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Ocular Manifestations In Paediatric Population With Nephrotic Syndrome: Study From Single Centre In North India

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Abstract

Background: Nephrotic syndrome (NS) is the most common glomerular disease among children aged 2-18 years. Systemic corticosteroids form the mainstay of its treatment. Ocular complications can arise due to nephrotic syndrome and/or its treatment. We conducted a descriptive retrospective study to assess the ocular morbidity among children with nephrotic syndrome, who came for ophthalmic examination to OPD at CNBC hospital, from January 2021 to April 2023.

Methods: The ophthalmic examination data of 95 patients aged 3-15 years diagnosed with nephrotic syndrome was retrospectively analysed. Variables including gender, age at presentation, sensitivity to systemic steroids were noted. Refraction data, anterior segment and posterior segment findings, intraocular pressure were reviewed and analysed.

Results: The mean age of patients at the time of initial ophthalmic examination was 7.21 years. 19 patients (20%) had steroid resistant nephrotic syndrome (SRNS). Prevalence of refractive errors in this study was 63.16 %. Compound myopic astigmatism(35%) was the most common refractive error, followed by astigmatism(30.8%). Among patients with astigmatism, myopic astigmatism was most common. Posterior subcapsular cataract was present in 13.7% of patients, while ocular hypertension was noted in 10.5% of all. Amblyopia was present in 8 (8.4%) patients. Prevalence of ocular morbidities was higher among SRNS patients.

Conclusions: In our study, refractive error is the most common ocular morbidity, followed by posterior subcapsular cataract. Ocular complications were found to be more prevalent in NS patients with steroid resistance.

Keywords: Nephrotic syndrome, corticosteroids, ocular complications, children

Introduction

Nephrotic syndrome is the most common renal glomerular disease in children and adolescents aged 2-18 years. Global prevalence of nephrotic syndrome (NS) is about 16 cases per 100,000 children, with incidence of 2 to 7 per 100,000 children, incidence varies by ethnicity and region [1,2]. Epidemiological studies have found its higher incidence among children of south Asian origin [3]. Nephrotic syndrome is idiopathic in 95% cases. It affects males more than females at ratio of 2:1 among children [2]. Its hallmark clinical features include massive proteinuria, edema, hypoalbuminemia and hyperlipidemia. Increased permeability of glomerular basement membrane results in significant protein loss

in urine, consequently decreasing the plasma colloid oncotic pressure. Hence more and more fluid enters interstitial spaces from intravascular compartment. Due to chronic relapsing nature of this disease, patients require prolonged and repeated courses of steroids and/or immunosuppressive agents such as cyclosporin A, cyclophosphamide, levamisole[4]. As per current guidelines, steroid sensitive nephrotic syndrome (SSNS) is defined as remission within 4 weeks of initiation of systemic glucocorticoid therapy. Nearly 60%-70% of patients initially classified as SSNS have >1 relapse. Among children who relapse, 30 % will either become FRNS or SDNS [5]. Frequently relapsing nephrotic syndrome (FRNS) is characterised by two or more relapses in the initial 6 months or, four or more relapses within 12 months, after complete remission. Infrequently relapsing nephrotic syndrome (IFRNS) is defined as having one relapse within first six months after achieving complete remission, or up to 3 relapses within 12-month duration. Steroid dependent nephrotic syndrome (SDNS) is defined as NS with two consecutive relapses when on alternate day systemic steroids or within 14 days of discontinuation of systemic steroids. Steroid resistant nephrotic syndrome (SRNS) is defined as failure to achieve complete remission after 6 weeks of daily therapy with corticosteroids [6,7,8]. SRNS accounts for nearly 15% of all NS cases [9]. Underlying pathophysiology can affect multiple organ systems, hence contributing to extra-renal manifestations. Ocular hypertension, glaucoma, cataract, refractive errors, blepharitis, repeated hordeolum are frequent ocular findings in paediatric population with nephrotic syndrome. Hypertensive retinopathy, serous retinal detachment, retinal vascular occlusions have been reported in some studies [10,11,12]. Ocular complications have been found to be more common in patients who received higher cumulative steroid doses [13].Thus longer treatment duration explains the greater frequency of ocular complications [14]. There is paucity of data that compares the ocular manifestations in children with SRNS and SSNS among Indian population. Present retrospective study has drawn comparison between the prevalence of ocular manifestations among SSNS and SRNS patients.

