



Predictive risk factors of steroid dependent nephrotic syndrome in children with idiopathic nephrotic syndrome

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ABSTRACT

Introduction: Steroid dependent nephrotic syndrome (SDNS) is a difficult and troublesome presentation of idiopathic nephrotic syndrome (INS) in children, with complicated management and increased morbidity.

Objectives: The aim of this study was to identify the predictive clinical and laboratory characteristics of patients with SDNS, for parents counseling, appropriate management and improving outcome.

Patients and Methods: A total of 374 children with steroid sensitive INS were evaluated in two groups as steroid dependent (group 1 = 199) and non-steroid dependent (group 2 = 175) INS. SDNS was defined as ≥ 2 relapses during steroid reducing treatment or 15 days after discontinuation of corticosteroids.

Results: Mean age at presentation was significantly lower in children with SDNS than those without steroid dependency ($P = 0.022$). Diagnostic age less than two years ($P = 0.016$), total relapses ($P < 0.001$), relapse/year ($P < 0.001$), body mass index (BMI) ($P = 0.002$) and serum cholesterol level ($P = 0.042$) were significantly higher in children with SDNS, compared to those with low-frequent relapse. Mean relapse rate decreased significantly in SDNS with immunosuppressive treatment ($P < 0.001$).

Conclusion: Age younger than two years at diagnosis, high BMI, high relapse rate/year and hypercholesterolemia at remission are suggested as predictors of SDNS in children with INS.

Implication for health policy/practice/research/medical education:

Management of idiopathic nephrotic syndrome (INS), especially with frequent relapses or steroid dependency has been a clinical challenge for both patients and parents. This study was conducted to investigate risk factors of steroid dependent nephrotic syndrome for better management and reducing complications of early and long-term steroid treatment.

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Introduction

Idiopathic nephrotic syndrome (INS) is the most common glomerular disorder in children, constitutes about 72% to 85% of all nephrotic syndrome (NS) in children. About 90% of children with the first episode of minimal change INS achieve remission by corticosteroid treatment. However, 70% to 80% of these children experience relapse and 30%-50% develop frequent relapses and also required to repeated courses of corticosteroid treatment. Frequently relapsing steroid-responsive NS is a clinical dilemma with the risks of steroid toxicity and complications of NS such as infection, thrombosis and acute kidney failure.

Management of frequent relapsing steroid responsive (FRNS) or steroid dependent nephrotic syndrome (SDNS) in children has been a clinical challenge for pediatric nephrologists (1,2). Different risk factors such as young age at diagnosis, male gender, duration to early steroid improvement, relapses during the first half year after the beginning of NS, decreased serum albumin level and hematuria have been reported in FRNS or SDNS, with conflicting results (3-5).

Objectives

This study was conducted to identify early clinical and

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laboratory findings that can predict the development of SDNS for better counseling of parents, avoidance of corticosteroid side effects, appropriate management with alternative steroid sparing treatments and decreasing further morbidities.

Patients and Methods

Study design

A total of 396 children with INS were investigated in a retrospective hospital based, cross-sectional multi-centric study, was conducted during 2009–2022. Among them, 22 children were resistant to steroid treatment and excluded from the study. Finally, 374 patients were sensitive to steroid treatment and included in this study. Steroid resistant NS was defined as $\geq 2+$ urine protein excretion after 6-8 weeks of initial steroid treatment. Steroid sensitive NS was considered as 0 or trace urine protein excretion for three times after 4-6 weeks of initial steroid treatment. These patients were classified in two groups as SDNS with frequent relapses (group 1 = 199) and non-steroid dependent with complete remission or recurrent NS (group 2 = 175). Patients with at least one year follow up were included and those with steroid resistant NS were excluded from the study. Relapse was defined as recurrence of nephrotic range proteinuria (>40 mg/kg/d), low-serum albumin and edema. SDNS as defined as two or more relapses during steroid reduction or 15 days after discontinuation of steroid treatment, without concomitant respiratory tract infection or allergic disorders. Frequent relapsing NS was defined as ≥ 2 relapses during six months or ≥ 3 relapses during 12 months.

Variables such as age at diagnosis, duration of disorder, initial steroid response, frequency of relapses, relapse per year, family history of allergy or other renal disorders, body mass index (BMI) and lipid profile during remission were evaluated in the selected patients.

All patients were treated with 2 mg/kg/d of steroid treatment for 4-6 weeks, followed by 2 mg/kg/alternate day for 4 weeks with further reduction of 10 mg/m²/day to the lowest dose necessary to maintain remission or discontinuation of treatment, if appropriate. All patients with SDNS who needs to high steroid dosage or steroid complications were treated with adjunctive treatments such as levamisole, cyclosporine, mycophenolate mofetil, tacrolimus or rituximab.

