Original Article

Behavioral problems in children with steroid-sensitive nephrotic syndrome: An ignored aspect!

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Received - 25 November 2018 Initial Review - 06 December 2018 Accepted - 20 December 2018

ABSTRACT

Background: Nephrotic syndrome (NS) is a common chronic renal disorder in children. Oral glucocorticoids are required in high doses for prolonged periods adding to various comorbidities including psychosocial issues and behavioral problems. **Objectives:** This study was done to analyze the behavioral profile of children with steroid-sensitive NS (SSNS), also its association with other factors such as mothers' education, socioeconomic status, and age distribution. **Materials and Methods:** This was a questionnaire (child behavior checklist)-based cross-sectional study conducted at a tertiary care center. Children from 6 to 15 years with diagnosis of SSNS for the duration of 1 year or more were included in the study. Cases were divided into two groups: Infrequent and frequent relapsing NS (IFRNS)/steroid-dependent NS (SDNS). Equal number of children in 6–15 years age group attending outpatient clinic was taken as controls. **Results:** Children with SSNS (n=161) had behavioral problems in significant percentage (39.13%) compared to the control group (8.75%). It was observed more in boys (73.02%) who had more hyperactive, aggressive behavior, and externalizing problems. Internalizing problems (anxious/depressed, withdrawn/depressed, and somatic complaints) were significantly more in the study group (17.39%) as compared to none in the control group. Children with FRNS/SDNS course had more significant problems compared to relapse IFRNS group. Age distribution, socioeconomic status, and mother's education had no significant effect on its occurrence. **Conclusion:** Significant behavioral problems are observed in children with SSNS and are related to the type of SSNS.

Key words: *Behavioral problems, Children, Steroid-sensitive nephrotic syndrome*

Nephrotic syndrome (NS) is common chronic renal disorder in children forming major bulk of children at pediatric nephrology clinic/center. Overall, the prevalence in developed countries is reported to be 20–40 per million populations and higher in the Indian subcontinent [1]. Disorder is characterized by massive proteinuria (>40mg/m^2/h), hyperlipidemia, and hypoalbuminemia, leading to generalized edema [2]. The chances of developing relapses frequent (FRNS) or infrequent (IFRNS) relapsing after the first episode is as high as 55–60% [3]. Mainstay of the treatment is oral glucocorticoids which are often required for long and variable durations. Prolong disease course and treatment both add to various comorbidities in any chronic illness. Besides physical problems, these children often suffer from abnormal psychological behavior.

Chronic illnesses are known to be associated with significant behavioral problems and various disorders in pediatric population [4-8]. In children with NS, there is wide variation in its occurrence (10–68%) reported in previous studies [9-19]. In adulthood, many of these children may continue to have various psychological problems such as anxiety, depression, and mood disorders. However, due to more emphasis on disease treatment, behavioral part is often neglected. This study was undertaken with objective to study behavioral profile of children who are diagnosed with SSNS for more than or equal to 1 year and to correlate factors associated with these problems so that early identification and management including follow-up care can be done.

MATERIALS AND METHODS

This was questionnaire-based cross-sectional study done at tertiary care center in India, for a period of 18 months. After taking the written consent from the parents, a total of 200 children in the age group of 6–15 years (including both age groups) with diagnosis of SSNS for the duration of 1 or >1 year attending pediatric nephrology clinic were included in the study. Steroid sensitivity was defined as children attaining remission (urinary protein trace or negative for 3 consecutive days) within 4 weeks of starting daily prednisolone at 2 mg/kg (max 60 mg/day). Ethical clearance from the institutional ethical committee was obtained to conduct the study. The exclusion criteria were the children with known psychological abnormalities before onset of illness, non-availability of caregiver for assessment,

