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Original Article

Evaluation of macula, optic nerve and choroid in children with joint hypermobility

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Abstract

Aim: To evaluate the macula, optic nerve and choroid layer by using Spectral Domain (SD)-OCT in children with joint hypermobility (JH)

Material and Methods: In this cross-sectional case control study, 25 eyes of 25 children with JH diagnosed by rheumatological examination and 37 eyes of 37 healthy children were evaluated. Images were taken with SD -OCT. Two groups were compared in terms of mean central macular thickness, macular volume, ganglion cell complex (GCC) thickness, retina nerve fiber layer (RNFL) thickness and choroidal thickness (CT). CT was measured at the fovea; other CT measurements were taken 1,000 µm away from the fovea at the nasal and temporal regions and 1000 µm away from the optic disc at the nasal and temporal regions.

Results: Mean subfoveal CT was 293.85±40.74 µm in JH group and 301.66±49.47 µm in the control group (p=0.548). There was no significant difference regarding to the mean macular and peripapillary CT values of all regions (P >0 .05 for all points). Moreover, the mean thicknesses of the RNFL, macula, and GCC did not differ between the two groups.

Conclusion: This study showed that CT of children with JH is similar to those of healthy controls. In addition, there was no difference in macular thickness, RNFL and GCC between the two groups. These findings suggest that posterior segment structures are not affected in individuals with JH.

Keywords: Joint hypermobility; choroid; macula; optic nerve.

INTRODUCTION

Joint hypermobility syndrome (JHS) is defined as a connective tissue disease manifested by musculoskeletal symptoms and generalized joint laxity (1,2). The prevalence of JH ranges from 5% to 30% whereas the prevalence of JHS was reported as 0.75% to 2% (3-7). Even though JH may be seen as a part of syndromes such as JHS, Ehler-Danlos Syndrome (EDS) and Marfan syndrome (8), it is not accepted as a disease and may be present in healthy people. Pathologic ocular findings such as laxity of the eyelids, conjuctivalchasis, keratoglobus, keratoconus, lens luxation, pathologic myopia, angioid streaks, scleral thinning and retinal detachment were found in these syndromes coexistent with JH. Collagen and connective tissues are mainly affected by these syndromes (9-13).

Cornea and sclera predominantly consist of type I collagen fibers (14). Small amounts of type 3 and type 5 collagen fibers are also found in sclera (15). Although few studies had investigated the relation between the anterior segment findings and JH, there is not any information regarding to the effect of JH on the posterior segment structures of the eye. A linear relationship between scleral thickness and choroidal thickness has been reported (16). Collagen defects that may generate changes in the sclera layer may affect the choroid layer in the presence of JH.

In our study, we aimed to determine whether there is a change in the macula, optic nerve and choroid of the children with JH by using SD-OCT.

MATERIAL and METHODS

This study was designed as cross-sectional case control study. Twenty-five eyes of 25 children with JH who

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attended to the pediatric rheumatology out-patient clinic of University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital were evaluated and they are accepted as JH group. Thirty-seven eyes of 37 patients who attended to the ophthalmology outpatient clinic of University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital for ophthalmic examination without any known systemic disease were enrolled as control group. The study was conducted in accordance with the approval of the ethics committee of University of Health Sciences Kanuni Sultan Suleyman Training and Research Hospital (approval number: KAEK/2018.3.3) and Helsinki Declaration. Informed consent was obtained from all participants and their legal parents.

All patients underwent detailed ophthalmic examination including refractive, biomicroscopic and fundoscopic evaluation. The refraction measurements were done by using auto-refractometer device (KR-800, Topcon, Tokyo, Japon). Axial lenghth (AL) measurements were done by using AL- Scan NİDEK biometry device. Patients who had a history of intraocular surgery and patients with ocular diseases other than refractive errors were excluded from the study. Participants with spherical equivalent (SE) more than 4 diopters with hyperopia or myopia and whose (AL) were shorter than 21 mm or longer than 24.50 mm were not included in the study.

Diagnosis of joint hypermobility (JH) is made according to Beighton score of 4 or more, which determines whether there is increased elasticity in 5 body regions of the spine/hip, elbow, 5th metacarpal joint, thumb-wrist and knee (17). A detailed rheumatologic examination was also performed to the control group and children whose Beighton score were under 4 were included to the control group. Participants who had any accompanying rheumatological disease were excluded from study.

