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Assessment of Ocular Manifestations in Children with Nephrotic Syndrome during steroid Treatment

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ABSTRACT

Background: Ocular problems are related to patients with nephrotic syndrome (NS) who use corticosteroids for long-term. They consist of ptosis, atrophy of the eyelid skin, keratitis, changes in the pigmentation of the macular area, and exacerbations of bacterial and viral infections. The precise prevalence, severity, and timing of the onset of these problems in the pediatric patient population have not yet been thoroughly investigated.

Aim: This study aimed to estimate the burden of youngsters with nephrotic syndrome's eye problems on steroid therapy or after cessation of treatment.

Patients and methods: This cross-sectional study was conducted at the Paediatrc Nephrology Clinic in association with the Department of Ophthalmology Clinic, Zagazig University Children Hospital for ocular examination. We studied 48 children with primary nephrotic syndrome received corticosteroids either alone or with other treatment modalities for more than three months. Clinical signs, lab test findings, and a kidney biopsy were used to make the diagnosis of nephrotic syndrome.

Results: The most frequent ocular manifestations were refractive errors in 38 patients (79.2%) followed by blepharitis in 26 patients (54.2%), then hypertrichosis in 25 (52.1%) of patients, and 12 (25%) of patients had repeated eye infection in the form of mucopurulent conjunctivitis. While, the least frequent manifestations were epiblepharon in 4 patients (8.30%) and ptosis in 3 patients (6.3%).

Conclusion: A sizable percentage of kids with nephrotic syndrome receiving long-term steroids experienced eye problems.

Keywords: Nephrotic syndrome, Ocular, Errors, Ptosis, Blepharitis, Glomerulosclerosis, Children.

INTRODUCTION

The most prevalent form of glomerular disease in children is nephrotic syndrome (NS), which is also one of the main causes of systemic glucocorticoid exposure in young children. Estimates of the annual incidence of NS to be 2-7 per 100 000 children **(1).**

Nephrotic syndrome is characterized by having proteinuria > 40 mg/m^2/h, serum albumin < 2.5 g/dl, hyperlipidemia and oedema. Pediatricians frequently utilize large doses of steroids for a prolonged period of time in patients with nephrotic syndrome, where there is a high risk of relapse and a markedly increased risk of developing steroid dependency and toxicity. During relapses, patients receive extended and repeated steroid courses **(2).**

Evaluation of steroid side effects is therefore essential in NS. Ptosis, atrophy of the eyelid skin, keratitis, changes in the pigmentation of the macular area, and exacerbations of bacterial and viral infections are among the common adverse effects of steroids on the eyes. **(3, 4).** Our aim was to determine the prevalence of ocular problems in kids with nephrotic syndrome who were receiving steroid therapy or stopped the medication.

PATIENTS AND METHODS

48 children with primary NS were involved in this cross-sectional study, which was carried out at the Pediatric Nephrology Unit of the Pediatrics Children Hospital from September 2022 to March 2023, Faculty of Medicine, Zagazig University. Cases were referred to the Outpatient Clinic of Ophthalmology Department, Zagazig University to complete their ocular examination.

Inclusion criteria: Patients with NS between the ages of 4 and 16 years. Antinuclear antibody (ANA), anti-double stranded DNA (anti dsDNA), antineutrophil cytoplasmic antibody (ANCA), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and normal complement (C3, C4) level serology results that are negative. Consumption of corticosteroids as the primary or supplemental component of treatment for longer than three months. Patient's companions who signed the consent form and agreed to participate in the survey.

Exclusion criteria: Children under the age of 4 (because to their poor cooperation) and those who had co-morbid ocular problems such as trauma and infection, or inflammation. Children with ocular congenital defects such as congenital cataracts, NS patients who are uncooperative for ophthalmologic examinations, and patients who have any systemic diseases other than NS.

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Complete histories of each patient including information on their age, sex, and family history of kidney disease, diabetes and autoimmune conditions such as systemic lupus erythematosus, or any eye issues in the past. Age at which NS first was manifested, the sorts of drugs used (corticosteroids and other drugs) and remissions and relapses. Age at which treatment began, total dose, and length of steroid therapy. Anthropometric measurements such as height, weight, and BMI were part of a general examination. International cutoff points for body mass index (weight/height in m^2) by sex for individuals between the ages of 2 and 18 were used to diagnose overweight and obesity [5]. Blood pressure was recorded. Local examination including edema all over the body especially lower limbs and eye lid puffiness, abdominal, cardiac, CNS and chest examination.

