Comparative ocular findings in children with steroid-sensitive vs. steroid-resistant nephrotic syndrome

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Abstract. Corticosteroids are the primary therapy for children with nephrotic syndrome (NS). The aim of the present study was to investigate the prevalence of ocular manifestations in patients with NS who had undergone prolonged treatments with steroids and to this prevalence in those with steroid-sensitive NS (SSNS) to those with steroid-resistant NS (SRNS). For this purpose, the present cross-sectional study enrolled 100 children with NS aged 2-18 years who had been treated between 2022 and 2023. The results revealed that out of 100 nephrotic children, 75 children had SSNS and 25 children were steroid-resistant. Systolic and diastolic pressures levels were significantly higher in patients with SRNS with a mean of 100.2±8.72 and 68.0±6.12, respectively. Frequent relapses were reported in 11 (14.7%) of the patients in the SSNS group. In comparison to the SSNS group, the patients with SRNS exhibited a substantially higher rate of bilateral increased intraocular pressure (IOP) (28 vs. 6.67%, P=0.009) and posterior subcapsular cataract (PSCC) (20 vs. 4%, P=0.022). The patients with SRNS had higher refractive errors than those with SSNS (44 vs. 118.7%, P=0.011). Esotropia and exotropia were less common, but of similar distribution. PSCC and refractive errors were significantly associated with older patients, with a mean age of 12.2±2.8 (P=0.002) and 10.3±3.8 years (P=0.001). Increased IOP (P<0.001) and PSCC (P=0.003) were associated with frequent relapses, while refractive errors were associated with a longer disease duration (P=0.004). Systolic pressure significantly increased in the three conditions. On the whole, the findings of the present study indicate that a considerable proportion of patients with NS are susceptible to corticosteroid-related ocular complications. Nevertheless, it is important to take into account the possibility of ocular involvement that is not responsive to steroid treatment in children with SRNS.

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Introduction

Nephrotic syndrome (NS) is a common renal disease affecting the pediatric population. This idiopathic condition is responsive to steroid therapy; however, 40-50% of patients experience frequent relapses or steroid dependence (1). Based on the response of the disease to corticosteroids, NS can be categorized as steroid-sensitive NS (SSNS) if full remission is achieved within 28 days of steroid treatment, steroid-dependent NS (SDNS) following two consecutive relapses or 14 days of treatment discontinuation, or steroid-resistant NS (SRNS) if full remission is not achieved after 8 weeks of steroid treatment (2). Although the KDIGO guidelines (3) reduced the glucocorticoids dose (60 mg/m^2/day) for the initial 4 weeks, and then to 40 mg/m^2 on alternate days for 8 to 20 weeks to mitigate the adverse effects of steroids (1), repeated and extended treatments with corticosteroids may be considered during relapses (4).

Among the severe adverse effects that are associated with corticosteroid treatment are ocular manifestations. The association between corticosteroid use and increased intraocular pressure has been documented in the early 1950s (5,6). The association of posterior subcapsular cataracts (PSCCs) with steroid treatment has also been documented with a strong association with the dose and duration of treatment (7). Patients with NS may also experience other eye-related issues, such as skin atrophy in the eyelids, ptosis, mydriasis, thinning of the cornea and sclera, keratitis, recurrent episodes of hordeolum (8). Although severe complications have been reported in patients with NS, a notable number of these children are unable to detect any deterioration in their vision and do not exhibit any symptoms that could potentially result in blindness. There are currently no established guidelines for the routine monitoring of patients with NS to facilitate the early identification and treatment of these severe complications and prevent the development of additional health complications (9,10).

The prevalence of steroid-dependent and independent ocular manifestations in children with NS has not yet been fully determined, particularly in the context of steroid response classification. Moreover, the association between the duration and dosage of steroid treatment has produced conflicting outcomes

in these globally performed trials (11-13). There is a scarcity of data that directly compares the ocular manifestations in children with SRNS and SSNS in Iraq. The present study aimed to investigate ocular manifestations in patients with NS who had undergone prolonged treatments with steroids and to compare the prevalence of these manifestations between those with SSNS and those with SRNS.