Hypoproteinemia in nephrotic syndrome decreases the plasma colloid osmotic pressure. In physiological aspects, kidney and eye are ‘paired ‘organs in the sense that renal glomeruli and choroid have comparable vascular framework, plus both organs share some transcription factors [15]. Hence the pathophysiology of nephrotic syndrome has ocular implications. Moreover, renin-angiotensin-aldosterone system (RAAS) is present in ocular tissues as well [16]. Regular ophthalmic examinations of nephrotic syndrome cases are essential throughout the course of disease, for early detection and treatment of ocular complications.

Materials And Methods:

Our study is a single-centre retrospective descriptive study of ocular complications found among children with confirmed diagnosis of nephrotic syndrome. Clinical records of total 95 children aged 3-15 years, with steroid sensitive and steroid resistant nephrotic syndrome, who attended ophthalmology outpatient department clinics from 2021 to 2023 at CNBC (Chacha Nehru Bal Chikitsalya) Delhi were reviewed. Information regarding age at presentation, and gender of patients, presence/absence of refractive errors, cataract, ocular hypertension, glaucoma, and amblyopia was noted.

Steroid-induced ocular hypertension is defined as intraocular pressure (IOP) >21 mm Hg, or an increase of >6 mm Hg from baseline, with or without glaucomatous optic neuropathy, after steroid intake in any form.

Statistical analysis: statistical analysis was done using SPSS software. Qualitative data were described using number and percent. p-value <0.05 was considered significant. Quantitative data were described using range (minimum and maximum), mean, standard deviation.

Results

In this study, we summarized and analyzed the ocular findings of 95 children with NS. The mean age of the patients at the time of initial visit in eye OPD was 7.21 (SD ±2.96) years (range- 3-15 years). Gender distribution of study subjects showed male predominance with male to-female ratio as 1.64.

Table 1 : Demographic data of the patients in the SSNS and SRNS groups.

Parameter	Patients with SSNS,	Patients with SRNS,	P-value

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	n=76	n=19	
Age at presentation (years), mean ± SD	7.04±2.97	7.89±2.89	0.213
Gender, n (%)			
Male	49 (64.5)	10 (52.6)	0.429
Female	27 (35.5)	9 (47.4)	

SSNS, steroid sensitive nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome.

Ocular morbidity was recorded in 71 patients (74.7%). Out of 95 patients, 19 (20%) had been diagnosed with steroid resistant nephrotic syndrome (SRNS) and rest 76 children had steroid sensitive nephrotic syndrome (SSNS) to begin with. Mean age at presentation was found 7.04 years in patients with initial diagnosis of SSNS, while it was 7.89 years in SRNS patients. Males accounted for the majority of both SSNS [49 (64.5%)] and SRNS [10 (52.6%)] patients. Table 1 depicts demographic data of patients in both SSNS and SRNS groups. Bilateral/unilateral posterior subcapsular cataracts (PSC) were present in 13 (13.7%) patients, among whom unilateral PSC was noted in 2 patients. Seven (53.8%) among all cataract cases had been diagnosed with SRNS.

Three cataract patients underwent cataract surgery with implantation of posterior chamber intraocular lenses. Frequency of developing cataract was more than four times higher among SRNS patients, as compared to SSNS cases. Toruan YML et al observed in their cross-sectional study that longer duration of steroid treatment led to a higher occurrence of PSC (17). A Japanese study had concluded the same [18]. In our study, children with PSC were generally older than those without it (Mean age 8.31 and 7.04 years, respectively) as depicted in Table 2. Frequency of ocular hypertension, cataract and refractive errors was found to be higher among female subjects in our study, though the difference was statistically insignificant (Table 2).

