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BURDEN OF STEROID TOXICITY IN CHILDREN WITH STEROID RESPONSIVE NEPHROTIC SYNDROME

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Abstract

Background: Nephrotic syndrome is a common pediatric kidney disorder with a relapsing course, where corticosteroids remain the mainstay of treatment. However, prolonged steroid therapy is associated with significant adverse effects. This study aimed to assess the burden and pattern of steroid toxicity in children with steroid-sensitive nephrotic syndrome (SSNS). **Methods:** A cross-sectional observational study was conducted in a pediatric nephrology outpatient clinic of a municipal teaching hospital in western India. Children below 12 years with SSNS, receiving oral steroids and followed over six months, were included. Patients were categorized as IRNS, FRNS, and SDNS. Steroid toxicity was assessed clinically, including cushingoid facies, growth parameters, blood pressure, BMI, ophthalmologic evaluation, and infections. Standard WHO and AAP guidelines were used for classification. **Results:** Among 27 children with SSNS, 16 (59.25%) developed steroid toxicity. The majority were males (81.25%), with 75% having disease onset before 3 years of age. SDNS was the most common subtype (37.5%), followed by equal distribution of IRNS and FRNS (31.25% each). Cushingoid facies was the most frequent toxicity (75%), followed by growth retardation (56.25%) and hypertension (56.25%). Obesity was observed in 37.5% and cataracts in 31% of cases, while infections were seen in 25%. Steroid toxicity was more common in children receiving therapy for more than 10 months, with growth retardation showing a significant association (p=0.048). Cataract (p=0.048) and hypertension (p=0.035) were significantly associated with type of nephrotic syndrome. No cases of fractures or mortality were observed. **Conclusion:** Steroid toxicity is common in children with SSNS, particularly with prolonged therapy. Early identification and regular monitoring are essential to reduce complications and improve outcomes.

Keywords: Steroid toxicity, Nephrotic syndrome, Hypertension, Obesity, Growth retardation

Introduction

Nephrotic syndrome (NS) is a common glomerular disease in children characterized by proteinuria (≥40 mg/m2/hr or urine protein/creatinine ratio ≥200 mg/mmol or ≥3+ protein on urine dipstick), hypoalbuminemia (<2.5gm/dl), generalized edema and hypercholesterolemia (> 200mg/dl).[1,2] It is one of the common childhood kidney diseases which affects up to 16 in 100,000 children.[3,4] However, there is substantial variability in the incidence of NS with ethnic background and geographical location.[5] It typically follows a relapsing and remitting course, leading to significant morbidity and healthcare burden. The majority of cases in childhood are idiopathic, with minimal change disease being the most common underlying pathology. Despite advances in understanding the disease, NS continues to pose therapeutic and monitoring challenges due to its recurrent nature and long-term complications.[6]

Corticosteroids remain the cornerstone of treatment for childhood nephrotic syndrome, with more than 90% of children showing remission with standard oral steroid therapy, thus classified as steroid-sensitive nephrotic syndrome (SSNS). However, a substantial proportion of these patients experience relapses. Approximately 60% of children develop frequent relapses (FRNS) or become steroid-dependent (SDNS), requiring repeated or prolonged courses of steroids to maintain remission or other immunosuppressants.[6,7] This prolonged exposure increases the risk of cumulative drug toxicity and negatively impacts the child's growth, development, and overall quality of life. Although steroids are highly effective, their long-term use is associated with multiple adverse effects such as cushingoid facies, obesity, growth retardation, hypertension, cataracts, behavioral changes, and increased susceptibility to infections.[8] The severity of these complications is closely related to the dose and duration of therapy. In children with FRNS and SDNS, repeated or prolonged steroid exposure significantly increases this risk. In such cases, alternative immunosuppressive agents may be required; however, these therapies may be less effective and can also have notable side effects, making management more challenging.[9]

In cases where steroid toxicity becomes significant, second-line immunosuppressive agents such as cyclophosphamide, calcineurin inhibitors, or mycophenolate mofetil are often used. However, these agents are not always as effective as steroids in maintaining remission and are themselves associated with potential side effects.[10] Therefore, understanding the burden and pattern of steroid toxicity in children with SSNS is crucial for early identification, timely intervention, and optimization of treatment strategies.[11] The present study aims to study the burden and common manifestations of steroid toxicity in children with steroid-sensitive nephrotic syndrome.

