A study of steroid-sensitive nephrotic syndrome among children attending nephrotic clinic of tertiary care hospital of North Gujarat

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ABSTRACT

Introduction: Nephrotic syndrome (NS) is an important chronic disease in children. About 80% of children with idiopathic NS show remission of proteinuria following treatment with corticosteroids and are classified as "steroid sensitive (SS)." Most patients have multiple relapses, placing them at risk for steroid toxicity, systemic infections, and other complications. **Objective:** The objective of the study was to determine the rate of steroid responsiveness in children with NS admitted to children's ward with classical idiopathic NS and also to study the long-term complications of high-dose steroid therapy. **Materials and Methods:** This prospective study was conducted from April 2016 to March 2018 (including 1 year follow-up period) in the pediatric ward of tertiary care hospital. Children with SSNS aged 6 months–10 years were included in the study. The demographic, clinical, laboratory data, response to various therapies, and 1-year follow-up data were collected. Data were captured and analyzed using Microsoft Excel software. **Results:** A total of 102 SSNS children were studied. The disease course at 1 year was categorized as non-relapse (38.2%), infrequent relapse (38.2%), frequent relapse (23.2%), and steroid dependent (14.7%). The major presenting symptoms were edema (100%), burning micturition (52%), and fever (44%) while the major presenting sign was anasarca. A total of 57.8% of the patients were presented with the first attack and the remaining 42.2% of patients presented in relapse. Acute kidney injury was observed in 14.29% of cases. Infections were the most common complication of NS. All the children were treated with standard guidelines given by the Indian Academy of Pediatrics nephrology group. 12% of patients with frequent relapse and 8% of patients with steroid-dependent NS were treated with long-term low-dose steroid. Remaining non-responsive patients had either levamisole or cyclophosphamide added to their treatment regimen. Cushingoid features (44.9%) were the most common side effect followed by hypertension (17.9%), gastrointestinal symptoms (6.7%), hyperglycemia (4.5%), infection 18%, and growth retardation (4.9%). **Conclusions:** A high proportion of patients with SSNS shows frequent relapse, risk factor for which was an early age at onset, inadequate initial therapy, and early relapse.

Key words: *Frequent relapses, Infections, Short remission period, Steroid-sensitive nephrotic syndrome*

Nephrotic syndrome (NS) refers to the tetrad of edema, "nephrotic range" (>1 g/m^2 bovine serum albumin) proteinuria, recurrent edema, hypoalbuminemia, and hyperlipidemia. NS remains the most common manifestation of glomerular diseases in childhood. Despite the initial response rate of 90–95% and the favorable prognosis in children with steroid-sensitive NS (SSNS), relapse occurs in 60–90% of the initial responders which can lead to increased morbidity, complications, and decreased quality of life [1-5].

The course of illness in children with SSNS varies from a single episode to infrequent or frequent relapses and, rarely, the occurrence of late steroid resistance [6-8]. The management of patients with frequent relapse, steroid dependence, and late resistance is difficult, often requiring the use of alternative agents. Information on the course of NS is available from multiple cohorts, including that of the International Study of Kidney Diseases in Children [2,11]. Risk factor for frequent relapses includes the early age of onset, short initial therapy, delay time to remission, and brief duration of the first remission [2,12-16]. The understanding of factors that determine the course is useful in decision regarding therapy and enables good counseling.

While the management of the initial episode and choice of alternative medication have changed over the years, there are limited contemporized data on the outcomes. We reviewed the case notes of recent patients, to examine the course of illness and its determinants.

MATERIALS AND METHODS

This was a prospective, observational, single center study carried out on patients attending a tertiary care hospital with NS. All the children between the age of 6 months and 14 years presenting with NS between April 2016 and March 2018 (including 1-year follow-up period) were included in the study. The study protocol

was approved by the institutional ethics committee and written informed consent from the parents or guardians was obtained before enrolling the patients into the study. All patients were followed for a minimum of 12 months.

A detailed history was taken and all the recruited patients were examined, and parameters such as clinical presentations, investigations, treatment, and other relevant parameters were recorded in the case record forms. NS was classified according to the consensus statements given by Indian Academy of Pediatrics nephrology group on SSNS. The course of disease during these 12 months was categorized as non-relapse, infrequent relapse, and frequent relapse. Frequent relapses were defined as the occurrence of >2 relapses in 6 months or >3 relapses in 12 months and steroid dependence as the presence of 2 consecutive relapses while on tapering doses of prednisone [17-18]. Failure to show remission of proteinuria despite 4 weeks' treatment with prednisolone (2 mg/kg/day) was termed as initial resistance when noted at the onset of diseases and late resistance if occurring in a patient previously responsive to steroids [17].

