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Choroidal thickness measurements in children with isolated growth hormone deficiency

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Abstract

Purpose   The aim of this study was to determine the choroidal thickness measurement values in cases with isolated growth hormone deficiency (IGHD), to compare them with the healthy control group by using enhanced depth imaging optical coherence tomography (EDI-OCT), and to evaluate the effect of growth hormone (GH) treatment on choroid.
Patients and methods   In this study, 23 cases who were diagnosed with IGHD as a study group and 46 healthy subjects as a control group were included. All patients and controls underwent a complete ophthalmologic examination, including an examination with EDI-OCT. Choroidal thickness (CT) was measured at the fovea and at 1000 μm intervals from the foveal center in both temporal and nasal directions.
Results   The mean subfoveal choroidal thickness (SFCT) was 329.04 $\pm$ 88.49 μm in the cases with IGHD and 365.35 $\pm$ 50.48 μm in the control group ($P = 0.033$). The mean CT at temporal 1 and 2 mm were thinner in the IGHD group than that of control group ($P = 0.033$ and $P = 0.043$, respectively). Nasal quadrant measurements were also found to be thinner in the IGHD cases than that of control group, but the difference was not statistically significant. We found a significant positive correlation between pubertal staging and SFCT ($r_s = 0.607$, $P = 0.006$). There was no statistically significant difference in CT values of the study group between before and 12 months after GH treatment ($P > 0.05$).
Conclusion   This study shows patients with IGHD has a thinner CT when compared with healthy pediatric cases. GH treatment seems to be not associated with the choroidal development.

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Introduction

Growth hormone deficiency is a condition with clinical, biochemical, auxological, and metabolic abnormalities in which the production of growth hormone (GH)-dependent hormones and growth factors are decreased as a result of insufficiency or deficiency of GH secretion with a complex etiology.[1] Isolated growth hormone deficiency (IGHD) can be defined as childhood growth retardation as a consequence of decreased GH that is not always accompanied by a lack of other pituitary hormone deficiencies or an organic lesion.[2] In a previous report, GH was said to have an effect on ocular development with endocrine, autocrine, and/or paracrine roles and also the eye was accepted as a target site for GH.[3] Many different ocular abnormalities have been reported in patients with GH deficiency.[4–8]

GH has been shown to have angiogenic effects and retinal cells are known as a domain of local growth factors, including insulin-like growth factor-I (IGF-I).[9] Reduced retinal vascularization in Laron syndrome (GH insensitivity syndrome) demonstrated that GH–IGF-I axis is crucial for normal vascularization of the human retina.[10]

The choroid accounted for most of the ocular blood flow and supplied the outer retina, consisting of choroiocapillaris and vessel layers.[11] Although choroid has a rich vasculature and is a possible target for angiogenic factors, no report has demonstrated any relationship between the choroid and GH–IGF-I.

Imaging of the choroid has been challenging even with optical coherence tomography (OCT) because of the limited penetration of the wavelength of the light source.[12] A newer technique using standard spectral-domain OCT (SD-OCT) named 'enhanced depth imaging

optical coherence (EDI-OCT)' provided possibility for choroidal visualization.[13]

The aim of this study was to evaluate choroidal thickness (CT) in children with IGHD, to compare it with those of healthy subjects, and to find out whether choroidal thickness is affected by the recombinant human GH treatment.

Materials and methods

Twenty-three patients diagnosed with IGHD at the Department of Pediatric Endocrinology of Gazi University Medical Faculty between January 2012 and September 2013 were included in the study. Forty-six healthy children carefully matched for age, gender, body mass index (BMI), and pubertal stage were chosen as a control group. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects. The study protocol was approved by the local institutional review board and ethics committee.