Materials and Methods

This cross-sectional observational study was conducted in the pediatric nephrology outpatient clinic of a municipal teaching hospital in western India. The study included successive children below 12 years of age diagnosed with steroid-sensitive nephrotic syndrome as per the International Study of Kidney Disease in Children (ISKDC) criteria. Patients were categorized into infrequent relapsing nephrotic syndrome (IRNS), frequently relapsing nephrotic syndrome (FRNS), and steroid-dependent nephrotic syndrome (SDNS) based on standard definitions. All enrolled children were receiving oral corticosteroids in standard doses and had been followed up over the preceding six months. Children with steroid-resistant nephrotic syndrome and those with SSNS who were not on steroid therapy but receiving other immunosuppressive agents were excluded from the study.

All eligible cases were systematically evaluated for features of steroid toxicity (ST). Clinical assessment included examination for cushingoid facies, anthropometric evaluation for growth parameters, and measurement of blood pressure. Suboptimal growth was defined as height velocity less than the 3rd percentile. Height velocity assessment was performed using standard growth charts: WHO charts for children aged 0–2 years, American Academy of Pediatrics (AAP) charts for 2–5 years, and Khadilkar height velocity percentiles for children aged 5–17 years. Hypertension was classified according to the AAP 2017 guidelines as elevated blood pressure (≥90th percentile to <95th percentile), stage I hypertension (≥95th percentile to <95th percentile + 12 mmHg), and stage II hypertension (≥95th percentile + 12 mmHg). Nutritional status was assessed using body mass index (BMI) based on WHO 2007 growth standards, where obesity was defined as BMI >2 standard deviations (SD) and overweight as >1 SD. Patients were also evaluated for other steroid-related complications including cataracts or glaucoma through periodic ophthalmologic examinations and for serious infections. Spontaneous bacterial peritonitis (SBP) was defined as a polymorphonuclear leukocyte count greater than 250 cells/mm³ in ascitic fluid in the absence of any evident intra-abdominal source of infection. Screening for osteoporosis could not be routinely performed in most patients. The number of children exhibiting features of steroid toxicity was recorded, and appropriate modifications in steroid dosage were made as per clinical indications.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. Descriptive statistics were used to summarize the data. Categorical variables such as gender, type of nephrotic syndrome (IRNS, FRNS, SDNS), and various manifestations of steroid toxicity were expressed as frequencies and percentages.

Continuous variables such as age at onset, age at presentation, duration of steroid therapy, and number of relapses were expressed as mean ± standard deviation (SD). Comparative analysis was performed to assess the association between steroid toxicity and clinical variables such as duration of steroid therapy and type of nephrotic syndrome. The Chi-square test or Fisher's exact test was applied for categorical variables as appropriate. A p-value of less than 0.05 was considered statistically significant.

Observations and Results

A total of 27 children with steroid-sensitive nephrotic syndrome were evaluated over a period of six months, of which 16 cases (59.25%) developed steroid toxicity. Among these, the majority were males (81.25%), with a male-to-female ratio of approximately 4.3:1. The mean age at onset of nephrotic syndrome was 28 months, and 75% of children had disease onset before 3 years of age. Serious infections were observed in 25% of cases, with spontaneous bacterial peritonitis being the most common (18.75%). The mean duration of steroid therapy was 11.6 months, with an average of 5 relapses per patient. Stage I hypertension being most common (43.75%) and 50% of the patients required one antihypertensive drug. Regarding nutritional status, 37.5% of children were obese, while 18.75% were overweight. Growth retardation (height velocity <3rd centile) was observed in 56.25% of cases, (Table 1).

