Ann Med Res 2020;27(6):1542-8

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.01.066

Original Article

Evaluation of macular thickness and retinal nerve fiber layer thickness in pediatric patients with malnutrition

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Abstract

Aim: To evaluate macular thickness and retinal nerve fiber layer thickness in pediatric patients with primary malnutrition.
Material and Methods: Macular and peripapillary retinal nerve fiber layer thicknesses of 90 pediatric patients with primary malnutrition were measured by spectral field optical coherence tomography. These findings were compared with the data of 50 age-matched healthy children.
Results: There were no statistically significant differences in terms of age, gender and refractive status between the groups. In the primary malnutrition group, 17 of 90 patients had decreased retinal nerve fiber layer values. There were no patients with decreased retinal nerve fiber layer values in the control group and this difference was statistically significant (p <0.001). Retinal nerve fiber layer was thinner in the patients with primary malnutrition with low serum vitamin D and ferritin levels. (p=0.025, p<0.001, respectively) We found that as the severity of malnutrition increased according to weight and height, the thinning of the peripapillary retinal nerve fiber layer increased, especially in the temporal segment. (r: -0.249 p=:0.003, r: -0.251 p=0.002, respectively).
Conclusion: Undernutrition with micronutrient deficiencies may cause retinal nerve fiber layer thinning in pediatric cases. Therefore, it should be treated early before vision defects occur.

Keywords: Child; malnutrition; optic nerve; retina

INTRODUCTION

Malnutrition is the inability of the body to receive the necessary amount of nutrients to maintain healthy tissues and organ functions (1). It covers both obesity and undernutrition as a term. Undernutrition can be manifested as stunting (low height-for-age), wasting (low weight-for- height), underweight (low weight-for-age) and micronutrient deficiencies or insufficiencies (a lack of important vitamins and minerals) (2). Malnutrition in pediatric cases is still one of the global health problems affecting more than 200 million of cases in the world. In 2010, nearly 171 million children were stunted which represents chronic malnutrition (3). Mortality rates associated to malnutrition remain high and morbidities related to malnutrition bring a big health burden in especially developing countries (4). Micronutrient deficiencies seen in malnutrition such as iron deficiency, vitamin A, D and iodine deficiencies are important public health problems which lead to detriment in health, education and productivity.

Neurological impairment is one of the most important outcomes of malnutrition (5). Undernourishment during vulnerable period that is from prenatal days to the end of second decade interrupts neurogenesis which ends up with neurodevelopmental delay (6). Low intake of micronutrients which are essential for neurogenesis is an important contributing factor to this impairment (7). Previous studies demonstrated that iron is one of the most important micronutrients for neurologic development (8). Algarin et al. (9) reported infants with iron-deficiency anemia had long lasting auditory and visual system dysfunctions due to defective myelination.

Visual ability is also disturbed in malnutrition states (10). Damages in retinal optic fibers and lens were seen in rats which underwent protein malnutrition (11). In another study topographical distribution was altered and retinal surface was diminished in malnourished rats (12). Importance of micronutrients for retinal health is well established with age related eye disease studies (13). Vitamin D insufficiency and iron deficiency were found to

Received: 25.01.2020 **Accepted:** 11.05.2020 **Available online:** 09.06.2020
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be associated with macular thickness or retinal nerve fiber layer thickness in previous studies.

In this regard we designed this study to evaluate whether macular thickness and retinal nerve fiber layer thickness were affected in pediatric patients who were undernourished due to low intake. As far as we know, our study is the first study to examine possible macular and optic nerve disorders that may lead to long-term visual impairment in pediatric patients with malnutrition.

MATERIAL and METHODS

The procedures followed in this study comply with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 2000. This study was approved by the Ethics Committee of the Scientific Research Ethics Committee of Kahramanmaraş Sütcü İmam University. (Approval number-54 / 11-14.02.2018). The study is an observational cross-sectional study performed between February 2018 and December 2018 in the ophthalmology and pediatric gastroenterology, hepatology and nutrition departments of Necip Fazıl City Hospital. Participation in the study was voluntary and written informed consent was obtained from the parents as well as the participants.

Group selection

The group with primary malnutrition: A total of 90 pediatric patients with primary malnutrition due to insufficient intake were randomly selected among the patients admitted to the department of pediatric gastroenterology, hepatology and nutrition.