Patients and methods

Study participants and inclusion/exclusion criteria. The present cross-sectional study was conducted at the Ibn AL-Haytham Teaching Eye Hospital (Baghdad, Iraq) during the period between 2022 and 2023. The research received approval from the Scientific and Ethics Committee of Alkadimayn Teaching Hospital (no.=5542) and Ibn AL-Haytham Teaching Eye Hospital (no.=964) (both in Baghdad, Iraq) in accordance with the Declaration of Helsinki.

A total of 100 children were referred from the pediatric nephrology clinic at the Alkadimayn Teaching Hospital with a confirmed diagnosis of NS. The inclusion criteria were pediatric patients aged 2-18 years receiving treatment with steroids for NS who exhibited proteinuria >40 mg/h/m^2 or >50 mg/kg/day, a protein/creatinine ratio >0.2 g/mmol (>2 g/g), and hypoalbuminemia <25 g/l with or without edema (14). The included patients had negative serology test results for anti-dsDNA, ANA, ANCA, C3, C4, CH50, anti-HIV, anti-HCV and HBS-Ag, and all had a histopathological confirmed a diagnosis of focal segmental glomerulosclerosis or minimal change disease. Written informed consents from the parents were acquired after providing them with all relevant information.

The participants who had received corticosteroids, cyclophosphamide, or cyclosporine treatment within the previous 6 months, as well as those with secondary NS and NS with an onset at a young age (<1 year) were precluded from the study. Additionally, children with congenital cataracts, syndromic NS, or any other eye condition that could cause complications such as inflammation, infection, or damage were excluded from the study. Furthermore, individuals who failed to comply with the requirements of a thorough ophthalmological examination were not included.

The standard treatment for the first episode was oral prednisolone at a dosage of 40-60 mg/m^2/d, taken in split doses for a period of 4-6 weeks. SRNS is defined as the inability to attain remission after a 4-week period of treatment with prednisone at a dosage of 60 mg/m^2, with or without three additional methylprednisolone pulses at a dosage of 10-20 mg/kg on 3 consecutive days (15,16). The prednisolone dosage was decreased to 40 mg/m^2 every other day for an extra duration of 4 weeks in all patients. Hypertension was defined as BP ≥95th percentile for age, height and sex (17). Frequent relapsing NS is defined as the occurrence of two or more episodes within a 6-month period or four or more episodes within a single year (18).

Pediatric cases were recruited from nephrology clinic at Alkadimayn Teaching Hospital by a specialist pediatrician. These cases were then referred to Ibn AL-Haytham Teaching Eye Hospital (specialist eye hospital) to be examined by a specialist ophthalmologist to conduct proper ophthalmological examinations.

A thorough ophthalmological examination included the evaluation of visual acuity (VA) using the Snellen visual acuity or another age-appropriate VA test. Visual impairment was graded according to the revised visual impairment definitions of the International Statistical Classification of Diseases (19). Intraocular pressure was measured and slit lamp biomicroscopy was used to examine the anterior segment of the eye in addition to dilated fundoscopy, and cycloplegic refraction.

Statistical analysis. The Statistical Package for Social Sciences software for Windows version 25 (IBM Corp.) was used for all statistical analyses. Observational data are presented in the form of frequencies and percentages. Continuous variables are expressed as the mean and standard deviation (SD). Comparisons of nominal variables of different groups were performed using the Chi-squared test or Fisher's exact tests, as appropriate. Comparisons of continuous variables were performed using the non-parametric Mann-Whitney test. A P-value <0.05 was considered to indicate a statistically significant difference.

Results

Of the 100 included children with NS, 75 children had SSNS and 25 children were had SRNS. The median age of the participants was 6.5 years, ranging between 2.2 and 15.2 years; no significant differences were found between the SSNS and SRN groups as regards age. The median duration of the disease was 33.6 months, ranging between 2.4 and 144 months, with no significant differences found between the study groups. Males constituted 70% of all patients, accounting for the majority of both SSNS [50 (66.7%)] and SRNS [20 (80%)] groups. Systolic and diastolic pressure levels were significantly higher in the patients with SRNS, with a mean of 100.2±8.72 and 68.0±6.12, respectively. Frequent relapse was reported in 11 (14.7%) patients in the SSNS group. The demographic data of the patients are presented in Table I.