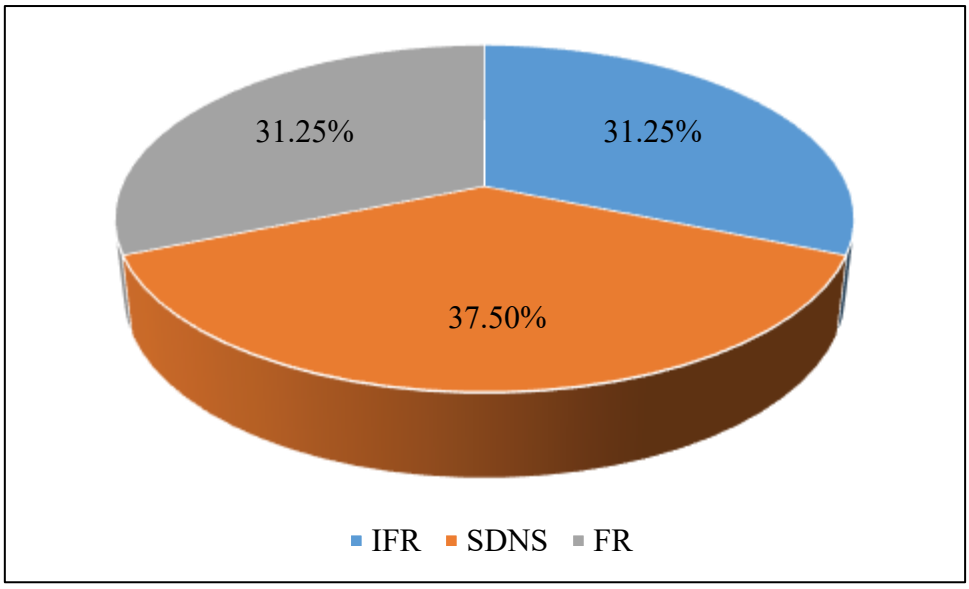
Table 1: Clinical Profile of Children with Steroid Toxicity (n = 16)

Clinical Parameters	Category	No. of Patients	Percentage (%)
Age at Onset (months)	< 12 months	02	12.5
	12–36 months	10	62.5
	> 36 months	04	25.0
Age at Presentation (months)	< 60 months	07	43.75
	60–100 months	05	31.25
	> 100 months	04	25.0
Gender	Male	13	81.25
	Female	03	18.75
Serious Infections	SBP	03	18.75
	Klebsiella	01	6.25
	None	12	75.0
Total Duration of Steroids (months)	< 10 months	05	31.25
	10–15 months	09	56.25
	> 15 months	02	12.5
No. of Relapses	1–3	06	37.5
	4–6	06	37.5
	> 6	04	25.0

Hypertension	Normal	03	18.75
	Elevated (BP>90th centile)	04	25.0
	Stage I (HTN >95th centile)	07	43.75
	Stage II (HTN >95th centile + 12 mm/Hg)	02	12.5
No. of Antihypertensives	0	03	18.75
	1	08	50.0
	2	02	12.5
	3	03	18.75
BMI	Normal (M to +1 SD)	07	43.75
	Overweight (>1SD)	03	18.75
	Obesity (>2 SD)	06	37.5
Height Velocity Centile	<3rd centile	09	56.25
	>3rd to <25th centile	03	18.75
	>25th centile	04	25.00