Laboratory tests included liver function test, kidney function test (serum creatinine and blood urea), T. protein and S. albumin, S. cholesterol, urine analysis (including protein in urine) and renal biopsy which was done before the study. Ophthalmologic examination [Snellen's chart visual acuity tests and best corrected visual acuity (BCVA) were also included and expressed in decimal system for analysis].

External ocular examination of the lid to detect ptosis (laterality, type, degree and elevator function) and presence or absence of epiblepharon. Examination of lashes to detect any abnormalities in color or number like hypertrichosis. Slit lamp examination of conjunctiva for signs of infection like redness and discharge, lid margin for signs of anterior or posterior blepharitis, inspection of the iris, lens, cornea, and anterior chamber. To find refractive errors, an autorefractometer examination was performed. To find any abnormalities in the optic disc, a fundus examination using an indirect ophthalmoscope was performed. Eye movements in all gazes were tested to look for any paresis or paralysis of the extra ocular muscles.

Ethics Considerations: This experiment was given ethical approval by the Institutional Review Board of the Faculty of Medicine, Zagazig University. All participants signed written consent forms after receiving all necessary information. This study was carried out in accordance with the Declaration of Helsinki, which is the International Medical Association's code of ethics for human subjects' research.

Statistical analysis

IBM SPSS Statistics for Windows was used to gather, tabulate, and statistically analyze all of the data (Version 23.0. Armonk, NY: IBM Corp.2015). Quantitative data were expressed as the mean ± SD & numbers and percentages were used to express the median (range) and qualitative data. Two groups' normally distributed variables were compared using the t test. The Mann-Whitney U test was utilized to compare not normally distributed variables of two groups. Every test had two sides. Statistical significance was defined as p-value $\leq$ 0.05 and p-value > 0.05 was considered statistically non-significant.

RESULTS

Table (1) showed that the studied patients are 24 males (50%) and 24 females (50%). Their mean age was 8.67 ± 2.55 years. Age of onset of nephrotic syndrome in studied patients ranged between 4-11 years with mean of 6.08 ± 2.1. The weight of studied children ranged between 15-53 kg with mean of 31.85 ± 9.42 kg. The height ranged between 104-192 cm with mean of 130.65 ± 14.68 cm. Body mass index ranged between 12-26.3 kg/m^2 with mean of 18.66 ± 3.43.

Table (1): Demographic characters of the studied patients

	Variables	N.S patients (n=48)	
		No	%
Sex	Males Females	24 24	50% 50%
Age (years)	Mean ± SD (range)	8.67 ± 2.55 (5-14)	
Age of onset of disease(years)	Mean ± SD (range)	6.08 ± 2.1 (4-11)	
Weight (kg)	Mean ± S.D (range)	31.85 ± 9.42 (15-53)	
Height (cm)	Mean ± S.D (range)	130.65 ± 14.68 (104-192)	
Body mass index (kg/m^2)	Mean ± S.D (range)	18.66 ± 3.43 (12-26.3)	

N.S= Nephrotic syndrome, SD= Standard deviation

The most frequent manifestation was refractive errors in 38 patients (79.2%) followed by blepharitis in 26 patients (54.2%). Then, hypertrichosis in 25 patients (52.1%), and 12 patients (25%) had repeated eye infection in the form of mucopurulent conjunctivitis. While, the least frequent manifestations were epiblepharon in 4 patients (8.30%) and ptosis in 3 patients (6.3%). The ptosis was mechanical due to eyelid edema. All 3 cases were mild (2 mm) with good levator muscle function and bilateral (Table 2).

Table (2): The ocular manifestations in studied patients

	N.S patients (n.48)	
Ocular manifestations	**no**	**%**
Eye infection	12	25%
Belphritis	26	54.2%
Ptosis	3	6.3%
Hypertrichosis	25	52.1%
Epiblephron	4	8.3%
Refractive errors	38	79.2%

Table (3) showed that there was no relationship between the above ocular manifestations in children with nephrotic syndrome and cumulative dose of corticosteroid, ($p > 0.05$).