Ocular manifestations were more frequently observed in the SRNS group; 17 (68%) of the patients with SRNS had such manifestations compared to only 19 (25.3%) patients with SSNS. The types and frequency of ocular findings are demonstrated in Fig. 1.

Compared with the SSNS group, the patients with SRNS had a significantly higher rate of bilateral increased intraocular pressure [7 (28%) vs. 5 (6.67)] and PSCC [5 (20%) vs. 3 (4%)], with obtained P-values of 0.009 and 0.022, respectively. Similarly, refractive errors were significantly more common in the patients with SRNS, observed in 11 (44%) patients compared to 14 (18.7%) patients in the SSNS group (P=0.011). Nonsteroid-dependent manifestations, such as esotropia and exotropia were less frequently observed, with no significant differences between the groups. The frequency of ocular findings the patients are presented in Table II.

PSCC and refractive errors were significantly associated with older patients, with a mean age of 12.2±2.8 (P=0.002) and 10.3±3.8 (P=0.001) years, respectively. Refractive errors exhibited a significant association with a prolonged duration of the disease (P=0.004), while increased IOP (P<0.001) and PSCC (P=0.003) were significantly associated with frequent

Table I. Demographic data of the patients in the SSNS and SRNS groups.

Parameter	Patients with SSNS, n=75	Patients with SRNS, n=25	P-value
Age (years), mean ± SD	7.95±3.66	8.12±3.45	0.837
Age at onset (years), mean ± SD	4.27±2.08	4.34±2.47	0.896
Sex, n (%)			
Male	50 (66.7)	20 (80.0)	0.313[a]
Female	25 (33.3)	5 (20.0)	
BMI (kg/m^2). Mean ± SD	17.58±2.74	68.60±9.86	**<0.001**
Systolic BP (mmHg), mean ± SD	95.54±8.09	100.2±8.72	**0.024**
Diastolic BP (mmHg), mean ± SD	60.27±8.3	68.0±6.12	**<0.001**
Duration of the disease (months), mean ± SD	44.2±32.3	45.3±35.9	0.936
Frequent relapse, n (%)			
No	64 (85.3)	19 (76)	0.357[a]
Yes	11 (14.7)	6 (24)	

Continuous variables were analyzed using the Mann-Whitney test. Categorical data were analyzed using the [a]Chi-squared test of Fisher's exact test. Values in bold font indicate statistically significant differences (P<0.05). SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; BMI, body mass index; BP, blood pressure.