Determination of the group with malnutrition

All patients participating in the study were measured using a calibrated vertical portable stadiummeter without socks and shoes. Digital electronic weighing scale was used for weight measurement. The cases were measured in light clothes. World Health Organization (WHO) data were used to measure height Z score, weight Z score, weight-for-height (WFH) Z score, and body mass index (BMI) Z score. Patients with a Z score below -2 in any of these parameters were considered as malnourished. Malnutrition severity was classified as follows (14).

Moderate underweight: Weight-for-age Z-score ≥−3 SDS to <−2 SDS

Severe underweight: Weight-for-age Z-score <−3 SDS

Normal: Weight-for-age Z-score >−2 SDS

Moderate stunting: Height-for-age Z-score ≥−3 SDS to <−2 SDS

Severe stunting: Height-for-age Z-score ≥−3 SDS

Normal: Height-for-age Z-score >−2 SDS

Control group

Fifty healthy children who participated in the ophthalmology department with nonspecific ocular complaints were randomly selected the control group.

Exclusion criteria

• Patients under the age of 6 and over 18 years were excluded (Patients between 6-18 yers of age were selected)

• Premature delivery, intrauterine growth retardation, celiac disease, cystic fibrosis, heart failure, chronic renal failure, cerebral palsy, Down's syndrome, chronic diarrhea, secondary malabsorption due to intestinal surgery, inflammatory bowel disease, patients who could have secondary malnutrition were excluded.

• Children who were wearing glasses for any reason or who had any previously known eye disease were not included in the study.

Laboratory evaluation

Patients were monitored for concurrent vitamin B12, folic acid, ferritin, vitamin D levels. Serum ferritin, vitamin B12, vitamin D and folate levels were measured with Cobas E601 (Roche Diagnostics, Mannheim, Germany) using electrochemiluminescence method. Vitamin D levels; <20 ng/ml were accepted as deficient, 21-29 ng/ml were insufficient and levels ≥30 ng/ml were accepted as normal (15). Levels of ferritin <30 ng / mL (16), vitamin B12 <300 pg/mL (17) and folate <4 ng/mL (18) were accepted as deficient.

Ophthalmologic Examination

The person performing the ophthalmological evaluation did not know of the child's nutritional status. All of the cases underwent a detailed ophthalmologic examination including best corrected visual acuity assessment, slit lamp biomicroscopy, fundus examination with 90 D lens, ocular motility testing. Refractive errors were measured with an auto-refractometer device (Canon RK-F1) after adequate cycloplegy with 1% cyclopentolate hydrochloride drops (cycloplegin R; Abdi İbrahim İlaç Sanayii İstanbul-Turkey). Intraocular pressure assessment was made by using air-puff tonometer (Tonopachy™ NT-530P NIDEK). Subjects who had refractive errors lower than ±1 D, introocular pressure lower than 20 mmHG were included. Subjects with retinal diseases, optic nerve pathologies or positive history of previous ocular surgery and incooperative subjects for optical coherence tomography (OCT) measurements were excluded. A spectral domain OCT device (Spectralis, Heidelberg Engineering, Germany software version of 6.3.4) was used for macular thickness and peripapillary retinal nerve fiber layer (RNFL) measurements by a single trained technician. For macular thickness measurement thickness map protocol was used and mean thicknesses from central circle with 1mm diameter and superior, inferior, nasal, temporal quadrants of outer circles with 3 mm (paracentral region) and 6 mm diameter (pericentral region) were obtained. Mean retinal nerve fiber measurements were obtained from superonasal (NS), superotemporal (TS), nasal (N), temporal (T), inferonasal (NI) and inferotemporal (TI) quadrants of the 3,5 mm diameter circle around the optic disc. Measurements from the right eyes were analysed.

The malnutrition group values and the control group values were compared.

Statistical analysis

The data were statistically analyzed with Statistical Package for the Social Sciences for Windows 22.0 (SPSS Inc, Chicago). The continuous variables were reported as the mean ± standard deviation whereas the categorical variables were defined as percentages. The data were tested for normal distribution using Kolmogorov–Smirnov test. Student's t-test, a one-way analysis of variance test or a Kruskal–Wallis test was used, as appropriate, to compare the continuous variables. Logistic regression analysis was performed to show the relationship between one dependent variable and one or more independent variables. We used the Pearson correlation test to measure the statistical relationship between two continuous variables. A chi-squared test was used to compare the categorical variables. Statistical significance was defined as p<0.05.