and steroid-resistant NS. Those with other comorbid chronic significant medical illnesses such as asthma, congenital heart disease, and chronic gastroenterological abnormalities were also excluded from the study. Sample size calculation was done using the formula, $n = \left(\frac{r+1}{r}\right)\frac{\bar{P}(1-\bar{P})\left(Z_{\beta}+Z_{\frac{\alpha}{2}}\right)^2}{(P_1-P_2)^2}$ where, n = Sample size in the case group, r = Ratio of controls to cases, $P_1 = 0.35$, $P_2 = 0.35$, $P = 0.28$, $Z_{\beta} = 0.35$, $Z_{\alpha} = 1.96$, Z_{β} = desired power, $Z_{\alpha de}$=level of statistical significance, and $\bar{P}$ = a measure of variability $(P_1\ P_2)^2$ = effective size. Therefore, minimum sample size was 161.

Questionnaire was based on detailed behavioral analysis done using Child Behavior Checklist (CBCL) which is one of the best validated and most widely used tool in childhood population [20]. Informed permission to use the tool as well as copies of questionnaire was obtained. After taking informed consent from parents/guardians, the details of personal, demographic profile, and signs and symptoms were recorded at the time of the first contact.

The study population (SSNS) was divided into two groups: Group A and Group B. Group A included 80 children with IFRNS (<2 relapses within 6 months or <4 relapses in a year). Group B included 81 children with FR (two or more relapse within 6 months of the initial episode or >3 relapses in any 12-month period) or steroid-dependent course (occurrence of two consecutive relapses during alternate day steroid therapy or within 2 weeks of its discontinuation). Group C had 160 children between 6 and 15 years attending pediatric outpatient department for minor illnesses such as acute diarrhea, upper respiratory infection, and poor appetite and fever for <7 days.

CBCL contains 113 behavioral items, which are scored as (0) absent, (1) occasionally present, and (2) very often present. Based on the responses to these parameters, syndromic scales profile for boys and girls are divided into internalizing (anxious/depressed, withdrawn/depressed, and somatic complaints) and externalizing (rule-breaking behavior and aggressive behavior) problems. T scores were deduced from normative data used in the formulation of scale. T score equal to or >70 was considered clinically significant. On the basis of T scores, behavioral problems between cases (children with NS) and controls and in between different group among cases were compared. Internalizing problems were diagnosed in anxious/depressed or withdrawn/depressed children, children with somatic complaints, social problems, or thought problems. Externalizing problems were diagnosed in the presence of attention problems, rule-breaking behavior, or aggressive behavior.

The education of the respective mothers was divided into five categories: (1) Up to 5th standard, (2) 6th–8th standard, (3) 8th–10th standard, (4) 11th–12th standard, and (5) graduate/postgraduate. Assessment of socioeconomic status was based on Modified Kuppuswamy scale, while the age distribution of all cases and controls were done in two groups 6–11 years and 11–15 years. Children with significant scores (T score ≥70) were referred to the department of psychiatry for detailed evaluation and management.

Categorical variables were presented in number and percentages and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then non-parametric test was used. Quantitative variables were compared using unpaired t-test or Mann–Whitney U-test (depending on whether the data sets were normally distributed or not), between the two groups. Qualitative variables were correlated using Chi-square test/Fisher's exact test, whereas $p<0.05$ was considered statistically significant. The data were entered into Microsoft Excel spreadsheet and analysis was done using the Statistical Package for the Social Sciences version 21.0.

RESULTS

Of 200 children, 39 children were excluded due to various reasons (in 20 cases, caregiver/parents were unwilling for assessment; in 10 children, caregivers were not available, and in 9 cases, caregiver/parents unable to answer the whole questionnaire). Therefore, 161 children of SSNS (80 cases in Group A and 81 cases in Group B) were considered finally for analysis (Fig. 1). Among all children with NS (Groups A and B, n=161), 63 (39.13%) had significant behavioral problems compared to 14 children (8.75%) in controls (Group C). Significant behavioral problems were noted more in boys, 73.02% in case group (A and B), and 71.43% in control group (C) (Table 1).

Internalizing problems mentioned earlier, with significant T score was seen more in cases (A+B), i.e., 17.39% as compared to controls Group C (0%) and the association was statistically significant (Table 2).

