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Retinal nerve fiber layer thickness and retinal vessel calibers in children with thalassemia minor

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Abstract

Objectives: Evaluation of the peripapillary retinal nerve fiber layer thickness, subfoveal choroidal thickness, and retinal vessel caliber measurements in children with thalassemia minor.

Methods: In this cross-sectional and comparative study, 30 thalassemia minor patients and 36 controls were included. Heidelberg spectral domain optical coherence tomography was used for peripapillary retinal nerve fiber layer thickness, subfoveal choroidal thickness, and retinal vessel caliber measurements.

Results: There was no statistically significant difference in retinal nerve fiber layer thickness and subfoveal choroidal thickness between the two groups ($p > 0.05$). There was no correlation between retinal nerve fiber layer thickness and hemoglobin values. Both the arterioral and venular calibers were higher in thalassemia minor group ($p < 0.05$).

Conclusion: There is increased retinal arterioral and venular calibers in children with thalassemia minor compared with controls.

Keywords

Thalassemia minor, nerve fiber, retinal vessel caliber, choroidal thickness

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Introduction

Beta-Thalassemias are a group of inherited hematological disorders most commonly seen in Mediterranean countries. The nature of mutation in the hemoglobin (Hb) beta-gene on chromosome 11 determines the severity of beta-thalassemia phenotypes ranging from severe anemia to asymptomatic individuals.[1,2] While beta-thalassemia major (th-major) occurs with severe anemia requiring regular blood transfusion in the first year of life, beta-thalassemia minor (th-minor) or carrier form of disease appears with a mild anemia not requiring transfusion.[2]

Retinal nerve fiber layer (RNFL) is formed by the expansion of the fibers of the optic nerve and mainly supplied by central retinal artery.[3] Choroid consists of a vascular structure and provides oxygen and nutrients to the outer parts of the retina.[4] Retinal vasculature can be directly visualized and may be affected in many conditions such as systemic hypertension, diabetes mellitus, or hypoxia.[5] Recent studies have shown that th-major and iron deficiency anemia (IDA) could decrease RNFL thickness.[6,7] There is a mild anemia in patients with th-minor that may cause chronic hypoxia.[1] Diseases resulting in hypoxia may affect RNFL.[6,8] Also, hypoxia may influence retinal and choroidal circulation.[9] To our knowledge, there are no data about the possible effects of th-minor on posterior pole structures of the eye. Therefore, this study was aimed at investigating RNFL thickness, choroidal thickness, and retinal vascular calibers in children with th-minor.

Methods

This cross-sectional and comparative study was approved by ethics committee of our university and adhered to the tenets

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of the Declaration of Helsinki. The study was conducted in the Department of Ophthalmology and the Department of Pediatric Hematology and Thalassemia Center. All participants provided informed consent by their legally authorized representatives (i.e. parents) to participate in the study.

Study population

The participants were 30 th-minor patients and 36 controls. Hematologic parameters including Hb, red blood cell indices, serum iron, iron binding capacity, and serum ferritin were measured. Th-minor diagnosis was established by the presence of hypochromic-microcytic anemia in complete blood count with Hb A_2 levels above 3.5%. One random eye from each participant was included in the study for the comparison of the parameters between the two groups. The exclusion criteria were having any ocular disease except for mild refractive errors, previous ocular inflammation or surgery, and any systemic diseases other than th-minor. The subjects had refractive errors lower than 2 diopters (D).

Examination techniques

All patients underwent detailed ophthalmic examination including evaluation of visual acuity, pupillary function, color vision, ocular motility, as well as anterior and posterior segment evaluations. All measurements were performed with the Heidelberg spectral domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Dossenheim, Germany) by two experienced observers (H.Ö. and H.A.) at the same visit. The observers were masked to participants. The peripapillary RNFL thickness was evaluated in four sectors including superior, inferior, temporal, and nasal. Subfoveal choroidal thickness (SFCT) was measured by manually from the outer border of the retinal pigment epithelium to the inner scleral border at the subfoveal region with enhanced depth imaging (EDI).[9] Only images ⩾25 dB were indicated by a blue quality bar accepted for analysis.

