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·Clinical Research·

Corneal properties in children with congenital isolated growth hormone deficiency

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Abstract

• AIM: To compare the corneal parameters of children with congenital isolated growth hormone deficiency and healthy subjects.

• METHODS: In this cross-sectional, prospective study, 50 cases with growth hormone (GH) deficiency treated with recombinant GH and 71 healthy children underwent a complete ophthalmic examination. The corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPcc) were measured with the Ocular Response Analyzer (ORA). Central corneal thickness (CCT) was measured by a ultrasonic pachymeter.

• RESULTS: The mean age was 13.0±3.0 years in the GH deficiency group consisting of 21 females and 29 males and 13.4 ±2.4 years in the healthy children group consisting of 41 females and 30 males. There was no statistically significant difference between the groups for gender or age (Chi-square test, *P*=0.09; independent *t*-test, *P* =0.28, respectively). The mean duration of recombinant GH therapy was 3.8±2.4y in the study group. The mean CH, CRF, IOPg and IOPcc values were 11.0± 2.0, 10.9±1.9, 15.1±3.3, and 15.1±3.2 mm Hg respectively in the study group. The same values were 10.7±1.7, 10.5± 1.7, 15.2 ±3.3, and 15.3 ±3.4 mm Hg respectively in the control group. The mean CCT values were 555.7 ±40.6, 545.1 ±32.5 μm in the study and control groups respectively. There was no statistically significant difference between the two groups for CH, CRF, IOPg, IOPcc measurements or CCT values (independent *t*-test, *P*=0.315, 0.286, 0.145, 0.747, 0.13 respectively).

• CONCLUSION: Our study suggests that GH deficiency does not have an effect on the corneal parameters and CCT values. This observation could be because of the duration between the beginning of disease and the diagnosis and beginning of GH therapy.

• KEYWORDS: child; corneal biomechanical parameters; central corneal thickness; growth hormone deficiency
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INTRODUCTION

The prevalence of congenital growth hormone (GH) deficiency is known to range from 1/3480 to 1/4018[1,2]. GH and its effect on growth through the production of insulin-like growth factor 1 (IGF-1) are essential for postnatal somatic growth [3]. The eye seems to be a target site for GH action and GH may have endocrine, autocrine or paracrine roles in ocular development and growth [4,5]. Although the mechanism of this observation is still not fully understood, previous reports showed an association between GH deficiency and increased central corneal thickness (CCT), optic nerve hypoplasia, reduced retinal vascularization, shorter axial length and hyperopia[4,6-9].

Investigative studies on animal models indicated that GH, IGF-1 and other growth factors exert an effect on the developing ocular tissues by influencing the synthesis of the extracellular matrix of the sclera [10-12]. Kirwan *et al*[13] suggested that the growth of the eye, with possible remodeling and stretching of collagen fibers, should play a significant role in the reduction of central corneal thickness. The association of GH with CCT may indicate the presence of some changes in corneal biomechanical parameters in children with congenital GH deficiency. To the best of our knowledge, corneal biomechanical changes in children with congenital GH deficiency have not previously been evaluated. Our aim in this study was to compare the corneal

biomechanical parameters of children with congenital isolated GH deficiency and healthy control subjects by using the Ocular Response Analyzer (ORA; Reichert Inc., Depew, NY, USA).

SUBJECTS AND METHODS

Our study involved 50 eyes of 50 cases with congenital isolated GH deficiency referred from the Endocrinology and Metabolism Clinic to the Ophthalmology Department and 71 age- and sex-matched control subjects who had applied to the Ophthalmology Department for a routine ocular examination. All of the study procedures were conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from the parents of all the participants. The cases were evaluated prospectively and their past medical histories were reviewed. This study was approved by the Ethical Committee of the Ankara University School of Medicine.

In the study group, cases that had a previous history of any systemic disease other than GH deficiency, glaucoma or elevated IOP, corneal disease, aphakia, contact lens use, chronic use of topical ocular medications, ocular trauma or ocular surgery were excluded from the study. The control group consisted of healthy subjects who did not have a history of any systemic disease, family history of glaucoma, or any ocular problems other than refractive error. Eyes with an appearance of glaucomatous optic nerve (cup disc ratio greater than 0.6, vertical cup asymmetry more than 0.2, neuroretinal rim loss or notching) were also excluded.