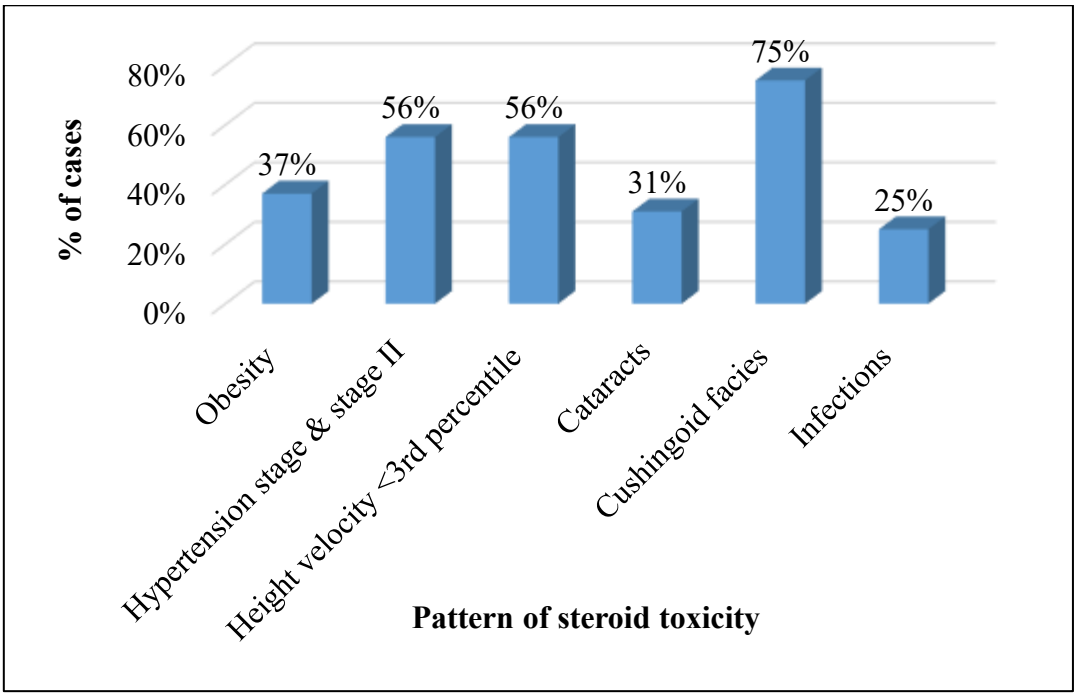
Based on diagnosis, SDNS was the most common (6; 37.5%), followed by equal distribution of IRNS and FRNS (5; 31.25% each) as shown in figure 1.

Figure 1: Diagnosis or type of nephrotic syndrome (n = 16)



Cushingoid facies were the most common steroid toxicity (75%), followed by growth retardation and hypertension (56% each). Obesity was present in 37% of cases, while cataracts were observed in 31%. Infections were the least common complication, seen in 25% of children, (Figure 2).

Figure 2: Pattern of steroid toxicity in children with SSNS



Most complications were more common in children receiving steroids for more than 10 months. Height velocity <3rd centile was significantly higher in the >10 months group (88.8%) compared to <10 months (11.1%) (p=0.048). Although cataract, hypertension, and overweight/obesity were also more frequent with longer duration, these associations were not statistically significant, (p>0.05), (Table 2).

Table 2: Profile of steroid toxicity as per total duration of steroids in nephrotic syndrome

Steroid Toxicity Profile	< 10 months (n=5)	> 10 months (n=11)	P value
Development of Cataract (n=5)	02 (40.0%)	03 (60.0%)	0.610
Hypertension stage I & stage II (n=9)	04 (44.4%)	05 (55.5%)	0.196
Overweight and Obesity (n=9)	02 (22.22%)	07 (77.7%)	0.377
Height Velocity <3rd Centile (n=9)	01 (11.1%)	08 (88.8%)	0.048*

Note: Distribution is shown among affected cases. Column totals may exceed the number of cases as patients can have multiple steroid toxicity manifestations.

Cataract (p=0.048) and hypertension (p=0.035) showed a significant association with type of nephrotic syndrome. Cataract was most common in SDNS (80%), while hypertension was highest in IRNS (55.5%). Overweight/obesity and growth retardation were more frequent

in SDNS but did not show statistical significance (p>0.05), (Table 3). There were no cases of bone fractures, and no mortality was observed in the study.

Table 3: Profile of steroid toxicity as per type of nephrotic syndrome

Steroid Toxicity Profile	SDNS (n=6)	FRNS (n=5)	IRNS (n=5)	P value
Cataract (n=5)	04 (80.0%)	01 (20.0%)	00 (00.0%)	0.048*
Hypertension stage I & stage II (n=9)	03 (33.3%)	01 (11.1%)	05 (55.5%)	0.035*
Overweight and Obesity (n=9)	04 (44.4%)	03 (33.3%)	02 (22.2%)	0.660
Height Velocity <3rd Centile (n=9)	05 (55.5%)	03 (33.3%)	01 (11.1%)	0.106