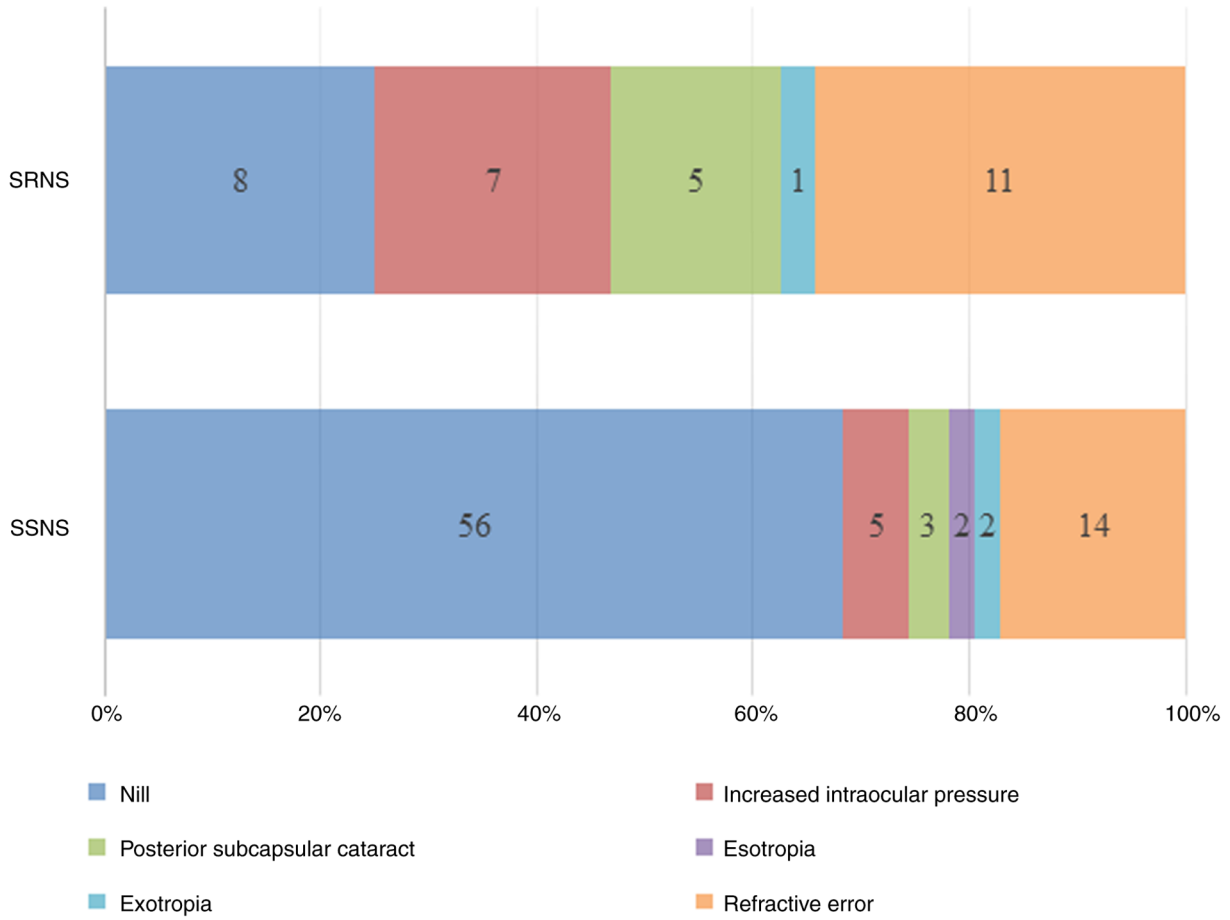

Figure 1. The prevalence of ocular manifestations in pediatric patients with SSNS and SRNS. SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.

relapses. The three conditions exhibited a significant association with increased higher systolic pressure, as shown in Table III.

The patients with NS also suffered from steroid-independent ocular pathologies, which included myopic astigmatism, exotropia, esotropia and anisometropic amblyopia. There was

Table II. Frequency of ocular findings in the SSNS and SRNS groups of patients.

Ocular findings	Total, n (%)	SSNS (n=75), n (%)	SRNS (n=25), n (%)	P-value[a]
Increased intraocular pressure				
No	88 (88)	70 (93.3)	18 (72)	**0.009**
Yes	12 (12.0)	5 (6.67)	7 (28.0)	
Posterior subcapsular cataract				
No	92 (92)	72 (96)	20 (80)	**0.022**
Yes	8 (8.0)	3 (4.0)	5 (20.0)	
Esotropia				
No	98 (98)	73 (97.3)	25 (100)	NS
Yes	2 (2.0)	2 (2.67)	0 (0.0)	
Exotropia				
No	97 (97)	73 (97.3)	24 (96)	NS
Yes	3 (3.0)	2 (2.67)	1 (4.0)	
Refractive error				
No	75 (75)	61 (81.3)	14 (56)	**0.011**
Yes	25 (25)	14 (18.7)	11 (44)	
Mild VA impairment	22 (88.0)	12 (85.7)	10 (90.9)	NS
Moderate VA impairment	3 (12)	2 (14.3)	1 (9.1)	

[a]Categorical data were analyzed using the Chi-squared test of Fisher's exact test. Values in bold font indicate statistically significant differences (P<0.05). SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; NS, not significant.

no statistically significant difference between the SSNS and SRNS, as shown in Table IV.

