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Original Article

Evaluation of Visual Acuity, Macular Thickness, and Level of Proteinuria in Children with Nephrotic Syndrome

Lam Mun-Wei[1,2,3], Mohd Yazid Aiman-Mardhiyyah[2,3], Abdul Aziz Hayati[1], Ilias Mohamad Ikram[4], Evelyn Li Min Tai[2,3], Ismail Shatriah[2,3]

[1]*Department of Ophthalmology, Sultanah Aminah Hospital, Johor, Malaysia*
[2]*Hospital Universiti Sains Malaysia, Kelantan, Malaysia*
[3]*Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia*
[4]*Department of Pediatrics, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Malaysia*

Purpose: Macular edema, serous retinal detachment, and retinal pigment epithelial detachment have been reported in patients with nephrotic syndrome. However, there is limited data about macular thickness in children with nephrotic syndrome. The aim of this study was to compare the mean macular thickness in children with nephrotic syndrome and in a control group and to correlate it with visual acuity and level of proteinuria.

Methods: The comparative cross-sectional study included 66 children aged 6 to 17 years with nephrotic syndrome and healthy control seen in two tertiary centers in Malaysia. We recorded demographic data, as well as visual acuity, level of proteinuria, and the mean macular thicknesses in both groups. The mean macular thickness was measured using Stratus optical coherence tomography according to nine areas of the Early Treatment Diabetic Retinopathy Study map.

Results: The mean foveal thickness was 238.15 ± 22.98 μm for children with nephrotic syndrome and 237.01 ± 22.60 μm for the control group. There was no significant difference in the mean macular thickness between the groups (p = 0.843). A significant correlation with visual acuity was observed in the superior outer macula (r = –0.41, p = 0.019), the nasal outer macula (r = –0.41, p = 0.019), and the inferior outer macula (r = –0.40, p = 0.021). There was no significant correlation between the mean macular thickness and level of proteinuria (p = 0.338), although those with higher levels of proteinuria demonstrated a trend towards increased macular thickness.

Conclusions: The mean macular thickness in children with nephrotic syndrome was similar to that of healthy children. A significant correlation between the mean thickness of the outer macular layer and the presenting visual acuity was observed. There was no correlation between the mean macular thickness and the level of proteinuria.

Key Words: Child, Macular thickness, Nephrotic syndrome, Proteinuria, Relapse, Visual acuity

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Corresponding Author: Ismail Shatriah, MD. Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian 16150, Malaysia. Tel: 60-9-767-6363, Fax: 60-9-765-3370, E-mail: shatriah@usm.my

Pediatric nephrotic syndrome is defined by the presence of nephrotic-range proteinuria, edema, hyperlipidemia, and hypoalbuminemia [1–5]. Children with nephrotic syndrome often require prolonged corticosteroids or immunosuppressive therapy. Visual threatening condition, namely

cataract-induced and steroid-induced glaucoma, are known to occur after long-term steroid therapy in children [6,7]. Neurosensorial retinal detachment and macular edema have been reported to cause acute visual loss in patients with nephrotic syndrome [8–12].

Recent studies have reported that children with nephrotic syndrome had a slight increase in macular thickness and reduction in retinal vessels density [13,14]. This has been attributed to the hypoalbuminemia induced fluid retention seen in this syndrome. However, the association of proteinuria with macular thickness has not been adequately investigated. Our study aims to add to the literature by comparing the mean macular thickness in children with nephrotic syndrome and healthy children and correlating it with visual acuity and proteinuria levels.

Materials and Methods

We conducted a comparative cross-sectional study of 66 children aged 6 to 17 years who attended the Ophthalmology and Pediatric Clinics at Hospital Universiti Sains Malaysia and Sultanah Aminah Hospital from May 2017 to April 2018. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Research and Ethical Committee of the School of Medical Sciences, Universiti Sains Malaysia (No. USM/JEPeM/16110498) and the Medical Research and Ethics Committee, Ministry of Health of Malaysia (No. NMRR-16-2233-33332). Written informed consent was obtained from all the parents or legal guardians, and verbal assent was given by the recruited children.

Nephrotic syndrome was diagnosed as a clinical syndrome of massive proteinuria characterized by presence of edema, proteinuria of >40 mg/m^2/hr (>1 g/m^2/day), or an early morning urine protein creatinine index of >200 mg/mmol (>3.5 mg/mg, hypoalbuminemia of <25g/L, hypercholesterolemia, urine albumin excretion >40 mg/m²/hr, or urine dipstick of ≥2+ for 3 consecutive days) [1,4].

