapses	4	14.8
Frequent relapses / steroid dependence	6	22.2
Subsequently became steroid-resistant	1	3.7

NS,32 patients (86.4%) had generalized edema; 18 patients (48.6%) had renal insufficiency; 14 patients (37.8%) had fever; 12 patients (32.4%) had hypertension; 9 patients (24.3%) had ascites; 8 patients (21.6%) had gross hematuria; 8 patients (21.6%) had microscopic hematuria; and 8 patients (21.6%) had pulmonary edema/pleural effusion.

Regarding the course of the disease with initial standard 8-week prednisolone therapy, there were 31 patients (83.8%) with initial response and 6 patients (16.2%) with no response. Thirty-one initial responders were divided into nonrelapsers, infrequent relapsers, frequent relapsers, and steroid dependence. In this study, frequent relapsers and steroid dependence were analyzed together, as prolonged prednisolone therapy made it difficult to discriminate these groups. Of the 31 initial responders, 4 patients had follow-up period shorter than 3 months and were still on prednisolone. The rest 27 patients had follow-up period for 8-36 months. There were 16 patients (59.2%) with nonrelapsers, 4 patients (14.8%) with infrequent relapsers, 6 patients (22.2%) with frequent relapsers/steroid dependence, and one patient (3.7%) with subsequent steroid-resistant. Of the 31 patients with initial response, the duration of treatment until the patient's urine became protein-free was noted. It took an average of 15.8 days to achieve initial remission (15.2 days in nonrelapsers and infrequent relapsers, N=20; 21 days in frequent relapsers/steroid dependence; N=7). The study was designed to find predictive parameters at first episode of NS that predicted the response of prednisolone therapy in 33 patients who had follow-up period for 8-36 months. The mean age at presentation was 7.85 years in nonrelapsers and infrequent relapsers (N=20) and 7.16 years in frequent relapsers/steroid dependence and steroid resistance (N=13). The initial parameters including ascites, pulmonary edema/ pleural effusion, hypertension, mild renal insufficiency (GFR 60-89 ml/min/1.73m^2), moderate renal insufficiency (GFR< 60 ml/min/1.73m^2), gross hematuria and microscopic hematuria were compared between "nonrelapsers/infrequent relapsers group," and "frequent relapsers/steroid dependence/steroid resistance group," as shown in. The percentage between 2 groups were 20:30.7, 15:30.7, 35:38.46, 45:15.4, 5:46.15, 20:30.7 and 20:23, respectively.

Six frequent relapsers/steroid-dependent patients had average frequency of relapses of 2.83 times (2-4 times). The average of follow-up period was 22.5 months with a range of 12.5 to 36 months. Three patients had complete remission without oral cyclophosphamide. The average of duration of complete remission was 3.6 months (2-7 months). Three patients treated with oral cyclophosphamide for 8 weeks had complete remission with average of complete remission duration 17 months (4-24 months).

Seven steroid-resistant patients were all treated with oral cyclophosphamide with the average of accumulative dosage of 164 mg/kg (112-240 mg/kg). The average of cyclophosphamide treatment duration was 11.6 weeks (8-16 weeks). Four patients had complete remission (25 months in 2 patients; 1.5 and 3 months in the other 2 patients). Two patients still had proteinuria off and on and were treated with alternate-day steroid therapy. One initial responder who became steroid-resistant was treated with oral cyclophosphamide with the accumulative dosage of 190 mg/kg for 14 weeks. He still had frequent relapses with oral prednisolone. Ten patients who were treated with cyclophosphamide had WBC count of 4,800-11,300/mm^3. Of thirty-seven patients who were treated with oral prednisolone, their average body mass index was 18.1 (14.8-27.3), and the average of height for age was 104% (95.8-111%).