Hypertension was defined as blood pressure higher than 95th percentile for sex, age, and height [19]. Short stature was defined as height < 2 SD (Z score) mean of age and sex to consider long term side effects of steroids while obesity was considered significant when body mass index was more than 3 SD for age and sex [20]. Patients had regular examination for visual acuity, intraocular pressure, and cataract. Tuberculosis was diagnosed if the tuberculin test was positive in the presence of clinical and radiological features.

Patients have received daily and alternate day prednisolone for 6 weeks each. Patients with frequent relapses or steroid dependence received prednisolone (0.3–0.7 mg/kg) on alternate days for 9–12 months. Those having relapses or steroid toxicity received alternative agents such as levamisole (2 mg/kg/day) for 6 months or cyclophosphamide (2 mg/kg/day) for 12 weeks. Data analysis was done using Microsoft Excel for Windows version 2007.

RESULTS

In the present study, a maximum number of the children (63.7%) had onset at the age between 1 and 5 years while the mean age of presentation was 3.5 years. Among the included children, 29.4% were of 6–10 years and the other 6.8% were >10 years. There were 62.8% of boys and 39.2% of girls. In the present study, 38.2% had sustained remission, (until follow-up for 1 year), 38.2% infrequent relapses, and 23.5% frequent relapse.

All the patients had spot albuminuria 3+ or more with 24 h urinary protein >2 g in 82% of patients. In serum biochemistry, all patients had serum albumin <2.5 g/dl and serum cholesterol >200 mg/dl. After starting steroids therapy in SSNS, 80.3% of patients responded within 14 days of daily dose of prednisolone (2 mg/kg/day) while 6.7% responded after 3 weeks, and 1.1% of patients responded late by 28 days. The present study shows that urinary tract infection was the most common infection (46.0%) while encephalopathy 3 (2.9%) being the least common as shown in Table 1.

Tables 2 and 3 show the treatment given to the enrolled patients and the factors which were responsible for the relapse of NS, respectively, in the patients.

In our study, Cushingoid features were the most common side effect of steroid in 40 (44.9%) patients, followed by infections 22 (21.5%), hypertension in 16 (17.9%), growth retardation 12(11.7%), gastrointestinal (GI) symptoms in 6 (6.6%), and hyperglycemia in 4 (4.4%) (Table 4).

DISCUSSION

We reported the course of SSNS seen at a tertiary care center in North Gujarat, including clinical features, complications

Table 1: Infections in patients with NS

Types of infections	Percentage of patients
UTI	46.0
Respiratory tract infection	24.5
Peritonitis	16.7
Skin infection	4.9
Tuberculosis	3.9
Encephalopathy	2.9

NS: Nephrotic syndrome, UTI: Urinary tract infection

Table 2: Treatment given in NS

Type of treatment	Number of patients (%)
Standard dose of steroid	39 (38.2)
Low-dose long-term steroids	54 (52.9)
Second-line drug-levamisole	6 (5.8)
Second-line drug cyclophosphamide	1 (0.9)

NS: Nephrotic syndrome

Table 3: Factors associated with the relapse of NS

Causes	Number of patients (%)
Infections	22 (21.5)
Drug defaulter	12 (11.7)
Hypocalcemia	2 (1.9)
Early age of onset (≤5 years)	65 (63.7)
Longer time required for remission (>3 weeks)	1 (1.2)
No relapse in <6 months after remission	24 (23.5)

Table 4: Complications of steroid therapy

Side effect	Number of patients (%)
Cushingoid features	40 (44.9)
Infection	22 (21.5)
Hypertension	16 (17.9)
UTI	15 (14.7)
Acute kidney injury	15 (14.7)
Growth retardation	12 (11.7)
GI symptoms	6 (6.7)
Candida	6 (4.9)
Hyperglycemias	4 (4.4)
Hypocalcemia	3 (2.9)

