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Anterior segment and corneal biomechanics of achondroplasia patients

Akondroplazi olgularında ön segment ve kornea biyomekaniği

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Abstract

Herein the anterior segment findings with Pentacam and corneal biomechanics with Ocular Response Analyser of 4 genetically proven cases of achondroplasia are reported. Four patients with heterozygous gain of function p.G380R mutation in fibroblast growth factor receptor 3 (FGFR3) gene were evaluated. Central corneal thickness was higher than normal in both eyes of one patient, and corneal hysteresis and corneal resistance factor was lower in three eyes of two patients with accompanying high intraocular pressure readings. As a result, the affection of FGFR3 in achondroplasia patients might cause changes in central corneal thickness, corneal hysteresis and corneal resistance factor.

Keywords: Achondroplasia, fibroblast growth factor receptor 3, genetics, Ocular Response Analyser, pentacam.

Öz

Genetik olarak tanı konmuş 4 akondroplazi olgusunun Pentacam ile elde edilmiş ön segment bulguları ve Ocular Response Analyser ile elde edilmiş kornea biyomekanik özellikleri sunulmuştur. Fibroblast growth factor receptor 3 (FGFR3) geninde p.G380R heterozigot fonksiyon kazanımı mutasyonu saptanan 4 olgu çalışmaya dahil edildi. Merkezi kornea kalınlığı bir hastanın iki gözünde normal değerlerden yüksek, korneal histerezis ve korneal rezistans faktörü iki hastanın üç gözünde eşlik eden yüksek göziçi değerleri ile normal değerlerden düşük bulundu. Sonuç olarak, FGFR3 etkilenmesinin akondroplazi hastalarında merkezi kornea kalınlığı, korneal histerezis ve korneal rezistans faktörü değerlerinde değişikliklere yol açabileceği öngörüldü.

Anahtar Sözcükler: *Akondroplazi, fibroblast growth factor receptor 3, genetik, Ocular Response Analyser, pentacam.*

Introduction

Achondroplasia is an autosomal dominant genetic disorder that affects the skeletal system (1). It is the most common hereditary disorder that causes dwarphism with a prevalence of 1/15.000 to 1/40.000 (1). Increased signal transduction from a mutated fibroblast growth factor Receptor 3 (FGFR3) causes an abnormality of cartilage formation (1). More than 97% of the patients have heterozygous gain of function p.G380R mutation in FGFR3 gene (2).

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Reported ophthalmic features associated with achondroplasia include keratoconus, simple microphthalmos, Crouzon syndrome, telecanthus, exotropia, inferior oblique overaction, angle anomalies, Duane retraction syndrome, cone-rod dystrophy, and chorioretinal coloboma (3).

Pentacam rotating Scheimpflug camera (Oculus Optikgeräte GmbH, Wetzlar, Germany) promises quantitative information and qualitative imaging of the anterior and posterior surfaces of the cornea and anterior chamber parameters such as anterior chamber depth (ACD) and anterior chamber volume (4).

Hysteresis is a measurement of viscous properties, whereas the corneal resistance factor (CRF) is dominated by elastic properties of cornea and is an overall indicator of the corneal resistance. It has been

shown that corneal hysteresis (CH) and CRF measured by Ocular Response Analyzer (ORA) are correlated with central corneal thickness (CCT) (5). These results suggest CH and CRF are closely related, but they do not represent the same physical/biomechanical properties. ORA (Reichert, Inc, Depew, NY) has been developed to measure the intraocular pressure (IOP) and CH and CRF.

Herein we report the ophthalmologic examination, Pentacam parameters and corneal biomechanics of 4 genetically proven cases of achondroplasia. To the best of our knowledge this is the first report on the corneal biomechanics of achondroplasia patients.

Case Report

Besides full ocular examination measurements with Pentacam and ORA were performed. Pentacam measurements were obtained under standard dim light conditions. The technique of Pentacam analysis has been described previously (4). This imaging provides measurements of ACD, anterior chamber volume, anterior chamber angle width, CCT, pupil size, and keratometry.

For ORA measurements, the patients were asked to fixate at the target in the instrument and a noncontact probe scanned the central area of the eye and released an air puff and then sent a signal to the ORA (5). ORA calculated and then displayed the CH, CRF, and IOP both as corneal compensated (IOPcc) and as Goldmann correlated (IOPg) on the computer screen attached to the ORA.