Exclusion criteria for the study were: a history of preterm or small for gestational age birth, a diagnosis of cardiovascular disease, thyroid disease as well as hepatic or renal disease, obesity, current hypertension, and the presence of chromosomal abnormalities. The detailed physical examination was performed in all subjects. The anthropometric measurements included weight, height, and BMI. Pubertal staging was assessed by Tanner stage according to breast development in girls and genital development in boys.[14] Bone age was evaluated by using the Greulich and Pyle atlas. Routine biochemical test, complete blood count, as well as thyroid function test and serum tissue transglutaminase antibodies were obtained from all patients. IGF-I and IGFBP-3 levels were also measured at baseline. GH stimulation test with L-DOPA and Klonidin was performed for each patient. Peak GH response after two stimulation tests below $10\,\mu g/l$ was accepted as inadequate. Finally, the diagnosis of IGHD was established by the clinical, auxological, and biochemical criteria of the GH Research Society.[15] After the diagnosis, recombinant human GH treatment was started at the initial daily dose of 0.025 mg/kg and dose adjustment was made during the study. All patients were referred to ophthalmology clinic from the Department of Pediatric Endocrinology for ophthalmologic examination.

Ophthalmologic examination

All patients and controls underwent a complete ophthalmologic examination, including an autorefractometer (RM8900; Topcon, Tokyo, Japan), best-corrected visual acuity (BCVA) measurement with a 6-m Snellen eye chart, slit-lamp biomycroscopy, fundus examination, and intraocular pressure measurement. Subjects with high myopia or hyperopia (>+6 or −6 diopters of spherical equivalent), BCVA <20/25, amblyopia, and any ocular disease were not included in the study.

Subjects underwent an examination with Heidelberg Spectralis-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) for the measurement of the CT. EDI-OCT images were obtained as the same technique reported by Spaide *et al.*[12] Images were acquired by the same experienced technician. OCT device was brought closer to the eye to get images invertedly. The average of 100 scans using the automatic averaging and eye tracking features were used to get these 9 mm horizontal images.[16] All patients were evaluated at baseline and after 12 months of GH treatment to determine any effect of treatment on the CT. At the follow-up visits, patients with poor compliance with treatment were not take into account while analyzing first-year effect of GH treatment on ocular parameters.

The choroid was measured manually using caliper tool by one clinician (NGY). Measurement was made between the highly reflective layer corresponding to the retinal pigment epithelium (RPE)/Bruch complex and the sclerochoroidal interface. The CT was measured from the foveal center and 1000 μm apart, starting from the foveal center, in the nasal and temporal directions for 4 other measurements.[17] Examinations were performed at the same interval of the day (1000–1200 h) in order to exclude the effect of diurnal change at CT. The value of CT at this time interval was relatively high according to the rest of the working time.[18]

Statistical analysis

Data obtained from the study were recorded using Excel for Windows (version 2010, Microsoft, Redmond, WA, USA) and statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 15.0, SPSS, Chicago, IL, USA). Right eyes of subjects were selected for statistical analysis because there was no difference between the measurements of the right and the left eyes. All groups were tested for normality using the Kolmogorov–Smirnov test. Continuous variables were computed as mean ± SD and median (min–max) where applicable. Differences between groups were assessed using independent samples *t*-test. Differences between values before and after GH treatment were evaluated using paired samples *t*-test. The degree of correlation between the values was evaluated by Pearson's or Spearman's correlation coefficients where appropriate. The statistical level of significance was set to $P < 0.05$.

Results

The demographic, clinical, and ophthalmologic parameters of all subjects are shown in Table 1. The BCVAs of all subjects were 6/6.

There was a strong positive correlation between the mean subfoveal choroidal thickness (SFCT) of the right eye and the left eye (Spearman's correlation test, $P < 0.01$, $r = 0.906$). The mean K average values of the patients (43.40 ± 1.61 D) was similar to the mean K average values of the control group (43.80 ± 1.49 D) ($P = 0.90$). Mean SFCT was $329.04 \pm 88.49 \mu$m in the study group and $365.35 \pm 50.48 \mu$m in the control group ($P = 0.033$). In both groups, CT was reduced in nasal direction and reached minimum level at 2000μm apart from the fovea center nasally (Figure 1). Mean SFCT and thicknesses of other 4 region of both groups were summarized in Table 2.