All pediatric patients who were diagnosed with primary nephrotic syndrome and attended both centers were recruited based on the inclusion and exclusion criteria. The inclusion criteria for the group with nephrotic syndrome were patients diagnosed as having primary nephrotic syndrome in relapse undergoing treatment, refractive error (in spherical equivalent) within ±4.00 diopters, and clear ocular media. Inclusion criteria for the control group were healthy children, refractive error (in spherical equivalent) within ±4.00 diopters, and clear ocular media. Exclusion criteria for both groups were patients with established retinal and macular disease, congenital glaucoma, optic nerve disease, and ocular trauma.

Visual acuity was recorded in the logarithm of the minimum angle of resolution (logMAR) unit. A complete examination of anterior and posterior segments was performed for both groups. The following data was documented and analyzed: age, sex, duration of disease, number of relapses, presenting visual acuity, intraocular pressure (IOP), lens status, and proteinuria level.

The right eye was selected for measurement of macular thickness. The examinations were performed on children with nephrotic syndrome within 24 hours after confirmation of diagnosis and hospital admission by a pediatric nephrologist. Macular thickness measurements were taken using spectral domain optical coherence tomography using the Cirrus HD OCT (Carl Zeiss Meditec).

Macular image was taken based on macular map protocol according to the Early Treatment Diabetic Retinopathy Study. This consists of three concentric circles with diameters of 1 mm (central fovea), 3 mm (inner macula), and 6 mm (outer macula). There were nine subfields in these circles that included the central fovea, the superior inner

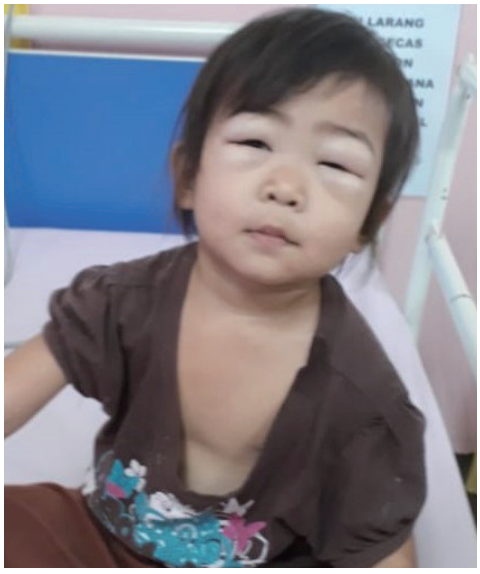

Fig. 1. A patient with acute relapse of nephrotic syndrome. The patient gave verbal assent and the patient's parent/legal guardian provided written informed consent for publication of the research details and clinical image.

macula, the inferior inner macula, the nasal inner macula, the temporal inner macula, the superior outer macula, the inferior outer macula, the nasal outer macula, and the temporal outer macula.

Data was analyzed using the IBM SPSS ver. 24.0 (IBM Corp). All continuous variables were described using mean ± standard deviation, whereas categorical data as frequency (%). Independent *t*-test analysis was used to compare mean macular thickness between children with nephrotic syndrome and the control group. A spearman correlation test was used to determine the correlation between mean macular thickness with visual acuity and level of proteinuria. A *p*-value less than 0.05 was considered statistically significant.

Results

Fig. 1 shows a patient with acute lapse. The present study showed the mean age of children with nephrotic syndrome was 10.55 ± 1.79 years old and that of the control was 10.20 ± 2.21 years old. The mean duration of disease was 3.21 ± 1.83 years. The mean number of relapses was 3.45 ± 1.06. Children diagnosed with nephrotic syndrome in relapse had a proteinuria level of 2+ (63.6%) and 3+ (36.4%). Of

Table 1. Demographic and clinical characteristics (n = 66)

Characteristic	Children with nephrotic syndrome (n = 33)	Control (n = 33)	*p*-value
Age (yr)	10.55 ± 1.79*	10.20 ± 2.21*	0.401†
6–10	19 (57.6)	18 (54.5)	0.463‡
11–17	14 (42.4)	15 (45.5)	
Sex			0.057‡
Male	23 (69.7)	22 (66.7)	
Female	10 (30.3)	11 (33.3)	
Duration of disease (yr)	3.21 ± 1.83*	-	-
1–3	19 (57.6)		
4–7	14 (42.4)		
No. of relapses (episodes)	3.45 ± 1.06*	-	-
2–3	16 (48.5)		
4–5	17 (51.5)		
Level of proteinuria		-	-
2+	21 (63.6)		
3+	12 (36.4)		
Hypertension		-	-
Yes	9 (27.3)		
No	24 (72.7)		
Hyperlipidemia		-	-
Yes	1 (3.0)		
No	32 (97.0)		
Medication		-	-
Corticosteroid	20 (60.6)		
Cyclosporine	5 (15.2)		
Corticosteroid and levamisole	4 (12.1)		
Corticosteroid and cyclosporine	4 (12.1)		

Values are presented as mean ± standard deviation or number (%).
*Statistically significant; †Independent *t*-test, equal variance not assumed; ‡Pearson chi-square test.