TABLE 3. Initial parameters of the initial diagnosed NS to predict the frequent relapser/steroid dependence and steroid resistance (N = 33)

Initial parameter	Non relapsers and Infrequent relapsers (N = 20) Case (%)	Frequent relapsers / steroid dependence and steroid resistance (N = 13) Case (%)	P value
Ascites	4 (20)	4 (30.7)	NS*
Pulmonary edema / pleural effusion	3 (15)	4 (30.7)	NS*
Hypertension	7 (35)	5 (38.46)	NS**
Renal insufficiency			
(GFR 60-89 ml/min/1.73m^2)	9 (45)	2 (15.4)	NS*
(GFR<60 ml/min/1.73m^2)	1 (5)	6 (46.15)	<0.05*
Gross hematuria	4 (20)	4 (30.7)	NS*
Microscopic hematuria	4 (20)	3 (23)	NS*
Mean age of first diagnosis (years)	7.85 years	7.16 years	NS***

NS indicates not significant (P>0.05)
*Fisher's exact test
**Chi-square test
***Student's t-test
#GFR=$\frac{k \times \text{height(cm.)}}{\text{Pcr(mg/dl)}}$ (ml/min/1.73m^2)

DISCUSSION

This study at Nakornping Hospital reports that the annual incidence of NS was at least 3.48 new cases per 100,000 children younger than 15 years of age which was relevant to previous reports. The male: female ratio was 2.7:1; this is consistent with other epidemiologic finding that the prevalence of the male was twice of the female. The average age of first diagnosis was 7.7 years. It was higher than previous reports because of economic, educational and transport conditions. Moreover, some patients had spontaneous remission in 8-15 days. Therefore, the patients came to hospital rather late. The most common initial presentation in this study

TABLE 4. Results of treatment in frequent relapsers / steroid dependence (N = 6)

Treatment	Number of patients with complete remission (Case)	Complete remission period (months) Mean (range)	Follow - up period (months) Mean (range)
With cyclophos phamide	3	17 (4 - 24)	29 (16 - 36)
Without cyclopho sphamide	3	3.6 (2 - 7)	16.5 (12.5 - 25)

was generalized edema (86.4%). The decrease in plasma volume was due to diminution of plasma oncotic pressure resulting from hypoalbuminemia, causing transfer of fluid from plasma to the interstitial space "underfilling" the blood compartment and resulting to secondary renal sodium retention. By contrast, some patients had initial plasma volume expansion with sodium retention from renal excretory defect.[8] Renal insufficiency was found in 48.6% of the patients, caused by reduction of intravascular volume or severe renal histopathology. Improvement in renal function occurred in 10 days to 4 weeks.[9] Fever was found in 37.8% of the patients due to various sites of infection causing by cellular and humoral immunity defect.[10] Hypertension was found in 32.4% of the patients which was higher than in previous reports. Hematuria was found in 43.2% of the patients (21.6% with gross hematuria, 21.6% with microscopic hematuria) which correlated with the study of Alexandru R et al (46.4%).[2] The incidence of hematuria was higher than in previous reports (30%), because in this study renal biopsy was not performed in initial NS and steroid resistance was not excluded. ISKDC reported that high proportion of children with primary NS had MCNS (77%) and responded to steroid treatment (93.1%). Most responders had MCNS (91.8%). It is a common practice to determine the response to initial treatment before biopsy. Stadermann MB et al[11] designed the study to evaluate the use of renal biopsies prior to cyclophosphamide therapy. Cyclophosphamide therapy was indicated because of a frequently relapsing course and steroid dependence. They found MCNS in 84 of 85 children (98.8%). They concluded that no renal biopsy was required prior to cytotoxic therapy in children with uncomplicated steroid-sensitive NS. At Nakornping Hospital, however, renal biopsy was not performed in primary NS both prior to steroid and cyclophosphamide therapy (including steroid resistance because of the lack of efficacy). Furthermore, the patients denied referring to other centers because of economic reasons.