Discussion

The present study documented whether the ocular manifestations in children with NS were steroid-sensitive or steroid-resistant. It was found that ocular findings were more frequent in SRNS (68%) compared to (24%) in SSNS, although a significant difference in the duration of the disease or presence of frequent relapses was not observed between the two groups. The increased prevalence of ocular complications in children with SRNS may be attributed to the fact that these patients are more likely to receive intravenous pulse methylprednisolone before transitioning to alternative treatments, which may expose them to the potential adverse effects of corticosteroids. A previous study reported that ocular abnormalities were more prevalent among patients who received steroids irrationally (47%) than those who received steroids according to the standard regimen (18%) (9). The rate reported by that study for the standard regimen was low compared to the rate in the SSNS group in the present study (18 vs. 24%); however, the median duration of the disease from the time of onset to the date of ocular assessment in the present study was 33.6 months, whereas this was not clear in the study by Agrawal *et al* (9). Olonan *et al* (20) found that cataract formation was more prevalent in pediatric patients who had been receiving steroid therapy for an extended period, accounting for 13.6%.

In the present study, refractive error was significantly higher in the SRNS group, accounting for almost half of these patients compared to only 18% of the SSNS group. In their study, Zulfiqar *et al* (6) demonstrated that refractive error was the most prevalent ocular manifestation, affecting 25% of children with NS and that it was more commonly observed in those with SRNS; this is in agreement with the findings of the present study. An Egyptian study reported a higher rate of refractive error in children with NS, reaching 79% (11).

Steroid-dependent findings were significantly more common in those with SRNS, where 28% had increased IOP and 20% developed PSCC compared to 6.67 and 4% in those with SSNS, respectively. Zulfiqar *et al* (6) observed 2 cases of glaucoma, 1 case of increased IOP in both eyes and 2 cases of PSCC. By contrast, an Indian study reported a higher percentage of patients with PSCC and elevated IOP (26.8 and 10.9%, respectively) (12). Elsharkawy *et al* (11) found no cases of increased IOP or PSCC, despite a high rate of refractive errors in 79.2% of the participants. An earlier Turkish study reported that ocular complications were observed in 27% of those with SRNS, but in no patients with SSNS, most of which were refractive errors while steroid-dependent complications were only 9% (21). In a study addressing steroid-induced glaucoma, Phulke *et al* (22) concluded that IOP elevation typically occurs within the initial few weeks of steroid administration in steroid-responsive patients. Nevertheless, it may be elevated within 1 h or for a number of years following chronic steroid use (22). Research suggests that variable IOPs from steroid use can cause myopic astigmatism by stretching the globe and lengthening the axial axis (23). However, Kyrieleis *et al* (24) discovered no causal association in this occurrence.

Table III. Association between ocular manifestations and patient characteristics.

	Bilateral IOP (mmHG)			PSCC			Refractive error		
Variables	Normal	High	P-value	Absent	Present	P-value	Absent	Present	P-value
Sex, n (%)									
Male	62 (88.6)	8 (11.4)	0.749[a]	65 (92.9)	5 (7.1)	0.694[a]	54 (77.1)	16 (22.9)	0.615[a]
Female	26 (86.7)	4 (13.3)		27 (90)	3 (10)		21 (70)	9 (30)	
Age (years), mean (SD)	8 (3.6)	8.2 (3.6)	0.722	7.6	12.2 (2.8)	**0.002**	7.2 (3.2)	10.3 (3.8)	**0.001**
Duration of disease, mean (SD)	43.1 (31.1)	54.5 (45.4)	0.562	42.1	72 (49.8)	0.088	39.2 (30.2)	60 (36.6)	**0.004**
Systolic BP (mmHg), mean (SD)	100 (16)	103 (7)	**0.05**	99 (12)	122 (28)	**0.009**	97 (10)	113 (20)	**<0.001**
Diastolic BP (mmHg), mean (SD)	53 (16)	40 (26)	0.206	52 (18)	45 (17)	0.269	52 (17)	49 (20)	0.732
Frequent relapse, n (%)									
No	79 (89.8)	4 (33.3)	**<0.001[a]**	80 (87)	3 (37.5)	**0.003[a]**	81 (84)	2 (80)	0.759[a]
Yes	9 (10.2)	8 (66.7		12 (13)	5 (62.5)		17 (16)	5 (20)	

Continuous variables were analyzed using the Mann-Whitney test. [a]Categorical data were analyzed using Fisher's exact test. Values in bold font indicate statistically significant differences (P<0.05). SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; BP, blood pressure.