Images were taken by using Cirrus HD-OCT 4000 (Carl Zeiss Meditec, Inc. Dublin, CA, USA) with Spectral Domain (SD) device from the all participants. Cirrus OCT device calculates the values of the macular thickness, macular volume, ganglion cell thickness by using the software of 512X128 macular cube measurement protocol software. This measurement protocol consists of 512 horizontal B Scan scanning sections in a 6mm X 6mm area and 128 scanning in each section. The retinal nerve fiber layer (RNFL) thickness values are also calculated by the software of the device after the optic disc measurement is done.

HD 5 line raster and 4096 A- scans by 6mm are facilities of the Cirrus SD-OCT device. The Cirrus-OCT 4000 analyzes the image of the vitreoretinal interface with a zero-delay technique. The Choroidal thickness (CT) was calculated by manual measurement of the distance between the inner surface of the sclera and the outermost highly reflective band represent the RPE as described in the literature (18). Horizontal lines of 1000 µm were created from the fovea and the optic nerve by using the software installed in the Cirrus HD-OCT-4000 device. The lines were also drawn up to the inner surface of the sclera from the RPE as perpendicular to the horizontal lines to measure the choroidal thickness. The device software automatically outputs the length of the lines. CT was measured at the fovea, 1 mm away from the fovea in the nasal and temporal regions, 1 mm away from the optic disc in the nasal and temporal regions by using previously described method (Figure 1). CT was measured by an experienced investigator (SEB).

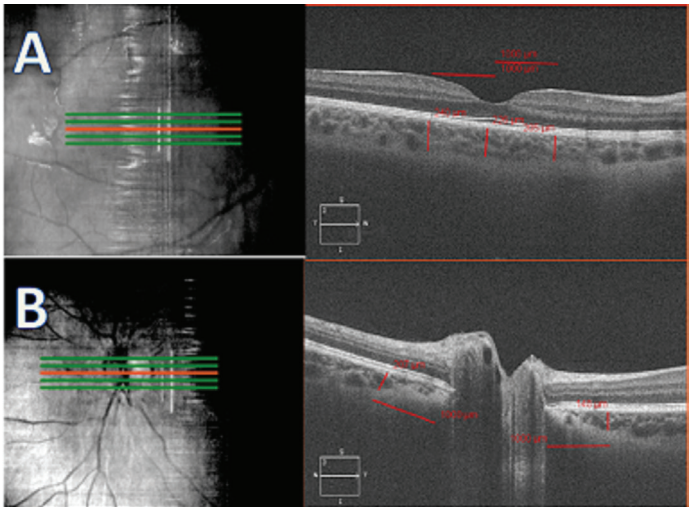

Figure 1. Perifoveal choroidal thickness measurement technique is shown on the upper side. Peripapillary choroidal thickness measurement technique is shown on the lower side

Statistical analysis used the SPSS (SPSS Inc, PASW Statistics for Windows, Version, 18.0, Chicago, USA). The normality of the data was confirmed by using the Kolmogorov- Smirnov test ($p > 0.05$). Study and control group data abiding by normal distribution were compared with the "independent t" test. P value less than 0.05 was accepted as statistically significant.

RESULTS

Demographic Findings

The mean age of the children with JH was 10.56±4.07 years and the mean age of the control group individuals was 11.29±2.65 years. There was no significant difference between the groups in terms of gender, AL, SE and body mass index (BMI) (Table 1).

Choroidal Thickness

The CT at the fovea and 1,000 µm away from the fovea and optic disc at the nasal and temporal regions are shown in Table 2. There was no statistically significant difference between the two groups.

RNFL, Macula, and GCC Thicknesses

There was no statistically significant difference between the groups in terms of macular thickness, RNFL and, ganglion cell complex (GCC) thickness (Table 2).

Table 1.Demographic Findings			
	Joint Hypermobility Group	Control group	p value*
Age (year)	10.56±4.07	11.29±2.65	0.39[1]
Axial Length (mm)	23.02±0.81	23.11±0.71	0.68[1]
Spherical equivalent (D)	-0.15±1.01	-0.10±1.17	1.0[2]
Body Mass Index: (kg/m²)	18.58±3.32	19.9±5.49	0.51[2]

D= Diopter; *0.05 considered statistically significant; [1]independent t test; [2]Mann Whitney U test