All measurements of CT were decreased in IGHD patient group than that of control group. Although there was a slight decrease in the thicknesses of nasal 1 and 2 mm of the patient group, a comparison of the two groups showed no statistically significant difference only in terms of the measurements of these two localizations.

Correlation coefficients between SFCT and age, height, BMI, pubertal staging, and biochemical values in patients with IGHD were analyzed and are shown in Table 3. There was a significant positive correlation between pubertal staging and SFCT ($r_s = 0.607$) (Figure 2). Other parameters and SFCT did not show any correlation.

There was no statistically significant change in CT values of the study group before and 12 months after the GH treatment ($P > 0.05$). Mean SFCT was $329.04 \pm 88.49 \mu$m at pretreatment visit, whereas mean SFCT was altered to $326.20 \pm 85.93 \mu$m at posttreatment final visit ($P = 0.812$). The CT of temporal region was $321.22 \pm 76.15 \mu$m at 1 mm distance from foveal center, and $318.17 \pm 69.08 \mu$m at 2 mm distance from foveal center before treatment. These values changed to $337.76 \pm 77.46 \mu$m and $317.06 \pm 85.09 \mu$m after treatment, respectively ($P = 0.291$ and $P = 0.956$, respectively). For nasal localizations, the CT was $299.26 \pm 90.04 \mu$m at 1 mm apart from foveal center and $290.60 \pm 94.59 \mu$m at 2 mm apart from foveal center before treatment. At posttreatment final visit, these values altered to $290.60 \pm 94.59 \mu$m for nasal 1 mm and $239.09 \pm 87.81 \mu$m for nasal 2 mm ($P = 0.599$ and $P = 0.608$, respectively).

Discussion

GH and GH receptor gene expression has been reported in the developing neural retina in rats, chickens, and mice.[19] In studies that show relationship between GH and cornea, GH was said to have an effect on postnatal growth of the eye via IGF-I production.[7,20,21] GH was

Table 1 Demographic, auxological, and ophthalmologic parameters of subjects

Parameters	Patients (n = 23)	Control (n = 46)	P-value
Age (year)	12.57 ± 2.33	11.43 ± 3.26	0.143[a]
Sex (F/M)	12/11	28/18	0.49[b]
Height (cm)	131.29 ± 11.83	143.1 ± 12.79	**0.001**[a]
Weight (kg)	35.07 ± 12.15	37.63 ± 10.3	0.395[a]
BMI	19.75 ± 4.52	18 ± 2.46	0.052[a]
Pubertal staging	2 (1–3)	2 (1–5)	0.054[b]
IOP (mm Hg)	16.26 ± 2.97	15.30 ± 2.55	0.169[a]
SE	-0.02 (-2.00 to 4.75)	-0.16 (-3.62 to 2.75)	0.768[c]

Abbreviations: BMI, body mass index; F, female; IOP, intraocular pressure; M, male; SE, spherical equivalent. [a]Independent samples *t*-test. [b]Pearson's χ^2 test. [c]Mann–Whitney *U*-test. Bold value shows statistically significant *P*-value ($P < 0.05$).

found in the vitreous of rat eyes in immunochemical studies.[22,23] In addition, GH and GH receptors have been shown in retinal ganglion cells. Consequently, most of the previous studies relevant with IGHD were focused on the retina.[4,8,24] Normal macular thickness and decreased retinal fiber layer thickness were found to be associated with IGHD according to these studies.