RESULTS

Clinical and demographic properties of the two group was summarized in Table 1. There were no statistically significant differences in terms of age, gender and refractive status between the groups. Weight, height, BMI, WFH Z score values in the malnutrition group were significantly lower than the control group (p<0.001).

Table 1. Demographic and clinical properties of the patients

	Malnutrition (90)	Control (55)	P
Age	11.41±3.51	11.1636±2.67	0.647
Sex			
Female	53 (%58.9)	26 (%47.3)	**0.173 α**
Male	37 (%41.1)	29 (%52.7)	
Weight Z score	-2.61±0.61	0.35±0.95	<0.001
Height Z score	-1.82±1.11	0.10±1.04	<0.001
WFH Z score	-1.07±0.83	0.33±0.91	<0.001
BMI Z score	-2.25±1.06	0.31±0.98	<0.001
Patients with RNFL abnormality	17(%18.9)	0	**<0.001α**

Statistic: Independent Student T test, α=Crosstabs-Chi-Square
RNFL: Retinal Nerve Fiber Layer; WFH: Weight-For-Height Z score, BMI: Body Mass Index Z score

The macular thickness evaluations in central region, all quadrants of paracentral and pericentral regions revealed no significant change between the two groups. The right eye mean central macular thickness was 266.31 microns in the malnutrition group and it was 266.43 microns in the control group (p=0.976). We evaluated the mean periapillary RNFL thicknesses in the 6 quadrants. There was statistically significant decrease in the T region in malnourished patients compared to the control group (p=0.047). These findings are summarized in Table 2.

Retinal nerve fiber layer analysis revealed that there were 17 out of 90 patients (%18.8) of the malnutrition group who had one or more segments with borderline RNFL values or segments with outside normal limits according to the OCT device data base. There were no patients with the abnormal RNFL values in the control group and this difference was statistically significant (p<0.001). The T, TI and TS segment RNFL values and global RNFL values were decreased in abnormal RNFL group significantly (p=0.002, p<0.001, p<0.001, p<0.001, respectively). The cases in the abnormal RNFL group also had minimal decreament in macular thickness measurements. This decreament was nearly significant in the perinasal segment (p=0.05) (Table 3).

Table 2. Mean central macular thickness and RNFL thickness values of the patients for right eye

	Malnutrition	Control	P
Central MT	266.31±27.25	266.43±19.13	0.976
Global RNFL	103.52±9.21	104.11±8.35	0.701
NS RNFL	111.27±19.86	111.53±18.18	0.938
TS RNFL	148.56±17.11	148.11±19.83	0.149
T RNFL	74.76±9.21	79.03±11.07	0.047
N RNFL	78.17±15.91	75.35±15.52	0.300
NI RNFL	118.30±21.00	114.92±22.40	0.364
TI RNFL	148.36±18.99	149.66±17.28	0.682

Statistic: İndependent Student T test
MT: Mean Central Macular Thickness; RNFL: Retinal Nerve Fiber Layer; NS: superonasal; TS: Superotemporal; N: Nasal; T: Temporal; NI: Inferonasal; TI: Inferotemporal

Table 3. Perinasal macular and RNFL thickness values of malnourished patients for right eye with and without RNFL abnormality

	Abnormal RNFL Group (17)	Normal RNFL Group (73)	P
Perinasal MT	314.47±17.69	324.78±19.62	0.050
Global RNFL	96.35±7.02	105.19±8.89	<0.001
NS	103.70±23.85	113.04±18.56	0.081
TS	130.17±13.20	146.68±16.46	<0.001
T	68.70±11.94	76.17±7.90	0.002
N	74.76±16.37	78.97±15.81	0.329
Nİ	115.76±28.66	118.89±19.00	0.583
Tİ	132±21.16	152.1±16.38	<0.001

Statistic: İndependent student T test
MT: Mean Central Macular Thickness; RNFL: Retinal nerve fiber layer; NS: Superonasal; TS: Superotemporal; N: Nasal ; T: Temporal; NI: Inferonasal; TI: Inferotemporal

Table 4. Evaluation of peripapillary RNFL findings of patients according to malnutrition severity

	Weight-for-age Z-score			
	Normal	Moderate underweight	Severe underweight	P
Global RNFL	104.41±3.46	102.79±8.81	105.10±11.29	0.461
NS	111.66±17.75	110.86±18.17	112.30±26.30	0.949
TS	148.25±19.74	143.57±16.24	142.70±20.10	0.292
T	**78.73±10.64 α**	75.01±8.35	**71.65±8.35 β**	0.011
N	75.06±15.53	77.08±15.43	83.00±16.89	0.154
Nİ	115.12±21.99	116.07±21.85	125.65±17.64	0.151
Tİ	150.94±17.13	146.97±17.18	149.4±24.68	0.483