Table 2:Association between ocular manifestations and patient characteristics

	Bilateral IOP (mmHg)			PSC			Refractive error		
Variables	Normal	High	P-value	Absent	Present	P-value	Absent	Present	P-value
Gender, n (%)									
Male	53(89.8)	6(10.2)	1	52(88.1)	7(11.9)	0.548	22(37.3)	37(62.7)	1
Female	32(88.9)	4(11.1)		30(83.3)	6(16.7)		13(36.1)	23(63.9)	
Age (years), mean (SD)	6.92±2.86	9.7±2.71	**0.006**	7.04±2.9	8.31±3.23	0.184	6.31±2.77	7.73±2.96	**0.019**

Continuous variables were analyzed using the Mann-Whitney test. Categorical data were analyzed using Fisher's exact test. Values in bold font indicate statistically significant differences (P<0.05). IOP, Intraocular pressure; PSC, posterior subcapsular cataract.

Bilateral ocular hypertension (OHT) was a documented finding in clinical records of 10 (10.5%) patients, among whom 6 cases (60%) belonged to SRNS group. Of 10 OHT cases, 3 had deep cupping with cup:disc ratio >=0.6:1. Two patients had both cataract and ocular hypertension. Patients with OHT had been prescribed topical antiglaucoma drugs. Figure 1 summarises prevalence of ocular findings in types of NS in our study.

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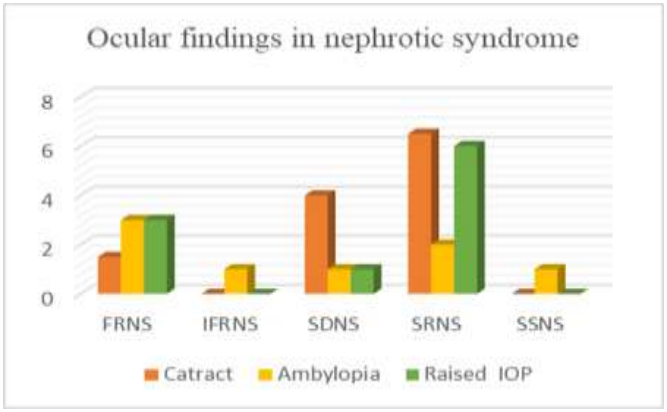

Figure 1: Prevalence of various ocular finding in patients of nephrotic syndrome

(Steroid sensitive nephrotic syndrome (SSNS), Infrequently relapsing nephrotic syndrome (IFRNS), Frequently relapsing nephrotic syndrome (FRNS), Steroid dependent nephrotic syndrome (SDNS) Steroid resistant nephrotic syndrome (SRNS), Intraocular pressure (IOP)

Records of 8 patients mentioned amblyopia, 6 being ametropic amblyopia and 2 cases of anisometropic unilateral amblyopia, with 2 amblyopia patients being in SRNS group. Among 14 amblyopic eyes, best corrected visual acuity was in range of 6/9 to 6/12 in seven eyes, 6/18 to 6/36 in six eyes, and 6/60 in one eye. Refraction data of 190 eyes revealed refractive errors in 120 (63.16%) eyes. Among all refractive errors, compound myopic astigmatism was found as most common refractive error in this study, at prevalence of 35 %, followed by astigmatism (30.83%) and then myopia (15%). Among SRNS patients, compound myopic astigmatism (CMA) was most common refractive error accounting for 46.43%, followed by astigmatism (25%). Patients with initial diagnosis of SSNS had astigmatism as most common (33.7%) of all refractive error, followed by CMA (31.5%). Figure 2 shows distribution of various refractive errors among types of NS in our study.

One patient had severe vernal keratoconjunctivitis, which was treated with topical antiallergic drugs. Two patients had intermittent esotropia, which was managed with optical treatment and occlusion therapy.

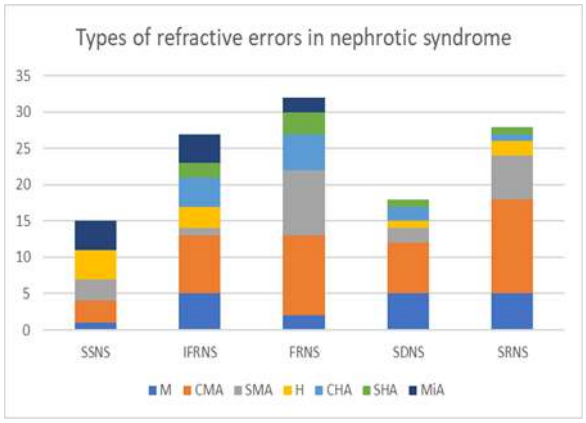

Figure 2 : Prevalence of various refractive errors in nephrotic syndrome patients