Although the mechanisms by which GH affects angiogenesis are not exactly known, GH has a role in retinal angiogenesis beside its influence on neural development. After birth, little or no vascularization occurs and most of the retinal vascularization happens during fetal period.[24] This process is regulated by several local produced growth factors as a response to hypoxia. Hormones and factors in circulation except GH alone affect the production and action of these local factors.[25,26] IGF-2 is believed to be more influential than IGF-I for ocular development in fetus.[27] In clinical studies, effect of deficiency of GH on retinal vascularization was demonstrated as decreased vascular branching points.[4,25]

Although these mentioned studies explored GH in retinal development, there were no previous published data about the relationship between GH and choroid. Choroidal layer was one of the areas in which GH and GH recombinant mRNA were identified in chick embryo.[28–30] Furthermore, the choroid nourishes the outer layers of the retina and is rich in blood vessels.[31] As a consequence, the choroid may be a pathway for GH in reaching retina and may be an action site for GH. To the best of our knowledge, this is the first study to explore GH effect on the choroid in a clinical study.

Visualization and evaluation of the choroid was performed with B-scan ultrasonography and indocyanine green angiography (ICG) before clinical use of SD-OCT.[32] Currently, EDI-OCT has become a frequently used method for evaluation of the choroid. It has been found to be more effective in terms of the visualization of the choroid and gives precious information about choroidal morphology in healthy eye and various diseases.[17] Because of the noninvasive and rapid nature of the
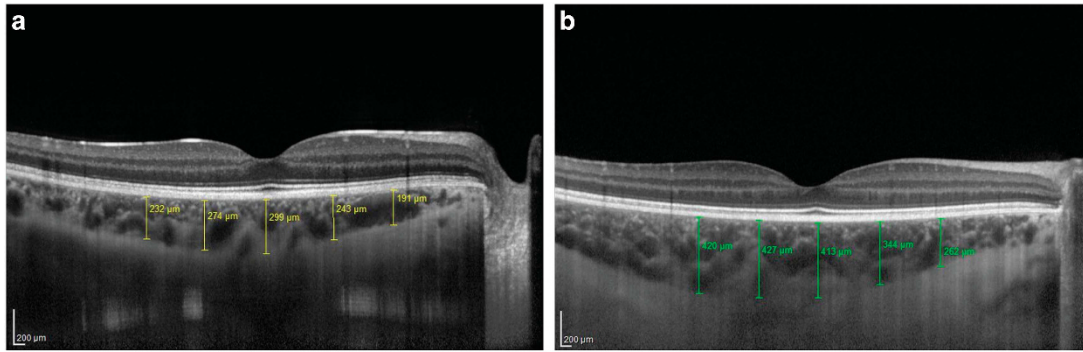
Figure 1 (a) Decreased choroidal thickness in an IGHD patient. (b) Choroidal thickness in a healthy control group patient.

Table 2 Measurements of choroidal thickness at five locations

CT (μm)	Groups		P-value[a]
	Patients (n = 23)	Control (n = 46)	
Subfoveal	329.04 ± 88.49	365.35 ± 50.48	**0.033**
Temporal 1 mm	321.22 ± 76.15	358.96 ± 63.32	**0.033**
Temporal 2 mm	318.17 ± 69.08	352.04 ± 61.96	**0.043**
Nasal 1 mm	299.26 ± 90.04	304.89 ± 54.34	0.747
Nasal 2 mm	235.30 ± 76.32	237.52 ± 53.36	0.889

[a]Independent samples t-test. Bold value shows statistically significant P-value ($P < 0.05$).

Table 3 Correlation coefficients between SFCT and age, height, BMI, pubertal staging, and biochemical values

	Correlation coefficients	P-value
Age	0.247	0.256[a]
Height age	0.380	0.109[a]
Height	0.382	0.107[a]
BMI	0.209	0.390[a]
Pubertal staging	0.607	**0.006**[b]
IGF-1	−0.062	0.801[a]
IGF BP3	0.000	0.999[a]

[a]Pearson's correlation test. [b]Spearman's correlation test. Bold value shows statistically significant P-value ($P < 0.05$).

examination of EDI-OCT, it has also been used in pediatric population.[33–36] In these studies mean SFCT ranged between 314 and 348 μm in healthy children. In the current study, we found mean SFCT (365.35) higher than that. On the other hand, Tenlik et al[37] also reported higher mean SFCT (388 μm) in healthy Turkish children. Thus, our data might be interpreted as a consequence of an ethnical difference on CT.