Discussion

In the present study, steroid toxicity was observed in 59.25% of children with SSNS, which is comparable to the prevalence reported in previous study done by Oh GJ et al[7] where they reported a similar burden of steroid-related adverse effects (62%) in children with proteinuric kidney disease, highlighting that prolonged steroid exposure significantly increases the risk of toxicity. The demographic profile showed a clear male predominance (81.25%) with a male-to-female ratio of approximately 4.3:1, which is consistent with earlier study by Mantan M. et al[6], they have also documented a higher incidence of nephrotic syndrome in males (74.28%). Additionally, 75% of children in our study had onset of disease before 3 years of age, which aligns with the known epidemiological pattern of childhood nephrotic syndrome, where peak incidence occurs in early childhood.[4]

The mean duration of steroid therapy in our study was 11.6 months, with an average of 5 relapses per patient, reflecting the chronic relapsing nature of the disease. Prolonged steroid exposure was associated with a higher frequency of complications, which is in agreement with findings from Lestari N et al[8], who reported that longer duration of corticosteroid therapy is significantly associated with obesity and other metabolic complications. Hypertension was another important complication observed in our study, with stage I hypertension being the most common (43.75%), and 50% of patients requiring at least one antihypertensive drug. Similar findings have been reported in previous study done by Flynn JT et al[12], where corticosteroid therapy has been associated with increased blood pressure due to fluid retention and metabolic effects. Growth retardation, as evidenced by height velocity <3rd centile in 56.25% of cases,

was also a significant finding and is consistent with the known adverse effect of steroids on growth, especially with prolonged use.

In the present study, SDNS was the most common subtype (37.5%), with equal distribution of FRNS and IRNS, which is comparable to study done by Oh GJ et al[7], showing a higher burden of complications in SDNS due to prolonged steroid exposure. Cushingoid facies was the most common toxicity (75%), followed by growth retardation and hypertension (56% each), which is consistent with known steroid side effects. The prevalence of obesity (37%) and growth retardation (56%) in our study is comparable to findings by Lestari N et al[8], who reported obesity rates of 35–43% in similar populations.[8] Cataracts were seen in 31% of cases, aligning with the wide range (5–60%) reported by Brocklebank JT et al.[10]

Steroid toxicity was more common in children receiving therapy for more than 10 months, with growth retardation showing a significant association (p=0.048), supporting previous evidence that prolonged steroid use increases adverse effects. SDNS patients showed a higher frequency of complications, which is in agreement with earlier studies.[11,13] Cataract (p=0.048) and hypertension (p=0.035) were significantly associated with type of nephrotic syndrome, with cataract more common in SDNS and hypertension higher in IRNS. IRNS group had a higher incidence of hypertension probably because most of the cases (4/5)80 % were in the preadolescent age group and have received a higher mean dose of steroids according to their body weight.

Cataracts seen in 31% of cases which were picked up in early stages and predominantly belonged to SDNS, all of them were reversible with reduction in steroid dose and did not require any surgical treatment. Stage I hypertension seen in 7/16(44%) cases requiring a mean of 1.5 (1-3) antihypertensive agents, stage II hypertension seen in 2/16 (13%) cases requiring a mean of 3 antihypertensives agents. Serious infections were infrequently seen in our patients (4/16) 25%, which could be possibly attributed to the timely vaccination against varicella and pneumococcal infections. The correlation of duration of steroids and toxicity profile from our study suggest that greater the duration of steroids more are the side effects. Children with SDNS have a greater risk of steroid toxicity.

The present study has some limitations, including a small sample size and short duration of follow-up, which may limit the generalizability of the findings. Being a single-center study, the results may not reflect the broader population. Additionally, some complications such as osteoporosis could not be routinely assessed, and reliance on clinical evaluation may have led to underestimation of certain steroid-related adverse effects.

Conclusion

Steroid toxicity is commonly observed in children with steroid-sensitive nephrotic syndrome, with cushingoid facies being the most common manifestation, followed by growth retardation, hypertension, and obesity. Hypertension and growth faltering represent the most important acute and chronic adverse effects, respectively. Children receiving long-term steroid therapy require regular monitoring for early detection of complications. Timely tapering of higher steroid doses is essential to prevent progression of these adverse effects and improve overall outcomes.

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