Table 2. Comparison of Optic Coherens Tomography Measuraments Between Hipermobil and Control Group			
	Joint Hypermobility Group	Control group	p value*
Retina Nerve Fiber Layer Thickness (µm)	94.57±8.78	97.67±7.68	0.166
Macular Thickness (µm)	236.33±22.61	233.62±25.19	0.685
Macular Volume (mm³)	9.92±0.37	9.95±0.40	0.776
Ganglion Cell Thickness (µm)	82.55±6.09	83.94±5.51	0.387
Subfoveal CT	293.85±40.74	301.66±49.47	0.548
CT at 1,000 µm away from the fovea in the nasal region	272.33±37.57	270.36±48.35	0.875
CT at 1,000 µm away from the fovea in the temporal region	297.33±64.29	307.63±57.72	0.543
CT at 1000 µm away from the optic disc in the nasal region	215.19±51.38	216.06±45.45	0.949
CT at 1000 µm away from the optic disc in the temporal region	196.95±41.80	226.55±57.78	0.052

CT: Choroidal Thickness; *independent t test

DISCUSSION

In the literature, there are few studies investigating the ocular findings of JH/JHS. Besides, there is not any study analyzing the macular thickness, macular and peripapillary CT, RNFL and GCC thickness in children with JH.

The incidence of high myopia and vitreous degeneration is increased in connective tissue diseases such as Stickler syndrome (19). Also, it has been reported that the incidence of pathological myopia increases in JHS EDS- Hypermobility type (HT) patients (10). There is increasing evidence that changes in the structure and composition of the sclera or vitreous extracellular matrix are the most important factors affecting the axial length of the eye (20). Therefore, it has been hypothesized that abnormalities of sclera, vitreous extracellular matrix, or both may contribute to myopia in JHS/EDS-HT (21). In a recent study investigating the anterior segment findings of JHS /EDS-HT, pathologic myopia and abnormal vitreous were reported in 15.9% of the patient group, whereas in the control group pathological myopia was not reported (10). In the aforementioned studies, we would like to note that myopia was increased in the JHS / EDS-HT group, not in the JH. In a study investigating the prevalence of JH in high school students, there was no difference in the frequency of myopia between the JH group and the control group (22). Because the high myopia and axial length were factors affecting choroidal thickness, patients with high refractive error and increased axial length were excluded from our study. Therefore, our study cannot give information about the frequency and severity of myopia in JH patients.

Choroid is the tissue between the retina and sclera and has one of the highest rates of blood flow in humans. Choroid tissue provides the oxygen and metabolite requirements of outer retinal layer by means of this high blood flow (23). Impairments in ocular hemodynamics and scleral layer adversely affects CT (24). Scleral thinning and increased AL with degenerative myopia causes thinning of the choroid layer. It is also known that thickening of the choroid layer is also observed in patients with high hypermetropia associated with increased scleral thickness (16,25).

In our study no significant difference were found between the groups in terms of parameters that may affect the thickness of choroid such as intraocular pressure, AL, SE and BMI. Being aware of the systemic causes that may affect the CT may be helpful to diagnose the ocular diseases. Vogt-Koyanagi-Harada disease is characterized by diffuse choroiditis and coexistent with the thickening of choroid (26). The thickening of the choroid also occurs in patient with central serous chorioretinopathy (27). The examination of choroid is crucial in differential diagnosis of the age related macular degeneration and polypoidal choroidal vasculopathy (28). JH had a prevalence reaching to 30% in the community, knowing whether CT is changing in these individuals may be helpful for diagnosis of ocular diseases. As far as we know, since there is no other study that evaluated the posterior segment structures with OCT method in individuals with JH or JHS / EDS-HT, there is

no available data to compare our results with previous studies.

In a study investigated extra-articular findings of JHS, no pathological findings were reported in sclera, iris and cornea in slit lamp examination. Tilted optic disc was reported in 5.1% of the patients and no retinal pathology was reported in any patient (29). Our study is compatible with the literature about this aspect.

CONCLUSION

In conclusion, this study showed that CT of children with JH is similar to those of healthy controls. In addition, there was no difference in macular thickness, RNFL and GCC between the two groups. These findings suggest that posterior segment structures are not affected in individuals with JH. This result should be taken into consideration when choroid, macula and optic nerve are evaluated in chorioretinal disease or clinical research.