Retinal vessel caliber (RVC) was measured manually on the enhanced depth macular analysis screen of SD-OCT. The largest three retinal arterioles and three retinal venules passing through an area one-half to one-disc diameter from the optic disc margin were measured for RVC analysis (Figure 1).[10] The mean thickness of these arterioles and venules was recorded for each participant.

Statistical analysis

Statistical analysis was performed by SPSS statistical software 21.0 (SPSS Inc., Chicago, IL, USA). Independent samples t-test, chi-square, and Pearson's and partial correlation were used for statistical analysis. Descriptive statistics were stated as mean ± standard deviation (SD). A value of $p < 0.05$ has been accepted as significant. According to the formula proposed by Hulley et al.,[11] we calculated sample size as

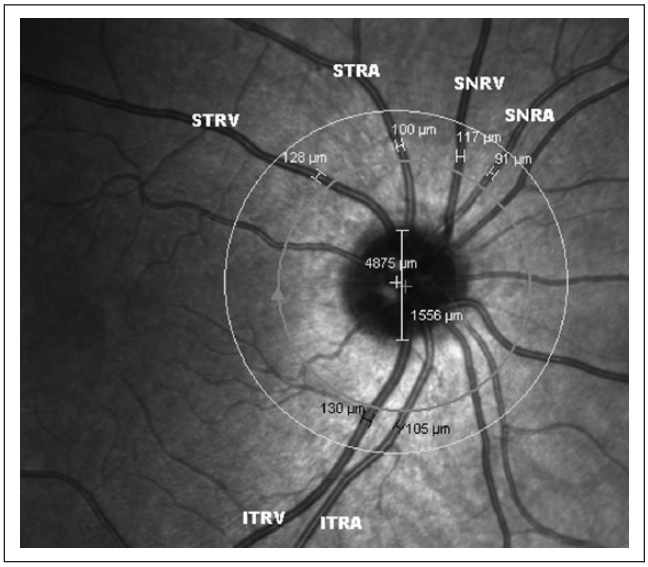

Figure 1. The method for retinal vessel caliber measurement is shown.
STRA: superior temporal retinal arteriole; ITRA: inferior temporal retinal arteriole; SNRA: superior nasal retinal arteriole; STRV: superior temporal retinal venule; ITRV: inferior temporal retinal venule; SNRV: superior nasal retinal venule.

60.09 subjects including both study and control groups by taking α (two-tailed) = 0.050, β = 0.80, q1 = 0.45 (proportion of subjects that are in Group 1), effect size = 0.580, and SD of the outcome in the population = 2.01.

Results

The mean age was 10.58 ± 4.24 (4–17) years in the th-minor group and 10.94 ± 3.65 (7–16) years in the control group ($p = 0.70$). There were 18 females and 12 males in th-minor group, and 21 females and 15 males in the control group ($p = 0.93$). Clinical characteristics of the groups are given in Table 1. Except mild refractive errors, there was no ocular problem in either groups. The difference in Hb level between the two groups was statistically significant ($p < 0.05$). There was no statistically significant difference in serum iron level, iron binding capacity, and ferritin level between the two groups ($p > 0.05$).

The peripapillary quadrantal RNFL thickness and SCFT of both groups are shown in Table 2. There was no statistically significant difference between the two groups in RNFL thickness and SFCT values. There was no correlation between Hb level and RNFL thickness in any quadrant in patients with th-minor (Figure 2). Also, there was no correlation between Hb level and RNFL thickness measurements when the correlation adjusted for age and gender.

Table 3 shows the RVC measurements of both groups. The mean arteriolar and venular measurements were wider in patients with th-minor and the difference between groups was statically significant ($p < 0.05$). However, the ratio of

Table 1. Clinical characteristics of the groups.

Characteristics	Thalassemia minor	Control	*p* value
Hemoglobin (g/dL)	10.1 ± 1.0	13.0 ± 0.5	0.02
Serum iron (µg/dL)	93.9 ± 8.3	95.7 ± 8.3	0.86
Serum ferritin (µg/dL)	34.7 ± 5.9	28.4 ± 5.6	0.33
Iron binding capacity (µg/dL)	273.2 ± 34.5	263.3 ± 32.0	0.53
Refractive state (D)	−0.25 ± 0.9	0.06 ± 1.03	0.98

D: diopter.