With ISKDC's standard 8-week treatment regimen with prednisolone, most had protein-free in urine within 10-15 days. Initial responder was found 85-90%. Ksiazek J and Wyszynska T[3] reported that after 8-week standard prednisolone regimen, the dose was 25% reduced each month and tapered off to 0 at the end of the sixth months. Sixty-three percent of them remained relapse-free within 6 months after prednisolone withdrawal and 50% throughout the 2-year follow-up period (compared with 8-weeks standard prednisolone regimen, 36.4% of them remained relapse-free within 6 months after prednisolone withdrawal and 27.3% throughout the 2-year follow-up period). The frequency of corticosteroid side effects such as hypertension, cushingoid obesity, and growth retardation did not increase after prolongation of the initial treatment. This study was well correlated with the study of Peco-Antic A,[5] Hodson EM et al[12] and Asinobi AO et al.[13] Lande MB et al[14] reported a long regimen consisted of daily prednisolone 60 mg/m^2 /day for 42 days, followed by alternate-day for 6-14 weeks might have a beneficial effect, but at the cost of increased side effects. Bagga A and Mantan M[15] reported prospective studies showing that prolonged duration of prednisolone therapy for the initial episode resulted in sustained remission and reduced the frequency of relapses. Remission of proteinuria following corticosteroid therapy had greater prognostic value, in relation to long-term outcome, than the precise renal histology. Bagga A et al[16] reported a regimen consisted of prednisolone 2 mg/kg/day for 4 weeks, 1.5 mg/kg/day for 4 weeks, and thereafter 1.5 mg/kg and 1 mg/kg on alternate days, each for 4 weeks. The study was, however, unable to show statistically significant differences with the standard group. Therefore, they suggested that this regimen might delay the occurrence of first relapse, but resulted in significant side effects. Prolongation of initial steroid therapy may be useful in developing countries where frequent infections often induce early relapses. With the above reviewed literatures, Nakornping Hospital used the 6-month regimen because of good responses, and few side effects and problems of infection control were found in Thailand. The relapse therapy consisted of 60 mg/m^2/day prednisolone until urine was protein-free for at least 3 days, followed by 40 mg/m^2 on alternate days for 4 weeks, thereafter decreasing the dosage by 15-20 mg/m^2 on alternate days for 6-12 months. After 60 mg/m^2 /day prednisolone until urine was protein-free for at least 3 days, Arbeitsgemeinschaft[17] used 35 mg/m^2 on alternate days for 6 months had good results.

Following the regimen at Nakornping Hospital, 83.8% were initial responder which correlated with the study of Peco-Antic A (85%).[5] The percentage was higher than that of the study of ISKDC (78%):[4] 16.2% were steroid resistance, compared with Kim JS et al (15%)[18] and Hachicha M et al (10%).[19] Kim JS et al found that 20% of steroid responders who subsequently became steroid-resistant. However, this study found only 1 case (3.7%) because of short follow-up period. The average days of treatment until the patient's urine became protein-free was 15.8 days, higher than that of Alexandru R et al (mean 13.9 days, ranged 6 to 42 days) because of their exclusion of steroid resistance. Twenty-seven responders were followed up more than 8 months. Twenty nonrelapsers and infrequent relapsers had their mean age of 7.85 years (SD=3.53). The average of protein-free days was 15.25 days (SD=5.59), compared with 7 frequent relapsers/ steroid-dependent patients who had the mean age of 7.14 years (SD=4.56). The average of protein-free days was 21 days (SD=12.6). The mean age of both groups had no statistically significant difference. Comparison for both groups with the remission days (protein-free urine), the frequent relapsers/ steroid dependence had the remission days longer than the nonrelapsers and infrequent

TABLE 5. Clinical and laboratory presentations in steroid resistance (N = 7)

Presentation	Number of patients (Case)	Number of patients (%)
Hypertension	4	57.1
Gross hematuria	3	42.8
GFR 60 - 89 ml/min/1.73 m^2	0	0
GFR < 60 ml/min/1.73 m^2	4	57.1

relapsers but they were not statistically significant (Student's t-test). It resulted from the small number of patients in two groups. Yap HK et al[20] suggested that the initial remission of 9 or more days was significant predictor of steroid dependency.

Correlation between predictive parameters at initial diagnosed NS and the steroid response therapy predicting for frequent relapsers/steroid dependence and steroid resistance found that both groups were not different in mean age (7.85 years in 20 nonrelapsers and infrequent relapsers, 7.16 years in 13 frequent relapsers/steroid-dependent and steroid-resistant patients). The second group had higher incidence of ascites, pulmonary edema/pleural effusion, moderate renal insufficiency, and gross hematuria than the first group except lower incidence of mild renal insufficiency. Only moderate renal insufficiency had statistically significant difference ($P<0.05$). Alexandru R et al[2] reported that the absence of hematuria found in the initial analysis suggested an infrequent relapse course but was not statistically significant.