One Way ANOVA β value was significantly lower than α value.
There was negative correlation between T value and weight SDS (r:-0.249, P=:0.003)

	Height-for-age Z-score			
	Normal	Moderate stunting	Severe stunting	P
Global RNFL	103.87±8.28	104±10.47	101±9.45	0.669
NS	110.93±17.08	114.60±23.38	102.87±23.64	0.273
TS	145.71±17.73	146.20±19.52	135.62±18.55	0.306
T	**77.49±9.63 α**	73.22±9.10	**69.12±11.48 β**	0.010
N	76.06±15.34	79.22±17.39	81.12±13.98	0.455
Nİ	114.24±19.72	123.40±25.30	124.37±20.55	0.057
Tİ	151.34±17.04	142.88±21.01	143.50±16.20	0.042

One Way ANOVA β value was significantly lower than α value.
There was negative correlation between T value and height SDS. (r:-0.251, P=0.002)
RNFL: Retinal Nerve Fiber Layer; NS: Superonasal; TS: Superotemporal; N: Nasal ; T: Temporal; NI: Inferonasal; TI: Inferotemporal

We evaluated the relation between the severity of malnutrition and the RNFL thickness and we saw that the temporal peripapillary RNFL thickness were significantly decreased in severe underweight patients according to weight-for-age Z-score (p=0.011). There was a significant weak negative correlation between the temporal RNFL thickness and the severity of malnutrition (weight-for-age Z-score) (r: -0.249, p=0.003) (Table 4).

The T and TI RNFL values were significantly reduced in severely stunted cases according to the height-for-age Z score (p=0.010, p=0.042, respectively). There was a significant weak negative correlation between the severity of malnutrition (according to height-for-age Z score) and temporal RNFL (r: -0.251, p=0.002) (Table 4).

Ferritin and vitamin D levels were analysed only in the cases with malnutrition. So comparison between the cases with malnutrition and the control group could not be made. However we compared the ferritin and the vitamin D levels between the abnormal RNFL group and the normal RNFL group and detected significant decrease in both ferritin and vitamin D levels in the abnormal RNFL group (p=0.025, p<0.001, respectively). Similarly anemia, vitamin D deficiency, iron deficiency incidences was significantly higher in the abnormal RNFL group.

Table 5. Clinical and laboratory findings of malnourished patients with and without RNFL abnormality

	With RNFL abnormality (17)	Without RNFL abnormality (73)	P
Weight Z score	-2.72±0.88	-2.58±0.53	0.379
Height Z score	-2.49±1.11	-1.66±1.05	**0.005***
WFH Z score	-0.73±0.75	-1.15±0.82	0.055
BMI Z score	-1.87±0.68	-2.34±1.11	0.100
Vitamin D (ng/mL)	13.09±6.58	18.88±9.97	0.025
Ferritin (ng/mL)	22.03±9.90	40.56±30.50	**<0.001***
Folate (ng/mL)	9.63±3.89	8.96±3.36	0.472
Vitamin B12 (pg/mL)	408.64±212.66	384.91±163.29	0.612
Anemia	8(%47)	16(%22.2)	**0.038****
Vitamin D deficiency	14 (%82.4)	38 (%52.1)	**0.048****
Folate deficiency	0	3 (%4.1)	0.395
Vitamin B12 deficiency	3 (%17.6)	4 (%5.5)	0.092
Iron deficiency	13 (%76.5)	26 (%36.1)	**0.003****

*Independent student T test
**Crosstab-Chisquare
RNFL: Retinal Nerve Fiber Layer; WFH :Weight-For-Height Z score, BMI: Body Mass Index Z score

Vitamin B12 and folate levels and the incidences of vitamin B12 deficiency or folate deficiency did not differ significantly between the two groups. When we compared anthropometric measures between the two groups height Z score values were lower in the abnormal RNFL group (Table 5). Correlation analysis between the RNFL thickness and the levels of vitamin and minerals revealed positive correlation between the ferritin level and the global RNFL, T, TI, T, TS, NS RNFL thickness measurements (r: 0.307 p=0.004, r:0.252 p:0.018, r:0.273 p=0.010, r:0.226 p=0.034, r:0.239 p=0.025, respectively).