Investigation of Gly380Arg mutation of FGFR3 gene was performed by sequencing. Genomic DNA was isolated from peripheral blood cells by standard techniques. To amplify the genomic region covering the mutation in the FGFR3 gene F: 5'- AGG AGC TGG TGG AGG CTG A -3' and R: 5'- GAG ATC TTG TGC ACG GTG G -3' primers were used. PCR products were sequenced by the dye termination method using a DNA sequencing kit (Perkin-Elmer, Foster California, USA) and analyzed using The ABI Prism 3100 sequence analyzer (Applied Biosystems, Foster, California, USA).

Visual acuity of all patients were 20/20 without any refractive corrections in both eyes. Anterior and posterior segment evaluation of the patients were within normal limits in both eyes. No topographic anomaly such as keratoconus or keratoglobus was detected in any of the patients. Pentacam and ORA evaluation of the cases are seen in Table-1. None of the patients had any abnormality of the posterior segment or the optic nerves including glaucomatous findings.

All patients were found to have heterozygous gain of function p.G380R mutation in FGFR3 gene.

Written informed consent was obtained from the patients for publishing the individual medical records.

Table-1. Pentacam and ORA Measurements of the Patients.

Patients	Age	Gender	R-CCT (µ)	L-CCT (µ)	R-ACD (mm)	L-ACD (mm)	R-K-mean (D)	L-K-mean (D)
DS	13	M	616	623	2.98	3.00	42.55	42.20
OE	9	F	599	592	3.02	3.01	44.55	44.85
TO	17	M	565	576	3.02	3.05	42.55	42.85
YY	3	M	583	570	2.85	2.98	42.60	42.70
	R-CH (mmHg)	**L-CH (mmHg)**	**R-CRF (mmHg)**	**L-CRF (mmHg)**	**R-IOPcc (mmHg)**	**L-IOPcc (mmHg)**	**R-IOPg (mmHg)**	**L-IOPg (mmHg)**
DS	12.7	11.6	13.4	11.9	16.5	16.3	18.9	17.3
OE	9.5	8.4	15.5	11.7	33.7	26.8	35.0	25.5
TO	11.9	11.8	11.3	10.8	13.3	12.0	14.3	12.6
YY	12.2	10.5	12.0	12.4	14.5	21.2	15.9	21.7

CCT: Central corneal thickness; ACD: Anterior chamber depth; Kmean: Mean keratometry; CH: Corneal hysteresis; CRF: Corneal resistance factor; IOPcc: Cornea compensated intraocular pressure; IOPg: Goldmann correlated intraocular pressure; IOP G: Goldmann applanation tonometry.

Discussion

As demonstrated in transgenic mice models FGF-3 plays a role in corneal development and epithelial differentiation (6). Immunoreactive FGRF3 was found throughout the cornea, and intense positivity was seen in the corneal epithelium, endothelium, Descemet's membrane, and fibroblasts of the substantia propria (7). FGFR3 is upregulated in skin wounds and in migrating neural crest cells during development (8). Therefore, FGF-3 and FGFR3 might participate in corneal healing and cell migration. Hence, their maldistribution in corneal tissue might cause unexpected changes on ophthalmological practice. As increased signal transduction from a mutated FGFR3 causes an abnormality of cartilage formation in achondroplasia, the

same mutation might lead to abnormality in corneal parameters such as CCT, CH and CRF.

The Pentacam Scheimpflug is a relatively new, non-contact optical system, specifically designed to image the anterior segment of the eye. It is an easy-to-use anterior segment analyser, and its high reliability and repeatability, have been documented (9).

ORA is a new non-contact tonometer developed by Reichert, that measures IOP and new metrics, CH and CRF. It uses a metered collimated air pulse to applanate the cornea and an infrared electro-optical system to record inward and outward applanation events. The air pulse deforms the cornea through an initial applanation event, then beyond into concavity, and gradually subsides, allowing the cornea to rebound through a second applanation. This dynamic assessment of corneal biomechanical properties provides metrics of both the cornea's viscous and elastic qualities as CH and CRF, respectively (5). Many studies showed that ORA values - especially CH – vary, some subjects with diseases have normal CH measurements whereas some normal subjects have abnormal CH values. This overlap of CH values presents major challenges when using ORA as a diagnostic tool (5,10). However, CH and CRF are accepted as pressure-independent risk factors for glaucoma (10). Lower the CH value higher the risk for glaucoma is.

Among the 4 achondroplasia patients CCT was over normal limits in both eyes of one patient, and CH and CRF was lower in three eyes of two patients with accompanying high IOP readings. Although we did not detect any glaucomatous damage in our suspected cases, these results might suggest that in achondroplasia the affection of FGFR3 could be related to a more prone situation for glaucoma formation. The lack of any glaucomatous damage in our suspected cases might be related to the young age of the patients. Further studies with larger number of achondroplasia patients are needed to demonstrate the effects of achondroplasia in cornea and corneal biomechanics.

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