Similarly, for externalizing problems, T score was statistically higher in children with NS (Group A+B), 4.91% compared to 1.25% in controls (Group C) (Table 3).

We observed that the attention deficit problems were more in (4.35%) cases (Group A+B) as compared to none in control group (Table 4).

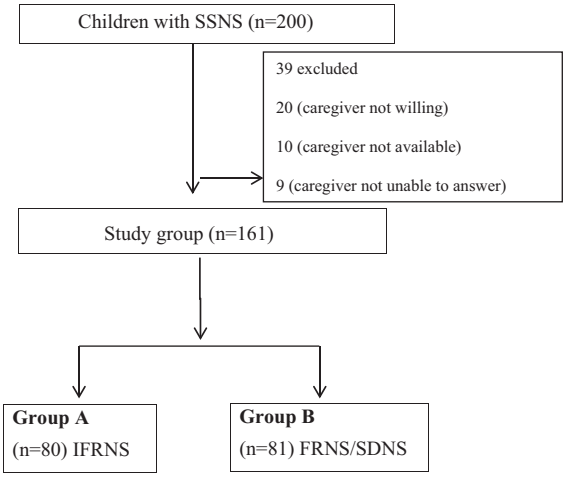

Figure 1: Flowchart showing enrolment and division of study groups

Table 1: Behavioral problems among cases (A+B) and controls (C) and comparison of behavior problem between males and females

Abnormality	Group		Total n (%)	p value
	Cases (A+B) n (%)	Control (C) n (%)		
Abnormal (T-score >70)	63 (39.13)	14 (8.75)	77 (23.99)	<0.0001
Normal (T-score <70)	98 (60.87)	146 (91.25)	244 (76.01)	
Total	161 (100)	160 (100)	321 (100)	
Group	**Abnormal behavioral problem**		**Total n (%)**	
	Yes n (%)	**No n (%)**		
Case				
Boy	46 (73.02)	59 (60.20)	105 (65.22)	
Girl	17 (26.98)	39 (39.80)	56 (34.78)	
Total	63 (100)	98 (100)	161 (100)	
Control				
Boy	10 (71.43)	66 (45.21)	76 (47.50)	
Girl	4 (28.57)	80 (54.79)	84 (52.50)	
Total	14 (100)	146 (100)	160 (100)	
Total				
Boy	56 (72.73)	125 (51.23)	181 (56.39)	
Girl	21 (27.27)	119 (48.77)	140 (43.61)	
Total	77 (100)	244 (100)	321 (100)	

Table 2: Internalizing problems T score between cases (Group A=B) and controls (Group C)

Internalizing problem	Group		Total (%)	p value
	Cases (A+B) (%)	Control (C) (%)		
Anxious/depressed T-score				
>70	37 (22.98)	8 (5.00)	45 (14.02)	<0.0001
≤70	124 (77.02)	152 (95.00)	276 (85.98)	
Total	161 (100)	160 (100)	321 (100)	
Withdrawn/depressed T-score				
>70	38 (23.60)	4 (2.50)	42 (13.08)	<0.0001
≤70	123 (76.40)	156 (97.50)	279 (86.92)	
Total	161 (100)	160 (100)	321 (100)	
Somatic complaint T-score				
>70	32 (19.88)	2 (1.25)	34 (10.59)	<0.0001
≤70	129 (80.12)	158 (98.75)	287 (89.41)	
Total	161 (100)	160 (100)	321 (100)	
Internalizing problem T-score				
>70	28 (17.39)	0 (0)	28 (8.72)	<0.0001
≤70	133 (82.61)	160 (100)	293 (91.28)	
Total	161 (100)	160 (100)	321 (100)	

Among the cases, children with FRNS/SDNS course (Group B) had significantly more internalizing problems (32.10%) as compared to Group A (2.5%), although there was no difference in anxious behavior (Table 5).