Table (3): Relation between corticosteroid cumulative dose (gm) and ocular affection in children with nephrotic syndrome

Variables		Number	Corticosteroid cumulative dose		
			Mean ±SD, (range)	u	p
Blepharitis	**Yes**	**26**	7.01±4.41 (2.35-22.63)	1.014	0.296
	No	22	7.55±7.76 (2.7-30.6)		
Epiblephron	**Yes**	**4**	8.25±6.61 (3.7-18.07)	0.45	0.65
	No	44	7.16±6.13 (2.35-30.56)		
Hypertrichosis	**Yes**	**25**	7.99±6.49 (2.4-28.22)	0.98	0.33
	No	23	6.45±5.7 (2.7-30.6)		
Eye Infection	**Yes**	**12**	7.11±5.48 (2.87-22.63)	0.12	0.91
	No	36	7.3±6.38 (2.4-30.6)		
Ptosis	**Yes**	**3**	7.47 ±4.02 (2.8-10.27)	0.53	0.59
	No	45	7.24±6.25 (2.35-30.56)		

(U: Mann Whitney u test, *p<0.05: significant, p>0.05: non-significant)

Table (4) showed that there was a significant increase in refractive errors and blepharitis in patients with nephrotic syndrome treated with steroids only versus combined treatment (P=0.01, P=0.013) respectively. But, there was no significant difference in occurrence of other ocular manifestations in patients treated with corticosteroids only and those who had combined therapy.

Table (4): Relation between protocol of treatment and ocular affection in children with nephrotic syndrome

Variables	N.S patients (n.48)					
	Type of treatment					p
	Corticosteroid only (n.27)		Combined Treatment (n.21)			
	n.	%	n.	%		
Errors of refraction	**25**	92.6	**13**	61.9	f	0.013*
Ptosis	**2**	7.4	**1**	4.8	f	0.99
Belphritis	**19**	70.4	**7**	33.3	6.5	0.01*
Epiblephron	**3**	11.1	**1**	4.8	f	0.62
Hypertrichosis	**15**	55.6	**10**	47.6	0.29	0.58

χ^2 Chi square test of significant f=Fisher Exact test, * p<0.05 significant , p>0.05 non-significant

Table (5) showed that serum creatinine ranged between 0.1-.09 mg/dl, blood urea was 8.6-31 mm/dl, serum cholesterol was 167-716 mg/dl, total serum protein was 3-7 g/dl and serum albumin was 1.5-5.5 g/dl. Regarding protein in urine in studied patients, 5 has (+) (10.4%), 12 has (++)(25%) and 2 has (+++) (4.2%).

Table (5): Renal function tests (blood urea and serum creatinine), serum cholesterol, total serum protein, serum albumin and protein in urine in studied patients

	N.S patients (n.48)	
	Mean ± SD,(range)	
S.creatinine (mg/dl)	0.37 ± 0.07	
Bl.Urea (mg/dl)	22.7 ± 5.4	
S.Cholesterol (mg/dl)	413.2 ± 12	
Total serum protein (g/dl)	5.06 ± 1.3	
Serum albumin (g/dl)	3.38 ± 0.23	
Protein in urine	**No**	**%**
Absent (-ve)	29	60.4%
+	5	10.4%
++	12	25.0%
+++	2	4.2%

Table (6) showed that the studied patients were 35 (72.9%) had MCD, 10 (20.8%) were not IX, and 3 (6.3%) had FSGS.

Table (6): Pathological finding of renal biopsy in studied patients

	N.S patients (n.48)	
Renal biopsy	**no**	**%**
M.C.D	35	72.9
NOT IX	10	20.8
FSGS	3	6.3

M.C.D= Minimal Change Disease, FSGS= Focal Segmental Glomerulosclerosis. NOT Ix= Not Investigate

Table (7) showed that the studied patients were 27 (56.3%) treated with corticosteroid only. The mean duration of treatment was 2.6 ± 1.6 years and ranged from 1-9 years. The mean cumulative corticosteroid dose during treatment period was 7.25 ± 6.11 and ranged between 2.35-30.56 gm. The mean corticosteroid dose (gm/year) is 2.89 ± 1.29 and ranged between 1.23-7.64 gm/year.

Table (7): Protocol of treatment in studied patients.

Protocol of treatment	N.S patients (n.48)	
	No	%
Steroid only	27	56.3%
Combined treatment	21	43.7%
Duration of treatment (years) Mean ± SD (range)	2.6 ±1.6 (1-9)	
Cumulative dose of corticosteroid (gm) Mean ± SD	7.25 ± 1.11	
Corticosteroid dose (gm) /year Mean ± SD	2.89 ±0.29	

Table (8) showed that there was a significant statistical difference in children age, weight and height between patients with frequent relapses and patients with infrequent relapses nephrotic syndrome ($p<0.05$). Otherwise, there was no statistical difference in sex or BMI between the two groups ($p>0.05$).