Statistical analysis

Analysis of data was conducted by SPSS version 24.0 for Windows (SPSS, Chicago, IL, USA). Quantitative and qualitative variables were expressed as mean \pm SD and frequency, respectively. Categorical variables were compared by the chi-square and Fisher's exact tests, when appropriate. Normally distributed continuous variables were evaluated by independent samples *t* test, whereas Mann-Whitney U test was employed for group

comparison of non- normal continuous variables. $P \leq 0.05$ was statistically significant.

Results

Of 374 patients with steroid sensitive INS, 77 (20.5%) had no relapse, 199 (53.2%) had steroid dependency or frequent relapses and 98 (26.3%) had less than three relapses. Mean age at diagnosis of NS was 4.7 ± 2.8 (7 months-15.7 year), which was significantly lower in patients with SDNS ($P=0.022$).

Mean age at the first relapse was 5.7 ± 2.9 years in all patients, which was significantly lower in SDNS ($P=0.013$). About 11.5% of patients had less than two years at diagnosis, with the higher incidence in patients with SDNS ($P=0.02$). About 4.9% of all patients had more than 11 years at diagnosis, with no significant difference between the two groups.

Males outnumbered females in all patients (1.87/1) and in those with SDNS, with no significant difference between the two groups ($P=0.26$).

Patients with SDNS had significantly longer follow up than the other group ($P<0.001$). Mean relapse rate was 2.92 ± 2.8 times in all patients, which was significantly higher in children with SDNS ($P<0.001$). Mean relapse/year (all relapses/duration of follow up) was significantly higher in children with SDNS ($P<0.001$). Mean duration until the first relapse and mean follow up until steroid dependency had no significant difference between the two genders.

Mean BMI at diagnosis was 17.2 ± 2.5 kg/m², which was significantly higher in patients with SDNS ($P=0.002$).

A total of 46.9% of all patients had increased serum cholesterol level during remission, with the higher incidence in patients with SDNS ($P=0.042$).

There was no significant difference regarding the age at diagnosis of older than 11 years ($P=0.34$), increased blood pressure ($P=0.31$) and family history of allergy ($P=0.56$) or renal disorder ($P=0.95$) among the groups (Tables 1 and 2).

Discussion

Steroid-sensitive NS has been considered a relapsing disorder with a favorable long-term outcome in the majority of patients. However, steroid dependency or frequent relapses occur in 30%-50% of patients with idiopathic NS, that needs to repeated courses of steroids treatment. This condition, however, will be accompanied by early and late complications of steroids treatment. In addition, the majority of these patients need to immunosuppressive treatment for improving the management of NS (5). Efforts have been made to identify the predisposing risk factors of frequent relapses in INS, with conflicting results. The aim of this study was to identify the predictive demographic and laboratory findings in patients with SDNS.

Table 1. Demographic and clinical characteristics of all patients

Variables	All Cases (n=374)	SSNS (n=175)	SDNS (n=199)	P value
Age at diagnosis (mean \pm SD) (y)	4.74 \pm 2.8	5.11 \pm 2.9	4.43 \pm 2.76	0.022
Duration of patients follow up (mean \pm SD) (y)	4.7 \pm 3.4	3.59 \pm 3.16	5.86 \pm 3.32	<0.001
Frequency of relapses (mean \pm SD)	2.93 \pm 2.8	1.01 \pm 1.2	4.6 \pm 2.7	<0.001
Relapse/year* (mean \pm SD)	0.68 \pm 0.64	0.37 \pm 0.5	0.94 \pm 0.64	<0.001
Body mass index (kg/m ²)	17.2 \pm 1.74	16.7 \pm 2.1	17.6 \pm 2.6	0.002
Gender (M%)	65.2	62.3	67.8	0.26
Age <2 at diagnosis (y)	11.5	6.3	13.6	0.02
Age >11 at diagnosis (y)	4.9	6.3	3.6	0.34
Allergy (%)	60.8	62.3	59.4	0.56
Family history (%)	18.9	18.8	19	0.95
Nephrotic history (%)	19.7	15.6	22.8	0.18
Hypertriglyceridemia (%)	34.6	39.7	60.3	0.4
Hypercholesterolemia (%)	46.9	36.6	53.4	0.042
Hypertension (%)	9.6	39	61	0.31

*Relapse/year; (all relapses/duration of follow up).