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REFERENCES

1. Grahame R, Bird HA, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 2000;27:1777-9.
2. Grahame R, Hakim AJ. Hypermobility. Curr Opinion Rheumatol 2008;20:106-10.
3. El-Garf A, Mahmoud G, Mahgoub E. Hypermobility among Egyptian children: prevalence and features. J Rheumatol 1998;25:1003-5.
4. Harreby M, Nygaard B, Jessen T, et al. Risk factors for low back pain in a cohort of 1389 Danish school children: an epidemiologic study. Eur Spine J 1999;8:444-50.
5. Qvindesland A, Jonsson H. Articular hypermobility in Icelandic 12-year-olds. Rheumatol (Oxford) 1999;38:1014-6.
6. Rikken-Bultman DG, Wellink L, van Dongen PW. Hypermobility in two Dutch school poulations. Eur J Obstet Gynecol Reprod Biol 1997;73:189-92.
7. Subramanyam V, Janaki K. Joint hypermobility in south Indian children. Indian Pediatr 1996;33:771-2.
8. Engelbert RH, Bank RA, Sakkers RJ, et al. Pediatric generalized joint hypermobility with and without musculoskeletal complaints: a localized or systemic disorder? Pediatrics 2003;111:e248-e54.
9. Cameron JA. Corneal abnormalities in Ehlers-Danlos syndrome type VI. Cornea 1993;12:54-9.
10. Gharbiya M, Moramarco A, Castori M, et al. Ocular features in joint hypermobility Syndrome/Ehlers-Danlos syndrome hypermobility type: a clinical and in vivo Confocal Microscopy Study. Am J Ophthalmol 2012;154:593-600.e1.
11. Green W, Friedman-Kien A, Banfield W. Angioid streaks in Ehlers-Danlos syndrome. Arc Ophthalmol 1966;76:197-204.
12. Segev F, Héon E, Cole WG, et al. Structural abnormalities of the cornea and lid resulting from collagen V mutations. Invest Ophthalmol Vis Sci 2006;47:565-73.
13. Whitaker JK, Alexander P, Chau DY, et al. Severe conjunctivochalasis in association with classic type Ehlers-Danlos syndrome. BMC Ophthalmol 2012;12:47.
14. Meek KM, Boote C. The organization of collagen in the corneal stroma. Exp Eye Res 2004;78:503-12.
15. Marshall G, Konstas A, Lee W. Collagens in ocular tissues. Br J Ophthalmol 1993;77:515-24.
16. Ikuno Y, Tano Y. Retinal and choroidal biometry in highly myopic eyes with spectral-domain optical coherence tomography. Invest Ophthalmol Visual Sci 2009;50:3876-80.
17. Fikree A, Aziz Q, Grahame R. Joint hypermobility syndrome. Rheum Dis Clin North Am 2013;39:419-30.
18. Spaide RF, Koizumi H, Pozonni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol 2008;146:496-500.
19. Snead M, McNinch A, Poulson A, et al. Stickler syndrome, ocular-only variants and a key diagnostic role for the ophthalmologist. Eye (Lond) 2011;25:1389-400.
20. Halfter W, Winzen U, Bishop PN, et al. Regulation of eye size by the retinal basement membrane and vitreous body. Invest Ophthalmol Vis Sci 2006;47:3586-94.
21. Malfait F, Hakim A, De Paepe A, et al. The genetic basis of the joint hypermobility syndromes. Rheumatology 2006;45:502-7.
22. Seçkin Ü, Tur BS, Yılmaz Ö, et al. The prevalence of joint hypermobility among high school students. Rheumatol Int 2005;25:260-3.
23. Alm A, Bill A. Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (Macaca irus): a study with radioactively labelled microspheres including flow determinations in brain and some other tissues. Exp Eye Res 1973;15:15-29.
24. Kang HM, Lee CS, Lee SC. Thinner subfoveal choroidal thickness in eyes with ocular ischemic syndrome than in unaffected contralateral eyes. Graefes Arch for Clin Exp Ophthalmol 2014;252:851.
25. Demircan A, Altan C, Osmanbasoglu OA, et al. Subfoveal choroidal thickness measurements with enhanced depth imaging optical coherence tomography in patients with nanophthalmos. Br J Ophthalmol 2014;98:345-9.
26. Hosoda Y, Uji A, Hangai M, et al. Relationship between retinal lesions and inward choroidal bulging in Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2014;157:1056-63.e1.
27. Gemenetzi M, De Salvo G, Lotery A. Central serous chorioretinopathy: an update on pathogenesis and treatment. Eye (Lond) 2010;24:1743-56.
28. Koizumi H, Yamagishi T, Yamazaki T, et al. Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy. Graefes Arch Clin Exp Ophthalmol 2011;249:1123-8.
29. Mishra MB, Ryan P, Atkinson P, et al. Extra-articular features of benign joint hypermobility syndrome. Br J Rheumatol 1996;35:861-6.