(Steroid sensitive nephrotic syndrome (SSNS), Infrequently relapsing nephrotic syndrome (IFRNS), Frequently relapsing nephrotic syndrome (FRNS), ,Steroid dependent nephrotic syndrome (SDNS) Steroid resistant nephrotic syndrome (SRNS), Myopia (M), Compound myopic astigmatism (CMA), Simple myopic astigmatism (SMA), Hypermetropia (H), Compound hyperopic astigmatism(CHA), Simple hyperopic astigmatism (SHA), Mixed astigmatism (MiA).

Discussion

Nephrotic syndrome is one of the major clinical entities, which account for childhood exposure to systemic glucocorticoids. Systemic steroids have intraocular penetration through bloodstream during long term intake as in treatment of nephrotic syndrome. We conducted a retrospective, single-centre study to provide additional insights into the pattern of ocular complications in relation with steroid response. Kumar J et al found mean age of onset of idiopathic nephrotic syndrome as 7.9 ± 5.1 years [19]. In present study, among 76 patients with initial diagnosis of SSNS, 62(81.6%) had one or more relapses. Of the 62 patients with relapses, 16 (25.8%) were found to be SDNS. Figure 3 summarises percent distribution of different types of NS in our study.

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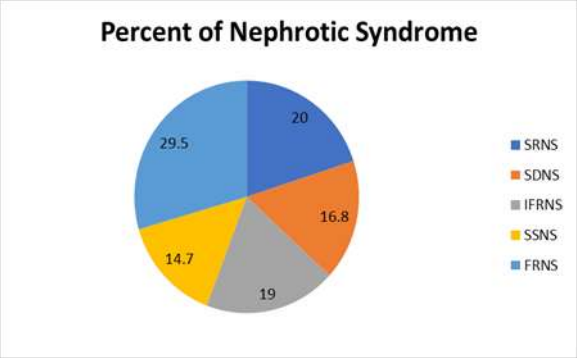

Figure 3 :Percentage of different types of nephrotic syndrome.

Steroid sensitive nephrotic syndrome (SSNS), Infrequently relapsing nephrotic syndrome (IFRNS),Frequently relapsing nephrotic syndrome (FRNS),Steroid dependent nephrotic syndrome (SDNS), Steroid resistant nephrotic syndrome (SRNS).

Corticosteroids inhibit cell migration, apoptosis and phagocytosis in trabecular meshwork (TM). Accumulated mucopolysaccharides cause swelling of TM framework, which aggravates resistance to aqueous outflow, and leads to ocular hypertension [20, 12]. Hypoalbuminemia in nephrotic syndrome may lead to compensatory stimulation of renin-angiotensin-aldosterone system [21]. Tissue RAAS may get activated by renin and/or angiotensinogen taken up from bloodstream [22]. Active local RAAS is present in human retina as well, which, if unregulated, may mediate retinal ischaemic injury. It explains retinal ganglion cell loss in presence of normal IOP [23].

Retrospective review done in our study found prevalence of OHT as 10.5 %. Children with OHT in our study were generally older (mean age 9.7 years) than those without it. Study conducted by Alkhafaji ZNH et al found higher mean age in cataract and OHT cases, compared to overall mean age of their study population[24]. Toruan YML et al and Al-Khafaji ZNH et al both had reported OHT in 12% of paediatric nephrotic syndrome cases treated with systemic steroids[17,24]. OHT was present in 16% patients enrolled in cross sectional study by Nakubulwa F et al [20]. Hypertensive retinopathy was not found in any patient in our study, similar to the result noted by Jezeela K et al[25]. Hypercoagulable state in nephrotic syndrome substantially builds up the risk of thromboembolic episodes, though it is less common in paediatric population [12].