Similar observation was seen on comparing the externalizing problems among two groups in cases. Group B had overall more significant T-scores in externalizing problems (19.75% vs. 10%) compared to Group A (Table 6).

Furthermore, on further analysis among all children with significant behavioral problems, age distribution, socioeconomic status, and mothers' education did not show significant difference from those without significant T-score (Table 7).

DISCUSSION

A total of 161 children with SSNS formed the case cohort in this study and were divided into two groups IFRNS (Group A) and FRNS/SDNS (Group B). Most of the previous studies were done with small sample size from 10 to 70 patients in contrast to the present study with good sample size adding power to the study [9-19]. Another group of 160 children in the similar age group (6–15 years) with minor illnesses, such as acute diarrhea, upper respiratory tract infection, poor appetite, and fever for <7 days attending pediatric outpatient clinic, was taken as controls (Group C). Depending on response to standard questionnaire

Table 3: Externalizing problems T score between cases (Group A+B) and controls (Group C)

Externalizing problem	Group		Total (%)	p value (%)
	Cases (A+B) (%)	Control (C) (%)		
Rule-breaking behavior T-score				
>70	23 (14.29)	2 (1.25)	25 (7.79)	<0.0001
≤70	138 (85.71)	158 (98.75)	296 (92.21)	
Total	161 (100)	160 (100)	321 (100)	
Aggressive behavior T-score				
>70	38 (23.60)	2 (1.25)	40 (12.46)	<0.0001
≤70	123 (76.40)	158 (98.75)	281 (87.54)	
Total	161 (100)	160 (100)	321 (100)	
External T-score				
>70	24 (14.91)	2 (1.25)	26 (8.10)	<0.0001
≤70	137 (85.09)	158 (98.75)	295 (91.90)	
Total	161 (100)	160 (100)	321 (100)	

Table 4: Social problems and attention deficit behavioral problems between cases (Group A+B) and controls (Group C)

Social and attention deficit problem	Group		Total (%)	p value
	Cases (A+B) (%)	Control (C) (%)		
Social problem T-score				
>70	4 (2.48)	2 (1.25)	6 (1.87)	0.685
≤70	157 (97.52)	158 (98.75)	315 (98.13)	
Total	161 (100)	160 (100)	321 (100)	
Attention problem T-score				
>70	7 (4.35)	0 (0)	7 (2.18	0.015
≤70	154 (95.65)	160 (100)	314 (97.82)	
Total	161 (100)	160 (100)	321 (100)	

Table 5: Comparing Group A and Group B for internalizing problems T score

Internalizing problem	Group		Total	p value
	Group A	Group B		
Anxious/depressed T-score				
>70	26 (32.10)	15 (18.75)	41 (25.47)	0.052
≤70	55 (67.90)	65 (81.25)	120 (74.53)	
Total	81 (100)	80 (100)	161 (100)	
Withdrawn/depressed T-score				
>70	29 (35.80)	9 (11.25)	38 (23.60)	0.0002
≤70	52 (64.20)	71 (88.75)	123 (76.40)	
Total	81 (100)	80 (100)	161 (100)	
Somatic complaint T-score				
>70	25 (30.86)	7 (8.75)	32 (19.88)	0.0004
≤70	56 (69.14)	73 (91.25)	129 (80.12)	
Total	81 (100)	80 (100)	161 (100)	
Internal T-score				
>70	26 (32.10)	2 (2.50)	28 (17.39)	<0.0001
≤70	55 (67.90)	78 (97.50)	133 (82.61)	
Total	81 (100)	80 (100)	161 (100)	

of CBCL, the presence of behavioral problems was considered significant only when calculated T-score was 70 or more as recommended by Thomas M. Achenbach of Achenbach System of Empirically Based Assessment (ASEBA) [20].

