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ORIGINAL PAPER

Evaluation of macular, retinal nerve fiber layer and choroidal thickness by optical coherence tomography in children and adolescents with vitamin B_{12} deficiency

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Abstract
Purpose To investigate macular, Retinal Nerve Fiber Layer (RNFL) and choroidal thickness in children and adolescents with vitamin B_{12} deficiency and no neurological examination finding.
Methods The study group includes of thirty-three children aged 8–17 years who were brought to the Pediatric outpatient clinic with the symptoms of fatigue and forgetfulness and whose Vitamin B_{12} levels were detected < 200 pg/ml. The control group was the 30 children and adolescents applied to the same policlinic with various symptoms and whose Vitamin B_{12} levels were found normal. Children and adolescents with chronic systemic/ocular disease history and myopia or hyperopia more than 4 diopters were not included in both groups. Spectral Domain-Optical Coherence Tomography (SD-OCT) was used for measurements.
Results Mean Macular thickness value was 261.2 ± 17.6 in the Vitamin B_{12} deficiency group and 267.7 ± 17.4 in the control group. Mean value of Retinal Nerve Fiber Layer (RNFL) thickness was 103.5 ± 7.5 in the Vitamin B_{12} deficiency group and 104.3 ± 8.9 in the control group. The mean values of Choroidal thickness were 360.1 ± 59.8 and 316.9 ± 95.4 in Vitamin B_{12} deficiency and control groups, respectively. There was a statistically significant increase in choroidal thickness in Vitamin B_{12} deficiency group compared to controls.
Conclusion Statistically significant increase in the Choroidal thicknesses of children and adolescents with Vitamin B_{12} deficiency is important in terms of shedding light on studies that will contribute to a better understanding of the relationship between vitamin B_{12} and inflammation.
Clinical trial registration This study is an observational study.

Keywords Vitamin B_{12} deficiency · Choroid thickness · Macula · RNFL · Children · Adolescent

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Introduction

Vitamin B_{12} plays an important role in the transfer of metal groups necessary for the synthesis of compounds such as neurotransmitters, choline, phospholipids and nucleotides [1]. The association of Vitamin B_{12} deficiency with neuropsychiatric disorders such as peripheral neuropathy [2, 3], Alzheimer's disease [4], cognitive impairment [5] and depression [6, 7] has been showed in previous studies. Vitamin B_{12} deficiency is caused by varied factors such as dietary intake (vegetarian, elderly individuals), long-term use of drugs (proton pump inhibitor, H2 receptor blocker, antacids), Pernicious Anemia due to autoimmune mechanism, atrophic gastritis or disruption of intestinal absorption due to gene mutations. Megaloblastic anemia is common in laboratory tests, but in some cases neurological symptoms without anemia are observed [8]. Although Vitamin B_{12} deficiency is known to be quite common in the elderly population, it is also prevalent in children [9]. Although often caused by low intake, it can be observed in children of mothers who are fed a poor diet of animal proteins. The children present with nonspecific symptoms such as fatigue, irritability and developmental retardation [10]. It has been emphasized that Vitamin B_{12} deficiency negatively affects cognitive and motor development in infants and children through disruption of myelination [11–13].

Retinal nerve fibers: It is in the inner layer of the retina and is formed by the axons of the ganglion cells. They are responsible for transmitting the stimulation of the photoreceptors to the central visual center through the optic nerve. As a result of axon damage, thinning of retinal nerve fibers leads to a decrease in visual acuity [14]. Few studies have shown that the neurophysiological tests involving the visual pathways were impaired in individuals with neurological symptoms due to Vitamin B_{12} deficiency without visual complaints, and the findings improved when Vitamin B_{12} was replaced with treatment [15, 16]. Magnetic Resonance Imaging (MRI) studies have also shown loss of myelinization of the spinal cord and *optic nerve* in patients with Vitamin B_{12} deficiency [17]. Vitamin B_{12} deficiency has been reported to be associated with Optic neuropathy, a rare condition that can lead to visual loss if not recognized early [18, 19]. Spectral Optical Coherence Tomography (S-OCT) is a non-invasive imaging method used for macular thickness, retinal nerve fiber thickness measurement and choroidal thickness measurement [20]. There are limited data except for two studies using OCT in asymptomatic individuals with Vitamin B_{12} deficiency: A recent study [21] evaluating Retinal Nerve Fiber Layer (RNFL) thickness and ganglion cell layer thickness in adult patients with Vitamin B_{12} deficiency and a study from Turkey which found a relationship between Vitamin B_{12} deficiency and thinning of RNFL thickness in adolescents [22]. Therefore, it was aimed to investigate the macular, RNFL and choroidal thicknesses in children and adolescents with Vitamin B_{12} deficiency but no neurological examination findings.