Table (8): Relation between frequency of disease relapse and demographic, anthropometric measurements

Variables	N.S patients (n.48)				χ^2	P
	Frequent relapse n=32		Infrequent relapse n=16			
	n	%	n	%		
Sex females males	19 13	59.4% 40.6%	5 11	31.2% 68.8%	3.37	0.066
Age (years) Mean ± SD (range)	9.5 ± 2.37 (5-14)		7.1 ± 2.1 (5-13)		t 3.4	0.001*
Weight(kg) Mean ± SD (range)	34.1 ± 9.6 (20-53)		27.43 ± 7.49 (15-46)		t 2.4	0.02*
Height(CM) Mean ± SD (range)	133.7 ± 14.9 (115-192)		124.5 ± 12.48 (104-150)		t 2.12	0.039*
BMI(kg/m2) Mean ± SD (range)	19.2 ± 3.36 (15-26.3)		17.56 ± 3.41 (12-23)		t 1.57	0.17

χ^2 Chi square test of significant, t:student't test ,* $p<0.05$ significant , $p>0.05$ non-significant

Table (9) demonstrated that there was a statistically significant variation in patients' refractive errors with frequent relapses and patients with infrequent relapses, ($p=0.001$). Otherwise, there was no statistical difference in ocular manifestations between patients with frequent and infrequent relapses ($p>0.05$).

Table (9): Relation between frequency of disease relapse and ocular manifestations

Variables	N.S patients (n.48)					
	Frequent Relapse (n=32)		Infrequent relapse n=16		χ 2	P
	n	%	n	%		
Refractive errors	30	93.75	8	50.0	f	0.001*
Ptosis	1	3.13	2	12.5	f	0.25
Belphritis	19	59.38	7	43.75	**1.05**	**0.31**
Epiblephron	4	12.50	0	.00	f	0.29
Hypertrichosis	18	56.25	7	43.75	0.67	0.41
Eye infection	6	18.75	6	37.5	f	0.18

χ^2 Chi square test of significant f=Fisher Exact test, t:student't test , p>0.05: non-significant

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DISCUSSION

The cornerstone of treatment for kids with nephrotic syndrome is corticosteroid medication. Despite its effectiveness, systemic administration is linked to multiple ophthalmic side effects complications, which included myopic astigmatism, ptosis, epiblepharon, impaired visual acuity, blepharitis with bacterial and viral infections [(6)]**.** Regarding ocular manifestations, according to a study, the most typical symptoms were refractive errors in 38 patients (79.2%), followed by blepharitis in 26 patients (54.2%) then Hypertrichosis in 25 patients (52.1%), 12 (25%) had repeated eye infection in the form of mucopurulent conjunctivitis (redness and discharge) which responded to topical antibiotics. The least frequent manifestations were Epiblepharon in 4 patients (8.30%) and ptosis in 3 (6.3%) of patients. Our study is in agreement with **Nakubulwa *et al.*** [(7)] who reported that a total of 80/100 (80%) participants had ocular complications. Seventy-one (71%) patients had hypertrichosis of the eye lashes, 56 (56%) had refractive errors, 37% had allergic conjunctivitis and 10% had blepharitis and bacterial conjunctivitis. Numerous researchers have proposed that fluctuating intraocular pressures stretch the globe and temporarily lengthen the axial axis, resulting in myopic astigmatism, but no direct link between the two has been discovered by **Kyrieleis *et al.*** [(8)]**.**

In our study blepharitis found in 26 children (54.2%). This contradicts the findings of the investigation by **Nakubulwa *et al.*** [(7)] who found that the prevalence of blepharitis was 10%. Steroid-treated nephrotic syndrome patients may occasionally have an atypical immune system and bacterial eye infection **Hayasaka *et al.*** [(9)]**.** Hypertrichosis in our study was found in 25 patients (52.1%). This is in agreement with **Nakubulwa *et al.*** [(7)] who found that hypertrichosis was the most frequent ocular complication in 70 patients (70%). Through an unidentified mechanism, systemic steroids promote facial hypertrichosis.