Table 2. RNFL thickness and SFCT of the groups.

µm	Thalassemia minor (n = 30)	Control (n = 36)	*p* value
Mean RNFL	105.85 ± 10.44	104.85 ± 10.02	0.70
Superior RNFL	132.25 ± 13.21	130.54 ± 12.57	0.60
Nasal RNFL	77.44 ± 15.54	77.02 ± 13.87	0.91
Inferior RNFL	139.67 ± 14.76	134.49 ± 18.94	0.24
Temporal RNFL	75.66 ± 14.18	77.40 ± 13.27	0.62
SFCT	344.00 ± 68.20	349.05 ± 71.46	0.83

RNFL: retinal nerve fiber layer; SFCT: subfoveal choroidal thickness.

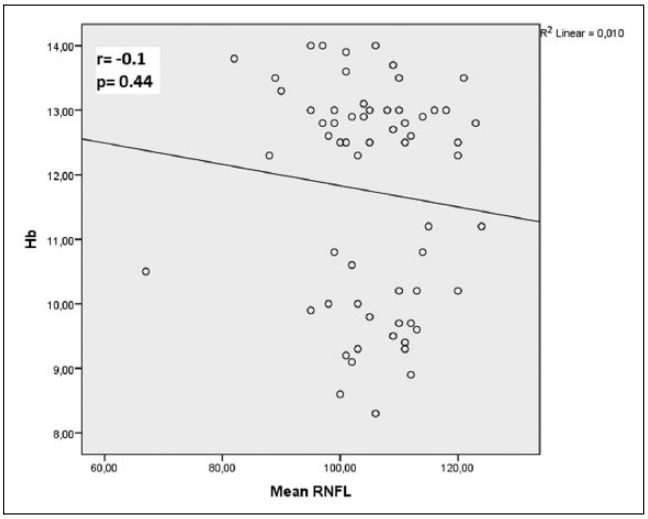

Figure 2. Correlation of Hb level with mean RNFL thickness in patients with th-minor.

mean arterial caliber to mean venular caliber was not different between groups ($p > 0.05$).

Discussion

This study demonstrated that there was no statistically significant difference in RNFL thickness and SFCT in children with th-minor compared with healthy controls. Also, Hb levels did not show a correlation with RNFL thickness. But

Table 3. Retinal vessel caliber measurements of the groups.

RVC	Thalassemia minor	Control	*p* value
Mean arteriolar caliber measurement	90.7 ± 13.8	83.9 ± 8.8	0.03
Mean venular caliber measurement	126.8 ± 17.0	115.8 ± 11.80	0.01
Ratio of mean arteriole to mean venular caliber measurement	0.72 ± 0.09	0.72 ± 0.07	0.71

RVC: retinal vessel caliber.

patients with th-minor had wider arteriolar and venular caliber measurements compared with controls. These findings may suggest that retinal microcirculation might be affected by the mild anemia, but RNFL or choroidal thickness is not affected in children with th-minor.

Türkyilmaz et al. found out that RNFL thickness was thinner in children with IDA. They supposed that RNFL thinning might be a result of anemic hypoxia or deficiency of iron element or both. They also reported that the Hb level correlated with RNFL thickness in some quadrants.[6] Aksoy et al.[7] reported that RNFL thickness was lower in children in all quadrants with th-major and in the inferior quadrant with IDA.