Method

The study group consisted of 33 children aged 8–17 years who were brought to the pediatric outpatient clinic of Ahi Evran University Education and Research Hospital with nonspecific symptoms such as fatigue or forgetfulness and B12 deficiency (< 200 pg/ml) were detected in laboratory tests [23]. Thirty children and adolescents in the similar age range who applied to the same outpatient clinic for minor problems and without Vitamin B_{12} deficiency were included in the control group. Children with a history of chronic systemic disease or previous ocular surgery/ trauma and who were on continuous treatment were not included in both groups. They were referred to Ophthalmology outpatient clinic after Vitamin B_{12} treatment (intramuscular injection) was started. The neurological examination findings of the participants were within normal limits. All the participants in our study consisted of those who received B12 deficiency for the first time. The visual acuity of children was measured with Snellen chart. Patients with more than 4 diopters of myopia or hyperopia were excluded. According to biomicroscopic and fundoscopic examination, Retinal diseases, optic disc disorders, corneal abnormalities, glaucoma, and strabismus were not included in the study. Choroidal thickness, macular thickness, and Retinal Nerve Fiber Layer (RNFL) thickness were measured by *Spectral Domain Optical Coherence Tomography (SD-OCT)* (6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany). This device produces high resolution images from low infrared light levels. The device has a wavelength of 870 nm and can achieve a scanning image of 40,000 A per second. Axial and transverse resolutions are 7 and 14 μm, respectively [20]. In our study, choroidal thickness measurements were performed manually in EDI-OCT mode by the same ophthalmologist in all subjects. The sections were measured at the sub-fovea. OCT measurements were performed between 9.00 and 12.00 in the morning to prevent the effect of daily change [24]. Before the data were taken into evaluation, a second ophthalmologist made measurements over the records again. Three cases with more than 10% difference between measurements were not included in the study. Measurements of the right eyes of all participants were evaluated. Written informed consent was obtained from the parents of all participants. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Kirşehir Ahi Evran University.

Statistical analysis

SPSS for Windows 17.0 was used for statistical analysis. Gender distribution of the groups was evaluated by Chi-square test. The mean age of the groups was compared with independent t test. Since the MCV (Mean Corpuscular Volume), Hb (Hemoglobin), mean Vitamin B_{12} level, macular thickness, RNFL thickness and choroidal thickness measurements did not fit the normal distribution, the difference between the groups was evaluated by Mann–Whitney U test. Descriptive statistics were shown as mean-standard deviation or frequency (%). Significance value was $p < 0.05$.

Results

The sample of the study consisted of 63 children and adolescents, 33 in the Vitamin B_{12} deficiency group and 30 in the control group; 45.4% of the patient group were male ($n = 15$) and 54.5% were female ($n = 18$); 50% ($n = 15$) of the control group were male and 50% ($n = 15$) were female. The mean age was 13.0 ± 2.4 and 13.1 ± 2.7 in the patient group and in the control group, respectively. There was no significant difference between the groups in terms of age and gender. In the Vitamin B_{12} deficiency group, the mean Vitamin B_{12} value was 143 ± 55 and in the control group, was 244 ± 87. Mean and standard deviation value of MCV (Mean Corpuscular Volume), which express the mean erythrocyte volume, was 81.50 ± 6.0 LL in the patient group and 82.20 ± 7.0 fL in the control group. The mean Hb (Hemoglobin) value was 14.05 ± 1.52 and 14.33 ± 1.76 in the patient and control groups, respectively. No anemia was detected in either group. Mean erythrocyte volumes were within normal limits. There was no statistically significant difference between the two groups in terms of Hb (p = 0.51) and MCV ($p = 0.67$) values.

Mean macular thickness value; was 261.2 ± 17.6 in the Vitamin B_{12} deficiency group and 267.7 ± 17.4 in the control group. Mean value of Retinal Nerve Fiber Layer (RNFL) thickness; was 103.5 ± 7.5 in the Vitamin B_{12} deficiency group and 104.3 ± 8.9 in the control group. The mean values of sub-foveal choroidal thickness were 360.1 ± 59.8 and 316.9 ± 95.4 in the patient and control groups, respectively. There was no statistically significant difference between the groups in terms of the macular thickness ($p = 0.15$) and the RNFL thickness ($p = 0.70$), whereas the sub-foveal choroidal thickness was significantly higher in the patients with Vitamin B_{12} deficiency compared to controls ($p = 0, 033$) (Table 1).

Dıscussıon

In this study, Macula, RNFL and Choroid thicknesses of children and adolescents with Vitamin B_{12} deficiency were measured by using SD-OCT and the values found were compared with those of controls without Vitamin B_{12} deficiency. As a result of our study, no statistically significant difference was observed between the groups in terms of the macular thickness and the Retinal Nerve Fiber Layer (RNFL) thickness, while it was found that the Choroid thickness was statistically significantly higher in the Vitamin B_{12} deficiency group compared to the control group.