GI: Gastrointestinal, UTI: Urinary tract infection

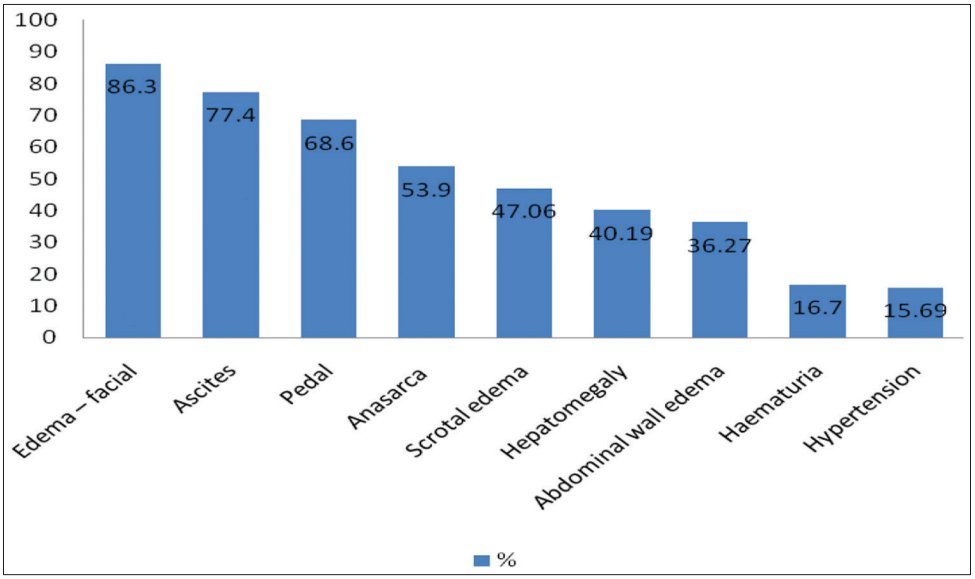

Figure 1: Signs observed in the patients

of steroid therapy, and number of relapses and risk factor associated with the frequent relapse. In our study, mean age of presentation was observed 44.3 months which is comparable to the studies done by Sinha *et al*. [6] (48.7 months), Safaei and Maleknejad [21] (4.8 months), Ahmadzadeh *et al*. [22] (4.5 years), and Gulati *et al*. [23] (52 months). The characteristics male preponderance of our patients was similar to that reported previously by Sinha *et al*. [6] (76%), Mishra *et al*. [24] (72%), Shrivastav *et al*. [25] (77%), Safaei and Maleknejad [21] (66%), and Adeleke *et al*. [26] (57%) in their studies.

The major presenting symptoms in children were swelling (100%), decreased urine output (83.3%), burning micturition (52%), fever (44%), edema (47.0%), and hypertension (15.7%). The most common sign was facial edema as shown in Figure 1. Among all children with NS, 38.2% had no relapse, 38.2 had infrequent relapse, 23.5% had frequent relapses, and 14.7% were steroid dependent. Children with NS were more prone to infection than the general population which is in accordance with the previous studies in India [27]. We have observed the high prevalence of UTI (46.0%) which is comparable to the studies done by Senguttuvam *et al*. [28] (46%) and Ibadin *et al*. [29] (44.8%). However, Gulati *et al*. [23] (13.8%), Mc Vicar [30] (21%), and Samuel *et al*. [2] (8.2%) reported a low prevalence of UTI in their study population.

In our study, after starting steroid therapy in SSNS, 80.3% of patients responded within 14 days of prednisolone (2 mg/kg/day). The other 6.7% responded in 3 weeks, and 1.1% of patients responded late by 28 days. In a study by Mishra *et al*. [24], 43.3% of patients responded in 2 weeks while 15.3% responded between 3rd and 4th weeks of treatment. Patients with SSNS, 93%, had remission within 2 weeks of starting steroid. Patients with frequent relapse or steroid dependence were treated by either low-dose long-term steroid or additional immunosuppressant drugs. Most of our patients responded well with low-dose long-term steroids, that is, 12 patients with frequent relapse (50%) and 8 patients with steroid dependence responded to low-dose long-term steroids while the remaining patients required additional immunosuppressant drugs.

In our study, the side effects of steroids include Cushingoid features (44.9%), infections (21.5%), hypertension (17.9%), GI symptoms (6.7%), and hyperglycemia (4.49%). Similarly, Sinha *et al*. [6] observed obesity (21%), hypertension (5.8%), growth retardation (4.9%), and cataract (1.6%) cases. Gulati *et al*. [23] observed Cushingoid features in 56.7%, hypertension in 28.9%, and GI symptoms in 5% of patients. Similar observations were made by Hahn *et al*. [31], Gipson *et al*. [32], and Davin *et al*. [5].

There is evidence that adequate initial therapy with corticosteroids is useful in reducing the risk of subsequent relapses. The present study also suggests that extension of initial therapy of 9–12 months was associated with reduced proportion of patients with frequent relapse. Findings from the present study confirm that an early age at onset of NS is associated with risk of frequent relapses [12,33,34]. This will help to parents for vigilant follow-up in nephrotic clinic in early years of life.

Our study had certain limitations such as short duration of follow-up of 1 year with the long-term outcome not known and lack of kidney biopsy to determine histopathology. The present study reconfirms the importance of age at onset of NS, the need for adequate initial steroid therapy, and duration of initial remission in predicting the risk of frequent relapses. The outcomes were satisfactory, and on follow–up, most of the patients were in sustained remission or had infrequent relapses.

CONCLUSIONS

NS in children is a widespread problem which is responsible for significant morbidity. In our study, approximately one-fourth patients with nephritic syndrome had frequent relapses and risk factors for which include onset age, short initial therapy, and shorter first remission.

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