Glucocorticoid-induced modulation of gene transcription in lens epithelium and other intraocular cells is believed to play role in steroid induced cataractogenesis. Possible role of indirect mechanisms via influence on growth factors has also been noted to affect crystalline lens metabolism [26]. Steroids which reach ocular tissues permeate into crystalline lens, promote abnormal proliferation and apoptosis of lens epithelial cells, accumulation of insoluble protein aggregates, hence resulting in opacification of lens [27]. A study found prevalence of posterior subcapsular cataract and glaucoma as 33.3% and 20% respectively, among nephrotic syndrome paediatric patients receiving prolonged steroids [28]. Steroid induced cataract has been found to be associated with higher cumulative dose and greater duration of corticosteroid intake [29].

Most of these cataracts are posterior subcapsular cataracts, which obscure the visual axis and significantly impair visual acuity. In our study, prevalence of cataract was found to be 13.7%, which was comparable to finding (13.6%) reported by Olonan LRN et al [30]. In their study, cataract had higher prevalence in children who had received steroid therapy for an extended period. Prevalence of PSC observed in present study is lower than that reported by Gaur S et al (26.8%) and Toruan YML et al (19.6%)[31,17]. Mean age of presentation (8.31 yrs) was higher among patients with PSC in our study. In agreement with the conclusion drawn in present study, Hayasaka et al had noted a strong association between older age of patient and the development of PSC[28]. Table 3 demonstrates frequency of ocular complications in both SSNS and SRNS groups.

It has been theorised that episodes of high intraocular pressure can influence axial length in nephrotic syndrome patients receiving steroid treatment. Long term steroid use in such cases may stretch the globe in axial dimension, causing increased prevalence of myopic astigmatism [28]. Decreased colloid osmotic pressure in nephrotic syndrome promotes fluid retention and may affect shape of lens, causing myopia. As corticosteroids impair collagen synthesis, it can potentially affect corneal structure and shape, and consequently corneal refractive power. Study has

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shown increased central corneal density and enlarged horizontal corneal diameter with flattening in paediatric NS patients [32]. Moreover, diuretics are supposed to bring changes in ionic composition of vitreous humour which may affect refractive status parameters [33].

Table 3:Frequency of ocular findings in the SSNS and SRNS groups of patients.

Ocular findings in number of eyes	Total, n (%) 190(100)	SSNS, n (%) 152 (80)	SRNS, n (%) 38(20)	P-value
INTRAOCULAR PRESSURE				
Normal intraocular pressure	170(89.5)	144(94.7)	26(68.4)	**<0.001**
Raised intraocular pressure	20(10.5)	8(5.3)	12(31.6)	
POSTERIOR SUBCAPSULAR CATARACT				
Clear lens	166(87.4)	141(92.8)	25(65.8)	**<0.001**
Cataract present	24(12.6)	11(7.2)	13(34.2)	
VISUAL ACUITY				
Normal vision	70(36.8)	60(39.5)	10(26.3)	0.188
Refractive error	120(63.2)	92(60.5)	28(73.7)	
AMBLYOPIC CHANGES				
Normal vision	176(92.6)	141(92.8)	35(92.1)	0.531
Amblyopia present	14(7.4)	11(7.2)	3(7.9)	

Categorical data were analyzed using the Chi square 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.

Refraction status data of 190 eyes in present study found prevalence of refractive errors as 63.16%. Nakubulwa et al found refractive errors among 56% of nephrotic syndrome cases, while this finding was reported as 50% by Jezeela et al and as 79.2% by Elsharkawy MM et al [20,25,34]. Prevalence of refractive errors in study conducted by Alkhafaji ZNH et al was found significantly higher among SRNS cases, compared to SSNS (50% vs 18%)[24]. Present study found compound myopic astigmatism as most common (35%) refractive error, followed by astigmatism and myopia (Figure 4).This is similar to the finding reported by Jezeela K et al, Gheissari A et al (24%), Nakubulwa et al (31%), wherein myopic astigmatism was the most common refractive error[25,35,20].