Table 2. Ocular profile (n = 66)

Variable	Children with nephrotic syndrome (n = 33)	Control (n = 33)	Mean difference (95% CI)	*t*-statistic (df)	*p*-value
Visual acuity (logMAR)	0.08 ± 0.12	0.03 ± 0.09*	0.47 (0.001–0.10)	2.01 (52.19)	0.049†
0–0.1	29 (87.8)	32 (96.9)			
0.2–0.3	2 (6.1)	1 (3.1)			
≥0.4	2 (6.1)	0 (0.0)			
Intraocular pressure (mmHg)	17.18 ± 1.76*	13.49 ± 2.10*	3.08 (2.12–4.07)	6.31 (61.10)	<0.001†
Cataract	7 (21.2)	0 (0)			

Values are presented as mean ± standard deviation or number (%).
CI = confidence interval; logMAR = logarithm of the minimum angle of resolution.
*Statistically significant; †A *p*-value of <0.05 was considered statistically significant based on independent *t*-test.

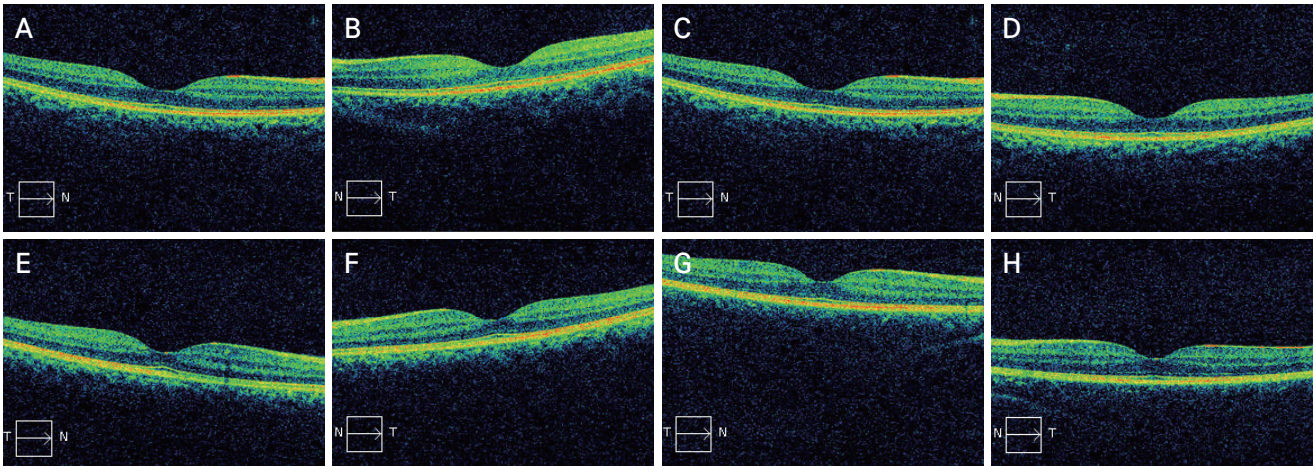

Fig. 2. Macular optical coherence tomography (OCT) in a healthy patient with visual acuity of (A) 0 logarithm of the minimum angle of resolution (logMAR) in the right eye (OD) and (B) 0 logMAR in the left eye (OS). Macular OCT in a patient with proteinuria 1+ and visual acuity of (C) 0 logMAR (OD) and (D) 0 logMAR (OS). Macular OCT in a patient with proteinuria 2+ and visual acuity of (E) 0 logMAR (OD) and (F) 0 logMAR (OS). Macular OCT in a patient with proteinuria 3+ and visual acuity of (G) 0 logMAR (OD) and (H) 0.1 logMAR (OS).