Anemia causes chronic tissue hypoxia, depending on its severity.[12] While decreased RNFL thickness was noted in both IDA and th-major, this was not the case in this study. Hb levels of both groups were lower than our patients, which was 8.9 ± 1.7 g/dL in IDA, 6.5 ± 0.7 g/dL in th-major, and 10.1 ± 1.0 g/dL in our patients with th-minor.[6,7] It is possible that in contrast to th-minor patients, the level of hypoxia in IDA and th-major was under the critical level that is essential for normal retinal nerve metabolism. While serum iron level is low in IDA, it ranges within normal limits in th-minor.[13] Iron is an element that has a crucial role in transporting oxygen to cells. It is the central atom of the heme group that binds molecular oxygen in the lungs and carries it to all the other cells in the body that need oxygen to perform their activities. Without iron in the heme group, there would be no site for the oxygen to bind, and thus no oxygen would be delivered to the cells, leading to cell destruction.[14] Therefore, it may be possible to transport adequate oxygen to specific cells that constitute RNFL in th-minor with normal iron levels. Iron also acts in nerve myelination and promotes normal dopaminergic function.[15,16] In contrast to th-minor, low iron levels in IDA may prevent healthy retinal nerve formation due to its role in nerve metabolism.

Patients with th-major have severe anemia with Hb levels <7 g/dL.[1] The main threatening problems in th-major are anemic hypoxia and iron overload due to hemolysis and regular blood transfusion.[1,17] Although iron is essential for normal metabolic processes as discussed above, the iron

overload can lead to excessive free radicals causing elevated oxidative status.[18,19] And in th-major, in addition to anemic hypoxia, increased oxidative status may damage RNFL as it may do to other tissues.[7] However, there are some reports about elevated oxidative stress in patients with th-minor associated with increased lipid peroxidation and decreased catalase activity.[20,21] But in th-minor the ferritin level is within normal limits and the anemia is usually not serious with Hb levels >9 mg/dL.[2] Eventually, the oxidative status is most likely less than th-major in th-minor. The normal RNFL values of th-minor patients in this study may reflect that the oxidative state in th-minor has no unfavorable effect on RNFL.

Retinal vasculature can be directly visualized and may help us to evaluate the systemic vascular condition. While narrower retinal arteriolar caliber is associated with elevated blood pressure, obesity, coronary artery disease, and higher hemotocrit levels, wider venular caliber is associated with diabetes, chronic kidney failure, cerebral hypoxia, and higher hemotocrit levels.[5,22–24] In this study, we found wider arteriolar and venular measurements in patients with th-minor. Retinal vascular dilatation may be a response to compensate mild hypoxia. Vascular response to hypoxia includes complex reactions with expression of angiogenic cytokines and growth factors. Proliferation of new capillaries from the existing retinal vessels or remodeling of collateral vessels may occur in severe retinal hypoxia.[25] There might be a mild hypoxia in th-minor which may affect retinal microcirculation. But there was no difference in the ratio of mean arteriolar caliber to mean venular caliber between groups.

The choroid has a rich vascular structure and plays an active role in maintaining oxygen and nutrients for the outer parts of the retina.[4] Previously, the detailed evaluation of choroid was not possible which is located under the retinal pigment epithelium.[4] Currently, three-dimensional structure of choroid and choroidal thickness can be assessed by EDI-OCT which may provide us advanced knowledge.[26] Choroidal thickness is usually measured on subfoveal area where the choroid is thickest.[27] SFCT measurements were correlated with ocular perfusion pressure in healthy individuals because of the highly vascular structure of choroid.[24] There are few reports about choroidal thickness changes in some ocular conditions including myopia and diabetic retinopathy.[28,29] Also, the choroidal and retinal circulation might influence each other and retinal hypoxia may be associated with decreased SFCT.[30] If there is a relation between retinal oxygenation and choroidal thickness, SFCT measurements may also be helpful to detect the retinal hypoxia. In this study, it was also shown that th-minor has no negative influence on SFCT which may support enough retinal oxygenation in these patients.

However, this study has several limitations. This study was designed as a cross-sectional study including only children, but longitudinal prospective studies may give better insight about the effects of th-minor on posterior pole structures. Also, the number of patients was low due to poor patient cooperation in pediatric group during OCT screening. Finally, the blood pressure values and the body mass index (BMI) of the children should be measured and correlated with our findings.

In conclusion, retinal microcirculation might be affected in children with th-minor. However, mildly lower Hb with normal blood iron values may have no unfavorable effect on RNFL and SCFT in children.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Pamukkale University Ethics Committee APPROVAL NUMBER/ID: 60116787-020/30525

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Informed consent

Written informed consent was obtained from the legally authorized representatives (i.e. parents) before the study.

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