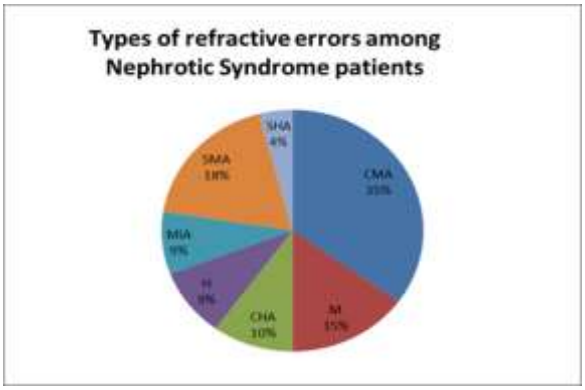

Figure 4 : The prevalence of various refractive errors in nephrotic syndrome patients.

Myopia (M),Compound myopic astigmatism(CMA), Simple myopic astigmatism(SMA), Hyperopia(H), Compound hyperopic astigmatism (CHA), Simple Hyperopic astigmatism(SHA), Mixed astigmatism(MiA)

Hypoalbuminemia and consequent fluid retention in nephrotic syndrome disrupt normal balance of

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electrolytes including sodium, potassium, chloride ions. This change in ionic milieu affects retinal ionic channels also. Changes in potassium channels and sodium-potassium-chloride cotransporter (NKCC) in retina can significantly interfere with refractive compensation to positive/negative defocus [36]. Such alterations may result in increased axial length causing myopia. It may be hypothesised that changes in biochemical composition in lens and/or vitreous fluid as a result of disease and/or therapy itself could influence determinants of refractive status of eye. Decreased colloid osmotic pressure in choroidal and retinal vasculature in NS patients facilitates interstitial fluid accumulation in choroid and retina. It results in oedema and thickening of choroid and retina [37].

As compared with the SSNS group, the patients with SRNS had a significantly increased prevalence of ocular hypertension [6 (31.58%) vs. 4 (5.26%)] and posterior subcapsular cataract [7 (36.84%) vs. 6 (7.89%)] respectively. Refractive errors were also significantly more common in the patients with SRNS, observed in 14 (73.68%) patients compared to 48 (63.16%) patients in the SSNS group. Figure 5 depicts overall prevalence of refractive errors among types of NS.

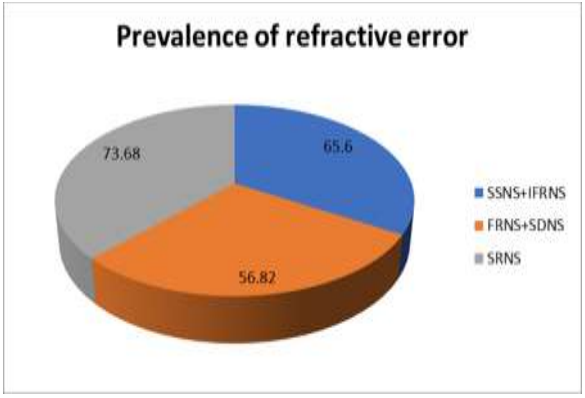

Figure 5: Prevelence of refractive errors among various types of nephrotic syndrome patients.

Steroid sensitive nephrotic syndrome (SSNS), Infrequently relapsing nephrotic syndrome (IFRNS),Frequently relapsing nephrotic syndrome (FRNS),Steroid dependent nephrotic syndrome (SDNS), Steroid resistant nephrotic syndrome (SRNS).

Patients with SRNS are more likely to receive intravenous pulse methyl-prednisolone before shifting to alternative treatment regimens. Hence their exposure to higher and prolonged doses of corticosteroids increases incidence and severity of ocular complications. Ozaltin F et al [38] had reported that ocular complications were observed in 27% of SRNS patients, while in patients with SSNS, most of the ocular manifestations were refractive errors while steroid-dependent complications were only 9%. Alkhafaji ZNH et al found that steroid-dependent ocular findings were significantly more common in SRNS group, where 28% had OHT and 20% developed PSC, as compared to 6.67% and 4% in SSNS group, respectively[24].

Conclusion

Our study found that ocular complications have increased prevalence among paediatric nephrotic syndrome cases with steroid resistance. Refractive error, followed by cataract is the most common ocular manifestation. Compound myopic astigmatism was the commonest refractive error noted. Early ophthalmic examination must be emphasised as a part of the routine follow-up of all children with nephrotic syndrome to detect ocular complications as early as possible.

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