Table IV. Frequency of steroid-independent ocular findings in the SSNS and SRNS groups of patients.

Steroid-independent ocular findings	SSNS (n=75), n (%)	SRNS (n=25), n (%)	Total, n (%)	P-value[a]
Myopic astigmatism				
No	65 (86.7)	19 (76)	84 (84)	0.220
Yes	10 (13.3)	6 (24.0)	16 (16.0)	
Exotropia				
No	73 (97.3)	24 (96)	97 (97)	NS
Yes	2 (2.7)	1 (4.0)	3 (3.0)	
Esotropia				
No	73 (97.3)	25 (100)	98 (98)	NS
Yes	2 (2.67)	0 (0.0)	2 (2.0)	
Anisometropic amblyopia				
No	73 (97.3)	25 (100)	98 (98)	NS
Yes	2 (2.67)	0 (0.0)	2 (2.0)	

[a]Categorical data were analyzed using Fisher's exact test. Values in bold font indicate statistically significant differences (P<0.05). SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; NS, not significant.

Patients with glaucoma often do not notice the gradual loss of vision until the disease has advanced, in contrast to cataracts, which usually cause noticeable visual symptoms from the beginning (25). Hence, ocular examinations should be a part of the routine follow-up of patients with NS to avoid irreversible damage, particularly since an elevated IOP can be reversed (26). The necessity of commencing ophthalmological surveillance in a timely manner was demonstrated by a previous study, which found eye-related complications occurred within 6 months of commencing steroid therapy (23).

In the present study, frequent relapses were associated with increased IOP, PSCC and refractive error in patients with NS. In addition, an increased age, duration of the disease and systolic pressure were associated with refractive error and PSCC. A recent study conducted on 45 Japanese children diagnosed with NS found an association between the dose and duration of the medication and the occurrence of PSCC; however, there was no identified link between treatment and increased IOP (23). Although in the present study, the precise duration of steroid treatment could not be included due to lack

of data, an association was found between the duration from the onset of the disease to the time of the eye examination, as well as the frequency of the relapse; this could indicate a prolonged duration of steroid treatment. In agreement with the findings of the present study, Hayasaka *et al* (23) found a strong association between an older age and the development of PSCC.

The present study has some limitations which should be mentioned. Due to the cross-sectional nature of the study, it was not possible to determine the precise time of the start of ocular disorders in the affected children. As a result, the impact of the dosage and duration of corticosteroid therapy and the development of ocular disorders may not be readily evident. Differences in sample size, the racial makeup of the population investigated, duration and the cumulative amount of corticosteroid therapy may account for the discrepancies in the prevalence found.

In conclusion, the findings of the present study indicate that a considerable proportion of children with NS are susceptible to corticosteroid-related ocular complications. Nevertheless, it is important to take into account the possibility of ocular involvement in children who have steroid-resistant disease.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZNHAK was involved in the conception and design of the study, in the literature search, in the analysis of clinical data, data analysis and statistical analysis, as well as in the preparation and reviewing of the manuscript. SHA was involved in the conception and design of the study, in data analysis, and in the preparation and reviewing of the manuscript. ZNHAK and SHA confirm the authenticity of all the raw data. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The research received approval from the Scientific and Ethics Committee of Alkadimayn Teaching Hospital (no.=5542) and Ibn AL-Haytham Teaching Eye Hospital (no.=964) (both in Baghdad, Iraq) in accordance with the Declaration of Helsinki. Written informed consents from the parents were acquired after providing them with all relevant information.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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