All the cases in the study group were referred from the Endocrinology Department with presenting findings such as short height (-2.0SD) and significantly delayed bone age. All these cases had been diagnosed with isolated congenital GH deficiency after complete pituitary examinations including the usual provocative GH testing and all had been receiving recombinant GH therapy. The cases in both the study and the control groups underwent detailed ophthalmologic examinations including best-corrected visual acuity with Snellen charts, cycloplegic refraction, slit-lamp examination and posterior segment examination with the direct ophthalmoscope.

Cycloplegic refraction measurement was performed in both eyes by means of a hand-held autorefractometer (Welch Allyn Sure Sight, software version 2.16 and 2.20; Welch Allyn Medical Products, Skaneateles Falls, NY, USA) 30min after the instillation of cyclopentolate 1% eye drops three times at 10min intervals.

Corneal biomechanical parameters including cornea hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated IOP (IOPg) and corneal compensated IOP (IOPcc) were measured between 09:00 and 11:00 a.m. by the same experienced physician (ES) according to normal clinical practice and manufacturer's guidelines. For each patient, 3 readings of good quality images were defined as having a waveform with 2 distinct, nearly symmetrical peaks. Irreproducible out-of-scale measurements were excluded from the analysis. The mean values of each parameter were used for statistical evaluation.

After the noncontact part of the study assessments was finished, topical anesthesia consisting of proparacaine hydrochloride 0.5% drops (Alcaine ophthalmic solution, Alcon, Turkey) was administered. The CCT measurement was recorded using a Tomey AL-1000 ultrasound biopachymeter (Tomey Corporation, Nagoya, Japan).

Only the right eyes were included in the study as a strong correlation was found between right and left eyes. The Pearson correlation test, Kruskal-Wallis test and Chi-square test were used for the statistical analysis, and statistical significance was set at $P<0.05$.

RESULTS

The mean age of the 21 (42%) females and 29 (58%) males for a total of 50 cases with GH deficiency was 12.9 ±2.9 (8-20) years and the mean age of the 41 (57.7%) females and 30 (42.3%) males for a total of 71 healthy children was 13.4± 2.4 (8-19) years (Table 1). There were no statistically significant differences between the two groups in age or gender distribution ($P=0.28$, independent t-test; $P=0.09$, Chi-square test respectively). In the study group, the mean duration of recombinant GH therapy was 3.8±2.4 (1-11)y.

The corneal biomechanical parameters of the groups are summarized in Table 2. There were no significant differences in CH, CRF, IOPg and IOPcc values between the 2 groups ($P=0.315$, $P=0.286$, $P=0.145$, $P=0.747$ respectively). Although the mean CCT of the study group was higher than the control group, the difference between the CCT measurements of the two groups was not statistically significant ($P=0.13$).

DISCUSSION

Over the past few years, the ORA has become one of the most important instruments for both research and clinical evaluation of cases with corneal diseases and glaucoma [14-16]. In addition to the most accurate IOP (IOPcc), it can also provide measurements of other corneal biomechanical parameters like CH, CRF and IOPg.

GH is known to have an effect on postnatal ocular growth through the production of IGF-1[3,4]. Immunochemistry studies have recently discovered GH in the vitreous fluid of human and rat eyes[17-19]. Also GH and GHmRNA proteins have been identified in the neural retina, optic nerve, choroid layer, ciliary body, cornea and lens epithelium of the chick embryo [12,20-22]. Some studies suggested that the eye seems to be a target site for GH action [4,5]. However, the roles for ocular GH in human eyes are currently unknown. But its deficiency is associated with some ocular abnormalities like mainly increased CCT and hyperopia related with short axial length [3,6-9,14]. It is also thought to have possible interaction with the physiological process of emmetropization [14].

Table 1 Clinical characteristics of the cases in the study

Parameters	GH deficiency group	Control group	*P*
Eyes (*n*)	50	71	
Mean age±SD (a) (min-max)	13.4±2.4 (8-19)	12.9±2.9 (8-20)	[1]0.28
Male *n* (%)	29 (58)	30 (42.3)	[2]0.09
Female *n* (%)	21 (42)	41 (57.7)	
Duration of GH treatment (a)	3.8±2.4 (1-11)		

[1]Independent *t* test; [2]Chi-square test.

Table 2 Corneal biomechanical parameters and central corneal thickness of the cases and their statistical distribution

Parameters	GH deficiency group	Control group	*P*
CH (mm Hg) (min-max)	11.0±2.0(6.4-18. 6)	10.7±1.7 (7.5-14.6)	0.315
CRF (mm Hg) (min-max)	10.9±1.9 (7.2-17)	10.5±1.7 (7-13.8)	0.286
IOP g (mm Hg) (min-max)	15.1±3.3 (9.8-23)	15.2±3.3 (7-21.3)	0.145
IOPcc (mm Hg) (min-max)	15.1±3.2 (7.5-23.0)	15.3±3.4 (8.1-23.7)	0.747
CCT (μm) (min-max)	555.7±40.6 (474-644)	545.1±32.5 (487-604)	0.13

Independent *t*-test; CH: Corneal hysteresis; CRF: Corneal resistance factor; IOPcc: Corneal compensated intraocular pressure; IOPg: Goldmann correlated IOP; CCT: Central corneal thickness.