There are many studies reporting increased the prevalence of behavioral problems in children suffering from various chronic systemic illnesses which can be either be due to chronic illness of disease or effect of drugs or both [4-8]. In this study, among cases

Table 6: Comparing Group A and Group B for externalizing problems T-score

Externalizing problem	Group		Total (%)	p value
	Group A (%)	Group B (%)		
Rule-breaking behavior T-score				
>70	17 (20.99)	6 (7.50)	23 (14.29)	0.023
≤70	64 (79.01)	74 (92.50)	138 (85.71)	
Total	81 (100)	80 (100)	161 (100)	
Aggressive behavior T-score				
>70	25 (30.86)	13 (16.25)	38 (23.60)	0.029
≤70	56 (69.14)	67 (83.75)	123 (76.40)	
Total	81 (100)	80 (100)	161 (100)	
External T-score				
>70	16 (19.75)	8 (10.00)	24 (14.91)	0.082
≤70	65 (80.25)	72 (92.00)	137 (85.09)	
Total	81 (100)	80 (100)	161 (100)	

Table 7: Relationship of factors such as age distribution, gender, mothers' education, and socioeconomic status on behavioral problems

Factors	Internalizing T score			External T score		
	>70 (%)	<70 (%)	p value	>70 (%)	<70 (%)	p value
Age distribution (years)						
6–11	21 (9.09)	210 (90.91)	0.708	17 (7.17)	220 (92.83)	0.307
12–15	7 (7.78)	83 (92.22)		9 (10.71)	75 (89.29)	
Gender						
Boy	20 (11.05)	161 (88.95)	0.093	26 (14.36)	155 (85.64)	<0.0005
Girl	8 (5.71)	132 (94.29)		0 (0.00)	140 (100.00)	
Mother education						
Up to 5th	1 (6.25)	15 (93.75)	0.666	0 (0.00)	16 (100.00)	0.516
6th–8th	16 (9.76)	148 (90.24)		15 (9.15)	149 (90.85)	
8th–10th	11 (9.17)	109 (90.83)		10 (8.33)	110 (91.67)	
11th–12th	0 (0.00)	14 (100.00)		0 (0.00)	14 (100.00)	
Graduate/post	0 (0.00)	7 (100.00)		1 (14.29)	6 (85.71)	
Socioeconomic status (Modified Kuppuswamy scale)						
Lower middle	27 (8.60)	287 (91.40)	0.475	26 (8.28)	288 (91.72)	1
Upper middle	1 (14.29)	6 (85.71)		0 (0.00)	7 (100.00)	
Total	28 (8.72)	293 (91.28)		26 (8.10)	295 (91.90)	

(n=161), behavioral problems were reported in 39.13% (n=63) compared to 8.75% (n=14) children in the control group. Many authors have reported the prevalence of behavioral problems in school-going children ranging from 2 % to 30% depending on different age group, gender, socioeconomic status, locations, and scales used [21-28]. In this study, 8.75% of children in control population had behavioral problem, whereas it was significantly higher in children with SSNS (39.13%) and was in the reported range of 10–68% in previous studies. Again this wide variation in the prevalence might be due to different study population in terms of duration and type of NS, different behavioral scales and cutoffs used in various studies. Besides CBCL, other scales used were developmental psychopathology checklist [12], pediatric symptom checklist (PSC) 17 [15], strengths and difficulties questionnaire scale [19], etc. Most of the studies using CBCL have used cutoff of ≥70 like in our study, Manti *et al*. used T score >69 as significant behavior problem.

Significant behavioral problems were observed more in boys in both the groups (73.02% in case group and 71.43% in control group). Boys had more hyperactive, aggressive behavior, and externalizing problems as reported in other studies [9,10]. However, in recent studies, some authors observed no effect of sex or even more behavior problems in girls compared to boys [12,15]. Overall, boys seem to have more externalizing behavioral problems, whereas girls are reported to have more internalizing and somatic problems.