Six frequent relapsers/steroid-dependent patients had average of relapse rates 2.83 times. Three had complete remission (average period 3.6 months by average of follow-up period 16.5 months). Three had complete remission after oral cyclophosphamide for 8 weeks (average period 17 months by average of follow-up period 29 months). This correlated with Durkan A et al's study[21] which suggested that cyclophosphamide significantly reduced the relapse risk compared with only prednisolone. Hachicha M et al[19] reported that steroid-resistant nephrosis represented 10% of idiopathic childhood nephrosis and progressed in almost half of cases to end-stage renal failure. In their report, 14.3% had hypertension, 35.7% had microscopic hematuria, 35.7 had transitory renal insufficiency, and 57% were FSGS. In this study, with 7 steroid-resistant patients treated with oral cyclophosphamide, 2 patients had complete remission for 25 months, 2 patients had complete remission for 1.5 months and 3 months, respectively. However, 3 patients were still treated with alternate-day steroid therapy. Fifty-seven percent had hypertension, 57% had renal insufficiency, and 42.8% had gross hematuria. This study found that the incidence of hypertension and gross hematuria were higher than Hachicha M et al's report.[19] Hafeez F et al[22] reported the treatment with oral cyclophosphamide and prednisolone had complete remission 50% (compared to this study, 57%).

Foster BJ et al[23] suggested that glucocorticoid therapy led to a cushingoid body with normal adult height. Ruth EM et al[24] reported that final adult height and body mass index (BMI) were normal in their study. Emma F et al[25] suggested that children with early onset of NS and adolescents who were still receiving prednisolone treatment after the age of 9 years in girls and 11 years in boys, were at higher risk for growth retardation. In addition, height measurements and BMI were available in all patients from the onset and follow-up period in this study. The height for age and BMI were normal in all children except 1 patient with BMI>25. Because of short follow-up period, this study was not able to conclude that long-term steroid therapy has no risk of permanent growth retardation.

CONCLUSION

The increasing average age of first diagnosis of primary NS may indicate that there are more frequent relapsers/steroid-dependent and steroid-resistant patients than in the past. The frequent initial presentations are generalized edema, renal insufficiency, hematuria, fever, and hypertension. The initial parameters that can predict the frequent relapsers/steroid dependence and steroid resistance are moderate renal insufficiency, gross hematuria, pulmonary edema/pleural effusion, and ascites. The frequent relapsers/steroid dependence and steroid resistance had more severe degree of renal insufficiency. The length of time of treatment that enables the patient's urine became protein-free may be a predictor of frequent relapsers/steroid dependence. The long regimen of steroid therapy for the initial episode may result in sustained complete remission and reduce frequency of relapses with few complications and growth retardation. The treatment of frequent relapsers/steroid dependence with cyclophosphamide may result in a longer complete remission. Failure of cyclophophamide therapy in steroid resistance indicates the consideration of other drugs (pulse cyclophosphamide, pulse methylprednisolone, cyclosporin, levamizole, mycophenolate mofetil and angiotensin-converting enzyme inhibitor).[26,27] Therefore, this study indicates the benefits of completed information collection which may improve the outcome of treatment and encourage the physicians to study further for more completed outcomes.

ACKNOWLEDGEMENTS

This study was supported by Dr.Virat Phanpanich (Director of Nakornping Hospital) who gave permission for this study, and Assist. Prof. Kanchana Tangnararatchakit, MD. (Ramathibodi Hospital) provided useful consultation. Hereby, I would like to thank them for their generous and kind supports.