Parentin and Pensiero [3] compared CCT of 45 children with GH deficiency with normal subjects and found statistically significant increase in their patients. They also found significant increase in prevalence of hyperopia in GH deficiency group and stated that both shorter axial length but also a greater CCT can represent a sign of a delayed growth of the eye relating to GH deficiency [3]. Similarly, Bourla *et al* [6] investigated cases with Laron syndrome which is related with primary GH resistance or insensitivity and found greater average ocular dimensions, larger axial length, deeper anterior chamber and higher lens thickness values in untreated cases than the once under GH replacement therapy. Kirwan *et al* [13] suggested that the growth of the eye, through the possible remodeling and stretching of collagen fibers, might play a significant role in the reduction of CCT. During the growth of the eye, this process may influence corneal biomechanical parameters by the remodeling and stretching of collagen fibers. On the basis of these corneal and other structural changes, our hypothesis stated that there should be some differences in corneal biomechanics in this illness and we aimed to compare biomechanical parameters of the cases with GH deficiency and normal subjects.

Corneal anatomical and biomechanical parameters determine corneal structural integrity and stiffness. CH predominantly reflects the viscous dampening properties of the cornea and CRF is mostly associated with corneal stiffness [23-25]. *In vitro* studies have shown that cross linking of collagen fibers may eventually result in increased stiffness of the cornea [26]. Any other changes in the regulation of the collagen fibers may also affect the stroma and therefore corneal stiffness including possible effect of GH. We compared CH, CRF, IOPcc and IOPg of our cases with age- and sex-matched normal subjects in addition to CCT of them. However, we could not find any significant differences between these corneal biomechanical parameters and CCT values. These results were unforeseeable for us especially insignificant difference in CCT and the reasons for these insignificant differences were controversial. But, this may be explained in two different ways. The stroma makes up 90% of the corneal thickness and is the most important corneal layer from the biomechanical point of view. First of all, we do not currently know the effects of GH on keratocytes that produce the collagen fibrils and extracellular matrix, the basic building blocks of the stroma. Also, there is no direct relationship between CCT and corneal biomechanical behavior. Kaushik *et al* [27] evaluated the relationship between the corneal biomechanical properties, CCT and IOP measured by Goldmann applanation tonometry in their study on a total of 323 eyes of 323 participants (normal subjects, cases with glaucoma suspect, ocular hypertension, primary angle-closure disease, primary open-angle glaucoma and normal-tension glaucoma) who had received no ophthalmic treatment. They stated that CH was a dependant variable showed significant association with IOP and CRF but not CCT. So higher CCT values in cases with GH deficiency reported before by previous reports cannot absolutely cause changes in corneal biomechanical behavior and because of this, no significant differences between corneal biomechanical parameters might be found in our study. Our cases of GH deficiency were found to have insignificantly higher CCT values than the control subjects. This insignificance was a different from the Parentin and Pensiero's study [3]. Furthermore, we had more cases with similar age distribution and mean duration of GH replacement therapy to those in Parentin and Pensiero's [3] study. One possible reason for this difference is that the duration between the beginning of disease and the diagnosis and beginning of GH therapy might have important role on corneal changes. So late diagnosis and delayed treatment

possibilities might cause these different results and our cases might have earlier GH replacement. Another and stronger reason is the fact that the mechanism of GH's effect on cornea is not clearly understood[4,5].

Cases with acromegaly may also have changes in CCT [4,28]. Ciresi *et al* [4] and Bramsen *et al* [28] showed significantly greater mean CCT values in acromegalic patients than healthy subjects. Ciresi *et al* [4] suggested that acromegalic patients with longer active and uncontrolled disease showed greater CCT values, supporting the hypothesis that GH excess may have stimulatory effects on the cornea as well as on other target organs. However, their cases were older than ours.

Our hypothesis in this study was that GH deficiency might cause a variation of the anatomic and biomechanical properties of cornea. We did not find any significant differences in corneal thickness and biomechanics between GH deficiency cases and normal subjects. More information is required to understand the underlying mechanism of growth hormone effects on the cornea.

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