Table 2. Demographic and clinical characteristics of both genders

Variables	All	Males (n=244)	Females (n=130)	P value
Age at diagnosis (mean \pm SD/year)	4.74 \pm 2.8	4.70 \pm 2.89	4.78 \pm 2.91	0.79
Duration of patients follow up (mean \pm SD/year)	4.7 \pm 3.4	5 \pm 2.4	4.8 \pm 3.7	0.66
Frequency of relapses (mean \pm SD)	2.93 \pm 2.8	3.2 \pm 3.1	2.8 \pm 3	0.2
Relapse /year* (mean \pm SD)	0.68 \pm 0.64	0.69 \pm 2.2	0.66 \pm 0.7	0.64
Allergy (%)	60.7	62	38	0.25
Hypertriglyceridemia (mg/dL)	34.6	72	28	0.045
Hypercholesterolemia (%)	46.9	62	38	0.5
Hypertension (%)	9.6	58.3	41.8	0.36

*Relapse/year: (all relapses/duration of follow up).

Our study showed that children with SDNS had a significantly higher rate of relapses, with a longer duration of follow up. These group had higher relapse /year (total relapse/duration of follow up) than those with remission or recurrent NS. In a report by international study of kidney disease in children (1982), the frequency of initial relapses was a predictor of subsequent course in children with steroid sensitive NS (6).

In the study by Kabuki et al, relapsing rate during the first year of presentation affected the final prognosis and long-term remission in these patients, which decreased over time (4).

Similar to our study, Andersen et al showed higher relapses among frequent relapse/steroid dependent (FR/SD) group than those with non-FR/SD (5).

Vivarelli et al showed a significant correlation between the time to achieve remission with relapses within

three months after steroid discontinuation, frequent relapsing or steroid-dependency (remission >seven days), maintenance steroid treatment and need to alternative treatments (7).

Patients with SDNS were significantly younger than two years at presentation compared with non-SD patients in our study. Similarly, Kabuki et al showed that age younger than four years at diagnosis of steroid sensitive NS was a reliable predictor of future relapse in the first year of NS, with a longer time to prolonged remission (4).

Meanwhile, the analysis of Andersen et al showed that age at the beginning of NS was lower in patients with frequent relapse/steroid dependent than non-FR/SD patients. About 90% of patients less than four years became FR/SD (5). However, Constantinescu et al did not find a correlation between age at diagnosis and the relapsing rate (8).

Male gender had no significant difference between those with and without frequent relapses in our study, which is similar to the study by Dakshayani et al (3). Nonetheless, male gender had a higher incidence among patients with SD/FR steroid sensitive NS in the study by Andersen et al (5).

Our patients had significantly higher incidence of increased serum cholesterol during remission than those with infrequent relapses. In addition, children with SDNS had significantly higher BMI, than those with non-relapsing course. Nevertheless, we did not find significant difference regarding to allergic disorders between the two groups. Similarly, Carter et al reported that the presence of allergic disorders and hematuria did not usefully predict worse disease outcome (9). About 43% of patients had frequent relapsing or steroid dependent course in the study by Dakshayani et al. Initial relapse during the first six months of diagnosis and concurrent infection were significant predictors of frequent relapses in their study. However, age at diagnosis, insufficient initial steroid treatment and serum albumin level had no effect on the incidence of frequent relapses (3).

Letavernier et al showed the highest incidence of SDNS in patients with late steroid remission after day 20 of the therapy and also in the early methylprednisolone treatment at the disease onset, which indicated the cyclosporine administration for the better control of the disease. They suggested that early identification and treatment of these patients with adequate immunosuppressive drugs might reduce the frequency of relapses, cumulative steroid dosage and its related morbidity (10).

In the study by Abdel-Hafez et al, maintaining the remission with a cumulative steroid dose of ≥ 140 mg/kg during the first six months of NS and delayed steroid remission after day 20 of the initial prednisolone course increased the incidence of steroid dependent NS with low-sensitivity (50%) and also high specificity (96%). In addition, they showed a significant association between the relapse rate and upper respiratory tract infections (11).

Furthermore, time to the initial response more than nine days, remission less than ten days of initial steroid treatment and alternative steroid regimen predicted a higher risk of initial relapse in some other studies (9,12).

Conclusion

Young age at diagnosis of INS, multiple relapses/year, high BMI and increased serum cholesterol level were predictive risk factors of SDNS in this study, which improved significantly with immunosuppressive treatment.

Limitations of the study

Although investigation of predictive risk factors was conducted in the appropriate number of children with SDNS, however, it is recommended to perform further studies in the larger groups of to identify the best

therapeutic options in these patients.

Authors' contribution

Conceptualization: EV.

Methodology: EV

Supervision: EV.

Formal analysis: PA and MF.

Investigation: BV.

Original draft preparation, review and editing: AN.

Validation: All authors.

Resources: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study. (Ethical code# IR.AJUMS.REC.1398.537). Written informed consent was taken from all participants before any intervention. This study was extracted from M.D., thesis of Bahareh Valavi at this university (Thesis#CRD-0001). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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