DISCUSSION

We observed no significant difference between the groups according to the mean central macular thickness values however mean RNFL measurements in the T-segment showed significant difference between the malnutrition group and healthy cases (p=0.047). There are not any previous studies related to macular or RNFL thickness of pediatric malnutritional cases in the literature. However previous studies concerning obese pediatric cases suggested decreased RNFL values in obese cases compared to the healthy ones (19,20). Another study reported a statistically insignificant decrease in the RNFL values of obese children. However, both studies suggest a negative correlation between the BMI Z score and the RNFL (21). Compared to the healthy cases, adult patients with anorexia nervosa had statistically significant decrease in the macular thickness and the retinal nerve fiber layer thickness in a previous study (22). The disease duration was 10.4±8.4 years in this study and there were negative correlation of these findings with the duration of the disease and the BMI. In our study the cases with abnormal RNFL had lower height Z score compared to the other malnourished cases. We found a negative correlation between the low height Z score, which is a chronic malnutrition indicator (23), and RNFL thickness (temporal region). This finding supports an inverse relationship between chronic malnutrition and especially the temporal region of RNFL.

Iron deficiency affects retinal structures and optic nerve in different ways. The most important one is hypoxia induced by decreased hemoglobin levels. Hypoxia causes ganglion cell loss through various mediators (24). Even in mild systemic hypoxia states pattern electroretinogram changes were detected due to decreased function of ganglion cells (25). Iron has a role in optic nerve myelination by involving in the oligodendrocyte functioning (26). There was persistant change in optic nerve morphology in iron deficient rats (27). In addition, nutritional iron-deficiency was reported to down-regulate dopaminergic activity (28). Dopamine is involved in the organization of the ganglion cell and the bipolar cell receptive fields and modulates physiological activity of photoreceptors (29). In our study we observed that iron deficiency was more common in the malnourished cases whose RNFL measurements were significantly thinner. In addition a positive correlation between ferritin level and global, T, TI, T, TS, NS RNFL thickness was observed. In a previous study RNFL of 40 children with iron deficiency anemia (IDA) were compared with those of healthy children and it was observed that average RNFL, superior and inferior quadrants of peripapillary RNFL values were significantly decreased in the anemic group (30). Another study which compared peripapillary RNFL thickness in children with thalassemia major(TH-M), IDA and healthy subjects revealed that RNFL was attenuated in all quadrants in patients with TH-M and it was only attenuated in inferior quadrant in cases with IDA (31).

In this study we also found out that vitamin D deficiency was significantly more common in malnourished cases with abnormal RNFL measurements. Vitamin D not only has a role in bone metabolism but also has neuroprotective, anti-inflammatory and anti-angiogenic functions which are mediated by vitamin D receptors found in neurons, glial cells and endothelial cells (32,33). There are also target cells in retina including bipolar cells, horizontal cells, amacrine cells and in addition ganglion cells (34). It was suggested that vitamin D may have a role in membrane calcium transport in these cells. In a previous study vitamin D deficiency in older patients was associated with reduced mean ganglion cell complex thickness without any significant change in RNFL thickness and it was suggested that this finding might represent an early stage of optic nerve damage, prior to RNFL loss (35). A supportive study by Graffe A et al showed reduced macular thickness without patent macular dysfunction in older patients with vitamin D deficiency (36). We detected 10.31 µm decreament in perinasal quadrant of the macula of the malnourished cases with the thinner RNFL. This location was in parallel with the thinner RNFL quadrants of the peripapillary region that were temporal, inferotemporal and superotemporal ones. Both studies were conducted with the older participants at mean age of 71.1±4.7 years and 71.2 ± 5.0. There are not any studies in pediatric age group to compare our results.

CONCLUSION

Small number of cases and absence of vitamin and element levels in control group were limitations of our study. However, it is noteworthy that our study was the largest OCT study which showed retinal properties in the pediatric patients with malnutrition.

In conclusion, our study revealed that the RNFL thickness in temporal region was negatively correlated with the severity of the malnutrition and in addition it was decreased in pediatric patients with malnutrition who had lower height Z score, vitamin D and iron deficiency. This is important for early procurement of macronutrients and micronutrients in these cases before any visual disturbances occur.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Ethics Committee of the Scientific Research Ethics Committee of Kahramanmaras Sutcu Imam University. (approval number-54 / 11-14.02.2018).

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