REFERENCES

1. Mcenery PT, Strife CF.Nephrotic syndrome in childhood. Management and treatment in patients with minimal change disease, mesangial proliferation or focal glomerulosclerosis. Pediatr Clin North Am 1982;29:875-94.
2. Alexandru R, Hetal B, Edward F, Lynne S. Predicting first-year relapses in children with nephrotic syndrome. Pediatrics 2000;105:492-95.
3. Ksiazek J, Wyszynska T. Short versus long initial prednisolone treatment in steroid-sensitive nephrotic syndrome in children. Acta Paediatr 1995;84:889-93.
4. International study of kidney disease in children. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisolone. J Pediatr 1981;98:561-64.
5. Peco-Antic A. Management of idiopathic nephrotic syndrome in childhood. Srp Arh Celok Lek 2004;132:352-9.
6. Abevagunawardena AS. Treatment of steroid-sensitive nephrotic syndrome. Indian J Pediatr 2005;72:763-9.
7. Karl S, Barbara H, James CM. Nephrotic syndrome: pathogenesis and management. Pediatri Rev 2002;23:237-48.
8. Klein M, Henschkowski J, Yu Z, Vogt B. Edema and the nephrotic syndrome. Ther Umsch 2004;61:655-60.
9. Agarwal N, Phadke KD, Garg I, Alexander P. Acute renal failure in children with idiopathic nephrotic syndrome. Pediatr Nephrol 2003;18:1289-92.
10. Soeiro EM, Koch VH, Fujimura MD, Okay Y. Influence of nephrotic state on the infectious profile in childhood idiopathic nephrotic syndrome. Rev Hosp Clin Fac Med Sao Paulo 2004;59:273-78.
11. Stadermann MB, Lilien MR, Van de Kar NC, Monnens LA, Schroder CH. Is biopsy required prior to cyclophosphamide in steroid - sensitive nephrotic syndrome? Clin Nephrol 2003;60:315-7.
12. Hodson EM, Knight JF, Willis NS, Craig JC. Corticosteroid therapy for nephrotic syndrome in children. Cochrane Database Syst Rev 2003:CD 001533.
13. Asinobi AO, Gbadegesin RA, Ogunkunle OO. Increased steroid respon siveness of young children with nephrotic syndrome in Nigeria. Ann Trop Paediatr 2005;25:199-203.
14. Lande MB, Gullion C, Hogg RJ,Gauthier B, Shah B, Leonard MB, et al. Long versus standard initial steroid therapy for children with the nephrotic syndrome. A report from the southwest pediatric nephrology study group. Pediatr Nephrol 2003;18:342-6.

15. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res 2005;122:13-28.
16. Bagga A , Hari P, Srivastava RN. Prolonged versus standard prednisolone therapy for initial episode of nephrotic syndrome. Pediatr Nephrol 1999;13:824-7
17. Arbeitsgemeinschaft fur Padiatrische Nephrologie. Alternate - day versus intermittent prednisolone in frequently relapsing nephrotic syndrome. Lancet 1979;24:401-3.
18. Kim JS, Bellow CA, Silverstein DM,Aviles DH, Boineau FG, Vehaskari VM. High incidence of initial and late steroid resistance in childhood nephrotic syndrome. Kidney Int 2005;68:1275-81.
19. Hachicha M, Kammoun T, Mahfoudh A, Aloulou H, Sfaihi L, Hammami Y,et al. The cortico - resistent idiopathic nephrotic syndrome of child. Tunis Med 2005;83:187-93.
20. Yap HK, Han EJ, Heng CK, Gong WK. Risk factor for steroid dependency in children with idiopathic nephrotic syndrome. Pediatr Nephrol 2001;16:1049-52.
21. Durkan A, Hodson EM, Willis NS, Craig JC. Non - corticosteroid treat ment for nephrotic syndrome in children. Cochrane Database Syst Rev 2005;18:CD 002290.
22. Hafeez F, Ahmad TM, Anwar S. Efficacy of steroids, cyclosporin and cyclophosphamide in steroid resistant idiopathic nephrotic syndrome. J Coll Physicians Surg Pak 2005;15:329-32.
23. Foster BJ, Shults J, Zemel BS, Leonard MB. Interactions between growth and body composition in children treated with high dose chronic glucocorticoids. Am J Clin Nutr 2004;80:1334-41.
24. Ruth EM, Kemper MJ, Leumann EP, Laube GF, Neuhaus TJ. Children with steroid - sensitive nephrotic syndrome come of age: long term outcome. J Pediatr 2005;147:202-7.
25. Emma F, Sesto A, Rizzoni G. Long term linear growth of children with severe steroid - responsive nephrotic syndrome. Pediatr Nephrol 2003;18:783-8.
26. Murnaghan WM, Vasmant D, Bensman A. Pulse methylprednisolone therapy in severe idiopathic childhood nephrotic syndrome. Acta Paediatr Scand 1984;73:733-9.
27. Moudgil A, Bagga A, Jordan SC. Mycophenolate mofetil therapy in frequently relapsing steroid - dependent and steroid - resistant nephrotic syndrome of childhood: current status and future directions. Pediatr Nephrol 2005;20:1376-81.

บทคัดย่อ

การศึกษาย้อนหลังโรคเนโฟรติกในเด็กไทย: ประสบการณ์โรงพยาบาลนครพิงค์

สุรชาย เล้าพรพิชยานุวัฒน์ พ.บ.