Internalizing problems were significantly more in study group (17.39%) as compared to none in control group similar to observation made by other authors [14-16,18]. Boraey *et al*. observed internalizing problems in 63.3% of cases with NS compared to 13.3% in control group [15]. High magnitude of effect may be due to different scale (PSC - 17) used by them. Among internalizing problems, children with NS (both Groups A and B) had significant T scores for anxiety, depressed, as well

as somatic complaints as compared to control group. Clinical symptomatology such as weight gain, edema, and Cushingoid facies may cause feeling of social exclusion and introvert attitude, leading to less inclination to engage in age-appropriate play and school activities. Besides, being a chronic illness requiring prolonged intake of medication, frequent hospital visits, and parental overconcern may also be a contributory factor for school absenteeism and withdrawal. All these can constitute psychological stress to these children.

Children with NS (Groups A and B) also had significant higher externalizing problems score in 4.91% compared to in 1.25% of children in control group. Boraey *et al*. reported nephrotic children to have externalizing problem in 17% of cases as compared to none in controls [15]. Others have also reported similar observations in their studies [9,14,16]. However, others such as Manti *et al*. and Soliday *et al*. did not find significant externalizing problems in children with NS [10,18].

Among other problems, a study cohort had significant attention problems in 12.42% of cases as compared to none in control group which was similar to the study by Mishra *et al.*, whereas Boraey *et al*. did not find attention problem to be significant in children with NS [14,15]. It was observed that among children with NS, those with FR/SDNS course (Group B) had significantly more behavior problems compared to IFRNS cases (Group A), with respect to both internalizing as well as externalizing problems. Anxiety behavior score in Group B (50.62%) was more than in Group A (38.75%), but difference was not statistically significant ($p=0.13$).

Children with withdrawn and somatic problems were also more in Group B (55.56% and 34.57%, respectively) compared to Group A (25% and 16.25%, respectively) and were statistically significant ($p<0.005$ and 0.008, respectively). Similarly, internalizing problems were significantly more in Group B as compared to Group A ($p<0.0005$). Overall, externalizing problems were observed more in Group B as compared to Group A although difference was statistically significant ($p=0.082$). This indicates that type of NS also affects occurrence of these problems as FRNS and SDNS are more severe varieties requiring more intense and longer therapy. Previous studies lack data on such difference. To summarize, children with NS, especially those with FRNS/SDNS course, had more significant behavior problems compared to those with IFR. They were more depressed, withdrawn, and had more somatic problems which can be explained with chronic nature of illness with FR. Remissions with added adverse effects of drugs were seen more in these cases due to more protracted and difficult course.

Secondary factors such as age distribution, mothers' education, and socioeconomic status were also studied and found to have no significant effect on behavior (internalizing as well as externalizing T score) as also reported in other studies [9,14]. However, Boraey *et al*. observed age to be significantly related to the occurrence of behavioral problems, especially internalizing problems. Guha *et al*. observed older age to be more associated with significant behavioral problems [12,15].

One of the main strengths of this study was good sample size. This study tried to analyze various types and also differentiating magnitude of behavioral problems found in different group of children with NS. Furthermore, effects of various associated factors in its occurrence were studied. Main limitation of this study was not studying contribution of glucocorticoids on the occurrence of behavioral problems. As steroids given for prolonged duration are known to cause various psychological effects, though, the exact mechanism is not known. It may be due to areas of brain such as hippocampus and amygdale which are rich in glucocorticoid receptors as hypothesized by various authors [10,11,13,17].

CONCLUSION

Children with NS show high magnitude of significant behavioral problems in both the sexes. However, males have more externalizing problems such as rule-breaking and aggressive behaviors and FR as well as steroid-dependent children have more behavioral problems compared to children with IFR course. Timely recognition and intervention may prevent adverse psychosocial impact in adulthood. Therefore, besides, medical management periodic psychological assessment and guidance should be a routine rather than exception to identify those who may require more detailed psychological evaluation and treatment.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Thakur PC, Sharma S, Kumar K. Behavioural problems in children with steroid-sensitive nephrotic syndrome: An ignored aspect!. Indian J Child Health. 2018; 5(12):724-730.

Doi: 10.32677/IJCH.2018.v05.i12.005