In our study one of the least frequent manifestations was Epiblepharon in 4 patients (8.30%). This is in disagreement with **Nakubulwa *et al.*** [(7)] who found that 46 (46.6%) of Japanese kids with nephrotic syndrome had epiblepharon in his study. **Hayasaka *et al.*** [(9)] reported that orbital fat projected further anteriorly in relation to the orbital rim in the lower eyelid and found that obesity and overweight were linked with Epiblepharon in children with nephrotic syndrome.

Regarding laboratory findings in the present results, the mean serum creatinine level was 0.37 mg/dl, blood cholesterol was 413.2 mg/dl, urea was 22.7 mg/dl, total serum protein was 5.06 g/dl, albumin was 3.38 g/dl, and 39.6% of cases had protein in urine. **Kyrieleis *et al.*** [(8)] who reported that while all of the patients' serum albumin levels were normal, three out of the fifteen patients had microalbuminuria and four out of the fifteen had albuminuria.

The current study found pathological finding of renal biopsy, which showed that 35 (72.9%) had minimal change disease (MCD), 10 (20.8%) had not done biopsy, and three (6.3%) had focal segmental glomerulosclerosis (FSGS). **Iijima *et al.*** [(10)] reported that in 22 patients (71%) there were kidney biopsies. They were divided into 16 patients (73%) with a minimal change in nephrotic syndrome and 6 individuals (27%), who had a non-minimum alteration. Lupus nephritis, membranous nephritis brought on by the hepatitis B virus, Henoch-Schönlein nephritis, mixed patterns of proliferative and mesangial change glomerulopathy, IgA nephropathy, and focal necrotizing glomerulonephritis were among the non-minimal changes. **Afifi *et al.*** [(6)] reported that minimal change disease and focal segmental glomerular sclerosis were the two most frequent diseases found during biopsy (70% and 20%, respectively) (25%).

Protocol of treatment in the current study showed that the studied patients were 27 (56.3%) treated with corticosteroid only. The mean duration of treatment was 2.6 ± 1.6 years and ranged from 1 to 9 years. The mean cumulative corticosteroid dose during treatment period was 7.25 ± 6.11 and ranged between 2.35 and 30.56 gm. The mean corticosteroid dose (gm/year) was 2.89 ± 1.29 and ranged between 1.23 and 7.64 gm/year. **Gaur *et al.*** [(11)] reported that all cases received steroids, the accumulative corticosteroid during treatment period was

338.9 mg/kg, and the mean duration of treatment was 4.95 years. **Nakubulwa *et al.* [7]** reported that 58% of cases had duration of treatment > 200 days. 81% had only steroids, and 19% had combined medications. 57% of cases had average daily dose of steroid per weight < 1 mg/kg/day.

The current investigation demonstrated a statistically significant difference between refractive errors and blepharitis in nephrotic syndrome patients receiving steroids only and those on combined therapy. But there was no significant difference in occurrence of other ocular manifestations in patients treated with corticosteroids only and those on combined therapy. Our study agrees with **Afifi *et al.* [6]** study, as they reported that none of the examined ocular metrics seemed to be significantly affected by either cyclophosphamide or cyclosporine (p >0.05).

Our investigation revealed a statistically significant difference in children age, weight, height between patients with frequent relapses and patients with infrequent relapses nephrotic syndrome. Otherwise, there was no statistical difference in sex or BMI between the two groups. This study revealed that there was a statistically significant difference in patients' refractive errors with frequent relapses and patients with infrequent relapses. Otherwise, there was no statistical difference in ocular manifestations between patients with frequent and infrequent relapses. Our results coincide with **Abd El-hameed *et al.* [12]** who aimed how corticosteroids affected anthropometric measurements in kids with nephrotic syndrome, they found a statistically significant positive association between cumulative steroid dose and weight and a negative link between cumulative steroid dose and height. **Williams *et al.* [13]** found that up to 80% of children with steroid sensitive nephrotic syndrome will experience at least one relapse, and more than half of these children will develop a frequent relapsing and/or steroid-dependent course, necessitating frequent exposure to corticosteroids and the side effects that come with it.

CONCLUSION

Children with nephrotic syndrome who had long-term steroid medication frequently experienced eye problems. Therefore, it is imperative to refer all kids with nephrotic syndrome or other diseases who are receiving prolonged systemic steroid therapy for ophthalmological examination in order to identify any early ocular complications that could develop even after the treatment is stopped. Additional research with a larger sample size and longer follow-up times is required to clarify whether there is a connection between ocular complications in kids with nephrotic syndrome and long-term steroid treatment.

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