กลุ่มงานกุมารเวชกรรม, โรงพยาบาลนครพิงค์, จ.เชียงใหม่ 50180. ประเทศไทย

วัตถุประสงค์ : เพื่อหาอุบัติการณ์ อายุ เพศ อาการสำคัญแรกวินิจฉัย ตัวแปรในการคาดคะเนการตอบสนองต่อยาสตีรอยด์ ผลการรักษาและภาวะแทรกซ้อนจากการให้สตีรอยด์แบบนาน รูปแบบการศึกษา : การศึกษาย้อนหลังเชิงพรรณนา ประชากร : ผู้ป่วยเด็ก 37 รายได้รับการวินิจฉัยเป็นโรคเนโฟรติกเป็นครั้งแรกที่รับการรักษาในโรงพยาบาลนครพิงค์ตั้งแต่วันที่ 1 ตุลาคม 2545 ถึง 30 กันยายน 2548

วิธีการ : วิเคราะห์จากรายงานผู้ป่วยโดยใช้สถิติเชิงพรรณนา สถิติ : ใช้สถิติเชิงพรรณนาในรูปร้อยละ ค่าเฉลี่ย มัธยฐานและส่วนเบี่ยงเบนมาตรฐาน วิเคราะห์เปรียบเทียบความแตกต่างใช้สถิติ Student's t - test, Fisher's exact test และ Chi-square test

ผลการศึกษา : พบผู้ป่วย จำนวน 37 ราย อายุเฉลี่ย 7.7 ปี (2 - 14 ปี) เป็นชาย 27 ราย อายุเฉลี่ย 7.7 ปี เป็นหญิง 10 รายอายุเฉลี่ย 7.7 ปี อัตราการเกิดโรคนี้ในจังหวัดเชียงใหม่พบอย่างน้อย 3.48 รายผู้ป่วยใหม่ต่อประชากรเด็ก 100,000 คน ที่อายุน้อยกว่า 15 ปี โดยมีค่าเฉลี่ยการรักษานาน 19.2 เดือน (2 - 36 เดือน) อาการบวมทั้งตัวพบร้อยละ 86.4 การทำงานของไตลดลงพบร้อยละ 48.6 ไข้พบร้อยละ 37.8 ความดันโลหิตสูงพบร้อยละ 32.4 ปัสสาวะเป็นเลือดสดพบร้อยละ 21.6 และ microscopic hematuria พบร้อยละ 21.6 ผู้ป่วยทุกรายได้รับการรักษาด้วยยาเพรดนิโซโลน 60 มก./ตร.ม./วัน ทุกวันเป็นเวลา 4 สัปดาห์ ต่อด้วย 40 มก./ตร.ม. วันเว้นวัน 4 สัปดาห์ จากนั้นลดขนาดยาร้อยละ 25 ต่อเดือนจนหยุดยาสิ้นเดือนที่ 6 ผู้ป่วย 31 ราย (ร้อยละ 83.8) ตอบสนองต่อยาสตีรอยด์ ผู้ป่วย 6 ราย (ร้อยละ 16.2) ไม่ตอบสนองต่อยาสตีรอยด์ ในกลุ่มที่ตอบสนองต่อยาสตีรอยด์ตั้งแต่แรก 31 ราย ผู้ป่วย 4 รายรับการรักษาน้อยกว่า 3 เดือน ที่เหลือ 27 ราย รับการรักษามากกว่า 8 เดือน ศึกษาพบว่ามีกลุ่มที่ไม่พบโรคกำเริบ 16 ราย (ร้อยละ 59.2) กลุ่มที่พบโรคกำเริบไม่บ่อย 4 ราย (ร้อยละ 14.8) กลุ่มที่พบโรคกำเริบบ่อย/กลุ่ม steroid-dependent 6 ราย (ร้อยละ 22.2) กลุ่มที่ตอบสนองแต่แรกแล้วกลายเป็นดื้อยา 1 ราย (ร้อยละ 3.7) ระยะเวลาเฉลี่ยที่ตรวจไม่พบโปรตีนในปัสสาวะ 16.4 วัน (กลุ่มที่ไม่พบโรคกำเริบและกลุ่มที่พบโรคกำเริบไม่บ่อย 15.2 วัน ต่อกลุ่มที่พบโรคกำเริบบ่อย/steroid-dependent 21 วัน) ผลการศึกษาหา predictive parameters เพื่อคาดคะเนการตอบสนองต่อการรักษา พบว่ากลุ่มที่พบโรคกำเริบบ่อย / steroid-dependent และกลุ่มที่ดื้อต่อยาสตีรอยด์พบน้ำคั่งในช่องท้อง, น้ำคั่งในช่องอกหรือน้ำท่วมปอด, การทำงานของไตลดลงระดับปานกลางและตรวจพบปัสสาวะเป็นเลือดสดมากกว่ากลุ่มที่ไม่พบโรคกำเริบและกลุ่มที่พบโรคกำเริบไม่บ่อยแต่พบการทำงานของไตลดลงระดับเล็กน้อยได้น้อยกว่ากลุ่มหลัง กลุ่มที่พบโรคกำเริบบ่อย /steroid-dependent 6 ราย มีอัตราการกลับเป็นซ้ำเฉลี่ย 2.83 ครั้ง ทั้ง 6 รายมี complete remission โดยผู้ป่วย 3 รายต้องใช้ยา cyclophosphamide และมีระยะเวลาโรคสงบนานกว่าไม่ได้ใช้ (17 เดือน ต่อ 3.6 เดือน) กลุ่มที่ไม่ตอบสนองต่อยาสตีรอยด์ 7 ราย รักษาด้วยยา cyclophosphamide ทั้ง 7 ราย มีเพียง 2 ราย (ร้อยละ 28.57) มี complete remission และมีระยะโรคสงบนาน 25 เดือน อีก 2 รายมี complete remission แต่มีระยะโรคสงบสั้นเพียง 1.5 และ 3 เดือน ในขณะที่อีก 3 ราย (ร้อยละ 42.8) ไม่สามารถหยุดยาสตีรอยด์ จากการติดตามดู body mass index และ height for age ในผู้ป่วยที่ได้ยาสตีรอยด์ดังกล่าวพบ height for age อยู่ในเกณฑ์ปกติ ส่วน body mass index มีเพียงผู้ป่วย 1 รายที่มากกว่า 25