Table 3. Comparison of mean macular thickness

Macular thickness (μm)	Children with nephrotic syndrome	Control	Mean difference (95% CI)	*t*-statistic (df)	*p*-value*
Foveal thickness	238.15 ± 22.98	237.01 ± 22.60	1.12 (–10.11 to 12.35)	0.20	0.843
Temporal inner	306.91 ± 17.45	305.23 ± 18.46	1.62 (–7.20 to 10.48)	0.37	0.713
Superior inner	317.15 ± 17.81	315.71 ± 25.82	1.38 (–9.52 to 12.30)	0.26	0.799
Nasal inner	319.76 ± 18.55	318.37 ± 20.18	1.37 (–8.17 to 10.90)	0.28	0.774
Inferior inner	312.52 ± 18.76	311.63 ± 19.61	0.86 (–8.59 to 10.29)	0.18	0.858
Temporal outer	267.42 ± 17.88	267.43 ± 10.95	–0.04 (–7.36 to 7.29)	–0.01	0.992
Superior outer	285.76 ± 17.83	288.30 ± 12.71	–2.60 (–10.24 to 5.03)	–0.67	0.497
Nasal outer	300.52 ± 17.28	302.20 ± 14.41	–1.68 (–9.49 to 6.16)	–0.43	0.670
Inferior outer	271.39 ± 15.09	273.33 ± 12.10	–1.92 (–8.66 to 4.79)	–0.58	0.567
Average	282.48 ± 15.31	282.93 ± 10.96	–0.45 (–7.01 to 6.10)	–0.13	0.890

Values are presented as mean ± standard deviation.
CI = confidence interval.
*A *p*-value of <0.05 was considered statistically significant based on independent *t*-test.

the children with nephrotic syndrome, 27.3% had hypertension and 3.0% had hyperlipidemia. The majority of the children received corticosteroids only or a combination of corticosteroids and levamisole/cyclosporine. All data are illustrated in Table 1.

The mean visual acuity was 0.08 ± 0.12 logMAR in children with nephrotic syndrome, and 0.03 ± 0.09 logMAR in the control group. There was a significant difference in mean visual acuity and IOP between children with nephrotic syndrome and control group (p = 0.049 and p < 0.001, respectively). Posterior subcapsular cataract were documented in 21.2% of the children with nephrotic syndrome. The above data are presented in Table 2. No cases of serous retinal detachment, macular edema, or retinal pigment epithelial detachment were documented.

Fig. 2A–2H shows the macular OCT in a healthy patient and patient with proteinuria. Table 3 presents the mean macular thickness of both groups. There was no statistically significant difference between the mean macular thickness in the children with nephrotic syndrome and control in all subfields of macular region (p = 0.890). There was a significant correlation between visual acuity and mean macular thickness in the superior outer macula (r = –0.41, p = 0.019), the nasal outer macula (r = –0.41, p = 0.019) and the inferior outer macula (r = –0.40, p = 0.021).

The correlation between the mean macular thickness and visual acuity is shown in Table 4. Two of our patients with visually significant cataracts were not included in this analysis. There was a trend of thicker mean macular thickness in children with proteinuria 3+ compared to proteinuria 2+. However, there was no statistically significant difference in any subfields of macular areas between children with different level of proteinuria (p > 0.05). The data is presented in Table 5.

Table 4. Correlation between mean macular thickness and visual acuity (adjusted)

Macular thickness (μm)	Visual acuity (logMAR)	
	r	p-value
Foveal thickness	–0.31	0.075
Temporal inner macula	–0.16	0.377
Superior inner macula	–0.16	0.362
Nasal inner macula	–0.19	0.285
Inferior inner macula	–0.09	0.622
Temporal outer macula	–0.23	0.193
Superior outer macula	–0.41	0.019*
Nasal outer macula	–0.41	0.019*
Inferior outer macula	–0.40	0.021*

logMAR = logarithm of the minimum angle of resolution.
*A p-value of <0.05 was considered statistically significant based on spearman correlation test.

Discussion

The published literature is confined to clinical pictures of children with nephrotic syndrome [7,15,16]. All children received corticosteroids for more than 1 year during their

Table 5. Comparison of mean macular thickness with the level of proteinuria

Macular thickness (μm)	Proteinuria 2+	Proteinuria 3+	Mean difference (95% CI)	t-statistic (df)	p-value*
Foveal thickness	237.62 ± 25.93	239.08 ± 17.66	–1.46 (–18.68 to 15.76)	–0.17	0.863
Superior inner	314.86 ± 18.05	321.17 ± 17.39	–6.31 (–19.46 to 6.84)	–0.98	0.335
Inferior inner	310.86 ± 20.32	315.42 ± 16.07	–4.56 (–18.53 to 9.41)	–0.67	0.510
Temporal inner	305.57 ± 18.47	309.25 ± 15.99	–3.68 (–16.69 to 9.34)	–0.58	0.568
Nasal inner	318.52 ± 18.14	321.92 ± 19.87	–3.39 (–17.24 to 10.46)	–0.50	0.621
Superior outer	282.86 ± 18.63	290.83 ± 15.79	–7.98 (–21.02 to 5.07)	–1.25	0.222
Inferior outer	270.48 ± 14.41	273.00 ± 16.76	–2.52 (–13.80 to 8.76)	–0.46	0.651
Temporal outer	265.71 ± 17.44	270.42 ± 19.02	–4.70 (–18.00 to 8.60)	–0.72	0.476
Nasal outer	298.95 ± 16.22	303.25 ± 19.44	–4.30 (–17.16 to 8.57)	–0.68	0.501
Average	280.52 ± 15.75	285.92 ± 14.49	–5.39 (–16.70 to 5.91)	–0.98	0.338