Furthermore, we found IGHD patients had lower CT than control group in subfoveal and temporal localization. Normally, CT was decreased in both directions but more nasally.[38] Therefore, in this study we may not have found a significant difference between the study group and the control group, although we observed
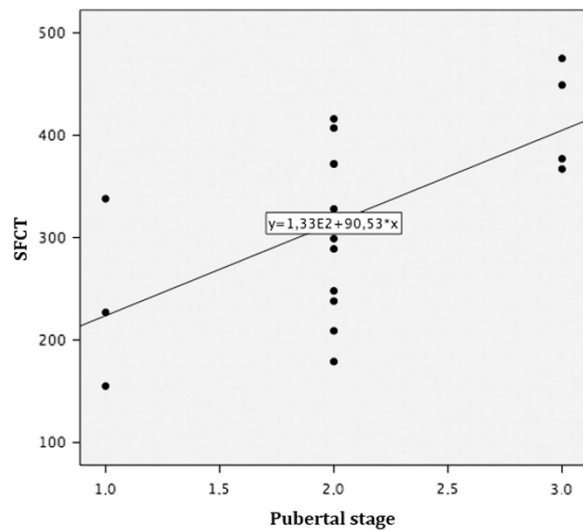

Figure 2 The correlation graphic related with the subfoveal choroidal thickness and the pubertal stage.

a slight decrease in the IGHD group in the nasal region. As known from the literature, axial length and choroidal volume correlated inversely with each other.[39] Thinning of the choroid may be a result of passive stretch mechanism with eye growth. As opposed to this hypothesis, Baudet et al[19] found decreased ocular axial length in GH receptor gene disrupted mice. Also, in early childhood CT was found to be increased until 12 years on average. It was hypothesized that thickening of the choroid may be a result of normal growth of the connective and vascular tissue.[33] According to these data, lower CT in IGHD patients in our study can be explained with the retardation of the eye growth in IGHD independently of the effect of GH on axial length. Thus, whether the GH effect on the choroid is independent of the influence of GH on ocular growth retardation cannot be inferred.

Age and CT were found to be negatively correlated with each other in adult people.[39] However in pediatric population the correlation between age and CT is controversial.[33,36,40] In our study, age and CT correlated

positively, although it was statistically insignificant. As the ocular growth might be disrupted in IGHD, the difference may not be statistically significant.

We found significant medium-degree positive correlation between only pubertal stage and CT. Li et al[41] found that CT was increased only in girls with puberty maturity. This is probably because pubertal stage is a part of growth, and in our study CT was higher in advanced stages of puberty.

Regarding the impact of GH treatment on CT, we found GH treatment had no effect on CT. This finding may indicate that GH has no effect on choroid in postnatal period. The mean age of our study group population was 12 years, and this is the age when CT is expected to reach almost its final adult values.[33] This information may be an explanation of why GH treatment did not seem to affect choroidal development in this study.

Our study has several limitations. The number of patients was relatively low. On the other hand, our follow-up period was 12 months compared with another published study in which significant increase in CT occurred in at least 18 months.[34] Our 1-year follow-up may be inadequate to observe choroidal growth and to detect any change in CT.

In conclusion, we showed decreased CT in IGHD compared with healthy subjects and GH treatment seems to have no effect on CT. The current study indicates that pubertal stage is well correlated with CT. Our study may be a guide for further studies to clarify GH effect on choroid. Future controlled longitudinal studies should be planned to shed light on these points.

Summary

What was known before
- Decreased vascular branching points as reduced retinal vascularization was demonstrated in IGHD. Decreased retinal fiber layer thickness was found to be associated with IGHD. Beside retina, choroid is a possible target for angiogenic factors, though there was no declaratory report on the relationship between choroid and GH–IGF-1.

What this study adds
- CT was decreased in IGHD compared with healthy subjects. GH treatment seems to have no effect on CT. The pubertal stage is positively well correlated with CT.

Conflict of interest

The authors declare no conflict of interest.

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