สรุป : อายุเฉลี่ยของผู้ป่วยที่วินิจฉัยเป็นโรคเนโฟรติกเป็นครั้งแรกสูงขึ้นบ่งชี้ว่าผู้ป่วยที่พบโรคกำเริบบ่อย/steroid-dependent และผู้ป่วยที่ดื้อต่อยาสตีรอยด์พบมากขึ้น โดยมีลักษะทางคลินิกที่พบบ่อยคือ บวมทั้งตัว การทำงานของไตลดลง ปัสสาวะเป็นเลือด ไข้และความดันโลหิตสูง ตัวแปรที่ใช้คาดคะเนว่าจะเกิดกลุ่มโรคที่กำเริบบ่อย /steroid-dependent และกลุ่มที่ดื้อต่อยาสตีรอยด์คือ การทำงานของไตลดลงระดับปานกลาง ปัสสาวะเป็นเลือด น้ำท่วมปอดหรือน้ำคั่งในช่องอกและน้ำคั่งในช่องท้อง จำนวน วันที่ตรวจไม่พบโปรตีนในปัสสาวะหลังได้ยาสตีรอยด์ถ้ายิ่งมากบ่งชี้ว่ามีโอกาสเกิดโรคกำเริบบ่อย/steroid-dependent ได้มากกว่า การรักษาด้วยยาสตีรอยด์แบบนานได้ผลดี เกิดภาวะแทรกซ้อนและมีผลต่อการเจริญเติบโตน้อย ส่วนกลุ่มที่เกิดโรคกำเริบบ่อย /steroid-dependent รักษาด้วยยา cyclophosphamide น่าจะทำให้ระยะโรคสงบนานขึ้น กลุ่มที่ดื้อต่อยาสตีรอยด์และรักษาด้วยยา cyclophosphamide แล้วไม่มีระยะโรคสงบควรพิจารณาให้ยาตัวอื่น การศึกษานี้ทำให้เห็นข้อมูลสำคัญที่ต้องบันทึกเพื่อเป็นประโยชน์ต่อการรักษาและติดตามโรค และยังกระตุ้นให้มีการศึกษาเพิ่มเติมที่สมบูรณ์มากขึ้น