Values are presented as mean ± standard deviation.
CI = confidence interval.
*A p-value of <0.05 was considered statistically significant based on independent t-test.

illness, and 84.8% of them were on corticosteroids during data collection. Cataracts were observed in 21.2% in our study. Two of our patients had visually significant cataracts, and the resulting visual acuity was worse than 0.4 (based on logMAR). The remaining patients had visual acuity ranging from 0 to 0.3 logMAR. In our study, children with nephrotic syndrome had significantly higher IOP compared to the control group, although the levels were still within normal range. This strongly suggests that regular monitoring is mandatory, even though visual field assessments would be challenging in children.

We observed no significant difference in the mean macular thickness ($p > 0.50$) between children with nephrotic syndrome and the control group. Beside those with visually significant cataracts, none of our patients had visual symptoms or had signs of macular edema or serous retinal detachment during clinical examination. We postulate that this was probably due to prompt treatment with diuretics after admission to the wards. De Benedetto et al. [8] and Izzedine et al. [10] reported that their patients with nephrotic syndrome who developed macular edema sustained a complete resolution and restoration of normal retinal anatomy after being treated with diuretic therapy.

Corticosteroids, which form the mainstay of treatment in nephrotic syndrome, also play a very important role in determining macular thickness. Systemic corticosteroids inhibit formation of both prostaglandins and leukotrienes, which confer local vasoconstrictive properties in the retinal layer. These vasoconstrictive properties lead to a reduction in intracellular and extracellular edema, and thus decreasing in sequestration of fluids into the interstitial space. Therefore, for nephrotic syndrome in relapse the combination of systemic corticosteroids and diuretic therapy in treatment has a synergistic effect in the rapid reduction of interstitial systemic fluids. In addition, macular edema in nephrotic syndrome might not manifest clinically because the anatomical and functional integrity of endothelium and blood-retinal barrier are relatively intact in children [17,18].

In contrast to our findings, Zhang et al. [13] reported slightly different data. They observed a significantly thicker macular layer in children with nephrotic syndrome and hypoalbuminemia. Zhang et al. [13], therefore, presumed that the above phenomenon could be related to the retention of liquid in the retina and choroid due to hypoproteinemia. This can be is explained by increased choroidal interstitial fluid, resulting in a decrease in colloid osmotic pressure in patients with nephrotic syndrome and hypoalbuminemia. The pressure difference between the choroid and retina may lead to reduced flow of fluid from the retina to the choroidal layer, culminating accumulation in the retina and subretinal region [13]. In our study, however, we found no significant difference in macular thickness between children with proteinuria and the controls. We postulate that proteinuria may not be a strong parameter that affects the mean macular thickness in children with nephrotic syndrome. However, more studies may shed further light on the relationship between nephrotic syndrome and macular thickness.

We observed that the mean thickness of the outer macula layers was significant correlated with visual acuity in children with nephrotic syndrome ($p < 0.05$). This may reflect the normal profile of the ganglion cell-inner plexiform layer (GCIPL) thickness as described by Mwanza et al. [19]: the GCIPL of the superior hemisphere of macula was thicker than the inferior hemisphere, and the nasal sector of GCIPL was significantly thicker than the temporal area of the macula. In healthy Asian adults, increased macular and GCIPL thickness have been associated with better visual acuity and visual function [20].

The strength of our study is its evaluation of macular thickness changes associated with proteinuria in a population free of systemic disease which might affect retinal thickness measurements. However, children with nephrotic syndrome often experience multiple relapses and remissions, which may be associated with subclinical macular edema and may result in chronic changes in retinal thicknesses, thus confounding measurements. In addition, we cannot exclude the possibility that varying responses to corticosteroids in prospective studies evaluating these changes over time and the effect of the various pharmacological therapies in this disease may improve our understanding of these processes.

In conclusion, the mean macular thickness was similar in children with nephrotic syndrome and control group. There was a correlation between outer macular layer thickness and mean visual acuity. Mean macular thickness has no correlation with the level of proteinuria.

Conflicts of Interest: None.
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