Vitamin B_{12} is important for the central nervous system as it is an essential molecule to produce the axonal myelin sheath. It is thought that many neurological and psychiatric problems seen in the case of Vitamin B_{12} deficiency may be associated with disruption of myelination [25–28]. In recent years, it has become possible to visualize retinal nerve fibers,

Table 1 Demographic and clinical findings

	Vitamin B_{12} deficiency group (*n* = 33) mean ± SD	Control group (n = 30) mean ± SD	z/x^2 value	*P* value
Macula thickness	261.2 ± 17.6	267.7 ± 17.4	1.47	0.15
RNFL thickness	103.5 ± 7.5	104.3 ± 8.9	0.384	0.703
Choroid thickness	360.1 ± 59.8	316.9 ± 95.4	**2.174**	**0.033**
Mean vitamin B_{12} value	143 ± 55	244 ± 87	**− 5.44**	**0.001**
MCV value (fL)	81.50 ± 6.0	82.20 ± 7.0	− 0.42	0.67
Hb value	14.05 ± 1.52	14.33 ± 1.76	− 0.67	0.51
Age (years)	13.1 ± 2.7	13.0 ± 2.4	0.55	0.87
Gender (boy) (%)	45.4%	50%	− 0.37	0.71

RNLF Retinal Nerve Fiber Layer, *MCV* Mean Corpuscular Volume, *Hb* Hemoglobin

which are considered to be extensions of the central nervous system, with SD-OCT, a noninvasive device. [29]. Özkasap et al. [22] showed that there was a significant thinning in the Retinal Nerve Fiber Layer (RNFL) using SD-OCT in children with Vitamin B_{12} deficiency compared to the control group. In another study, Türkyılmaz et al. [30] found that the average RNFL thickness and temporal quadrant RNFL thickness values were lower in Vitamin B_{12}-deficient adults compared to the controls. In the same study, average and temporal quadrant RNFL thicknesses were correlated with Vitamin B_{12} levels. In our study, mean RNFL and macular thickness were lower compared to the control group, but the difference between the two groups was not statistically significant.

An important finding of our study is that the Choroidal thickness was significantly higher in the Vitamin B_{12} deficient group compared to the controls. The choroid is the layer of the eye that feeds the outer two-thirds of the retina with its structure consisting of a dense capillary network. In the limited number of studies evaluating choroidal thickness in children, there are conflicting results reporting Choroidal thickness in healthy children [31, 32]. Increases in Choroidal thickness have been showed in previous studies in many inflammatory diseases with vascular involvement, particularly in the active phase of the disease [33–36]. In ocular pathologies, especially in Central Serous Chorioretinopathy, Choroidal thickness has been demonstrated to be increased, and separation of the neurosensory retina from the pigment epithelium has been associated with increased vascular permeability and increased hydrostatic pressure as a result of inflammation [37]. In a study conducted with adults with posterior uveitis due to Behçet's disease; increase in the subfoveal Choroidal thickness measured by EDI-OCT in the active phase of the disease, and decrease after treatment contributes to understanding the relationship between inflammation and choroidal thickness [34]. It has been discussed for a long time that Vitamin B_{12} has an immunomodulatory role, especially in cellular immunity [38, 39]. According to the results of our study, increased Choroidal thickness in children and adolescents with vitamin B_{12} deficiency compared to controls may be associated with dysregulation of inflammatory mechanisms because of Vitamin B_{12} deficiency.

The limitations of our study are the small sample size, the cross-sectional structure of the study, and the lack of analysis of the values of folate and homocysteine molecules, which are frequently discussed in the etiology of neurodegenerative disorders. Another limitation of our study is that the wide age range and the change in choroidal thickness were not measured after vitamin B12 supplementation. Although we could not find a significant decrease in RNFL and macular thickness in the patient group compared to the control group, we think that the statistically significant increase in choroidal thickness in children with vitamin B_{12} deficiency is a finding that will shed light on the role of vitamin B_{12} deficiency in choroidal thickness.

In studies conducted with mothers whose children had low vitamin B_{12} levels during pregnancy, cognitive functions were examined in different age groups and with different measurement methods and contradictory results appeared [13], 40. The evaluation of children and adolescents with Vitamin B_{12} deficiency with structured cognitive tests in accordance with Magnetic Resonance Imaging in future studies will contribute to the understanding of the effects of Vitamin B_{12} deficiency on the Central Nervous System (CNS). Clarifying the association among Vitamin B_{12}, inflammation and choroidal thickness may make it possible to use choroidal thickness as a marker in the follow-up of the disease in patients with Vitamin B_{12} deficiency.

Author contributions TA and MY are responsible for acquisition of the subjects and/or data, analysis and interpretation of the data. TA and AG were responsible for the preparation of the article. AB, RD and OAP were responsible for the selection of the patients into the study who met the inclusion criteria. AB and AG revised the article critically for important intellectual content. AG is responsible for the study concept and design. All authors have approved the final version of the article.

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Data availability The datasets generated during and/or analyzed during the current study are available in the TAHA AYYILDIZ (obirtahadir@hotmail.com).

Compliance with ethical standards

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. The authors have no conflicts of interest to declare that are relevant to the content of this article. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article. There has been no conflict of interest during the preparation of the study, data collection, interpretation of results, and article writing.

Consent to participate Verbal informed consent was obtained from parents prior to the interview.

Consent to publish Verbal consent was obtained from all participants to publish the data.

Ethical approval Approval was obtained from the ethics committee of Ahi Evran University, Faculty of Medicine (2020–04/37). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

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