Choroidal Thickness in Lipoid Proteinosis

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Sanliurfa Egitim ve Arastirma Hastanesi

Research Article

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Abstract

Purpose: To assess choroidal thickness in patients with lipoid proteinosis versus healthy subjects using enhanced depth imaging optical coherence tomography.

Methods: 40 eyes of 20 patients and the same number of age and sex-matched healthy individuals were enrolled. Comprehensive ocular examinations including measurement of best-corrected visual acuity, spherical equivalent values of refractive errors, and axial length were performed. Choroidal thickness at three points (subfoveal, 500 μm nasal and temporal regions) were measured.

Results: The mean age was 15,68 ± 5,98 years in the patient group and 16,48 ± 5,69 years in the control group. Mean choroidal thickness was statistically significantly thicker at each point in patients with lipoid proteinosis compared to the healthy controls: subfoveal, temporal and nasal choroidal thickness measurements were 414,13 ± 53.88, 359.97 ± 64.75, 322.10 ± 56.74 in the study group; 341.60 ± 42.01, 329.55 ± 41.30, 295.44 ± 43.07 in the control group, respectively ($P < 0.05$).

Conclusion: Patients with lipoid proteinosis have thicker choroid compared to control eyes. Hyalin deposition and ensuing potential inflammation in the disease process may explain this finding.

Introduction

Lipoid proteinosis, also named as Urbach-Wiethe's disease or hyalinosis cutis et mucosae is an exceedingly rare autosomal recessive disorder first defined in 1929 by Urbach and Wiethe and is characterized by deposition of amorphous hyaline substance in multiple tissues.[1, 2] Although the disease may be seen anywhere in the body, the skin and mucous membranes of the mouth and the upper airways are affected in the overwhelming majority of patients.[3, 4] It is characterized by a constellation of systemic findings; hoarseness of voice, which is usually the first sign noticed by parents at birth or early childhood, skin lesions such as nodules, papules and acneiform scaring, difficulty in swallowing according to the tongue involvement, neurological and psychiatric manifestations, and pathognomonic yellow-white coalescing papules on the eyelid margins called moniliform blepharoris.[5–7] The extracellular matrix protein 1 (ECM1) gene, which plays a pivotal role in the proliferation and differentiation of epidermis, regulation of angiogenesis and basement membrane, binding of dermal collagens, has been implicated as a trigger factor for the disease when a gene mutation occurs.[3]

The choroid, which provides nourishment to the outer layers of the retina, is a highly vascularized region of the eye comprising connective tissue, melanocytes, and mast cells.[8] It has been shown that the choroidal thickness can vary depending on many factors and measurement of that using optical coherence tomography (OCT) has conferred an essential benefit not only in ophthalmic diseases but also in different systemic diseases, particularly of which there is a vascular component.[9–11] Enhanced depth imaging OCT (EDI-OCT) is a revised technique of OCT in which the device is advanced further towards the eye than usual, thereby obtaining better visualization of choroidal details by bringing the images closer to the zero point.[12]

Knowledge about how the choroidal structure is affected in eyes with lipoid proteinosis is limited. There are only a few cases shown infiltration of the vascular structure of the choroid by hyaline deposits; however, no data was found analyzing the choroidal thickness in patients with lipoid proteinosis in published papers.[13] Therefore, in this prospective controlled study, We aimed to measure the choroidal thickness in patients with lipoid proteinosis using EDI-OCT.

Materials And Method

Study Design

This prospective, comparative, clinical study was conducted in patients with LP having been diagnosed in the Dermatology Department, Şanlıurfa Training and Research Hospital, Sanlıurfa, between January 2016 and August 2020

Ethics

The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee (approval number: HRU/20.16.13). Informed consent was obtained from the participants or their parents.

Study population

A total of 23 patients diagnosed based on clinical features and histopathological evaluation, were called to the ophthalmology department by phone in September 2020. Two patients were excluded because of noncooperation to the EDI-OCT, and one patient was excluded because of retinal disease and low vision. Twenty age and gender-matched healthy subjects were added as a control group. Exclusion criteria were as follows: (1) Subjects having any other systemic and ocular diseases; such as myopia and hypermetropia greater than 3 dioptres of spherical equivalent, glaucoma, best-corrected visual acuity less than 6/6, (2) previous ocular surgery, (3) topical or systemic medication in the last three months, and (4) low-quality image due to cooperation difficulties. Participants were instructed to abstain from caffeine for at least 12 hours before measurements.

Study protocol

Detailed medical information was obtained from all subjects, and a comprehensive ophthalmic examination including spherical equivalent values of refractive errors (SE), the assessment of the best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement with a pneumatic tonometer, slit examination of the anterior and posterior ocular segments, axial length (AL) measurement using A-scan ultrasound, anterior segment photography and fundus photography with cycloplegia (%1 cyclopentolate,

Alcon) (Visucam, Carl Zeiss), OCT with EDI mode (RS-3000, Nidek) were performed at a single visit. EDI-OCT images were taken before administration of the cycloplegic drops, and between 1.30 and 4 p.m so that potential effects of cycloplegia and diurnal variation in CT were minimalized.

EDI-OCT analysis

The choroidal thickness was manually measured by using the linear measurement tool of the device at the fovea and 500 µm nasal and temporal to the fovea from the outer border of the Bruch's membrane to the hyperreflective border of the inner sclera (Figure 1). All measurements were performed by the same experienced technician without any information on the eye.

Statistical Analysis

Statistical analysis was performed using the SPSS program (Version 22 software for Mac, IBM, Corp, Armonk, New York, USA). Descriptive statistics were shown in mean and standard deviation. The normality of the data was checked by the Kolmogorov-Smirnov Z test, histograms and Q-Q plots were used to assess the normality of the data. Comparisons between variables were performed using independent t-test and Mann–Whitney U test. Correlations between variables were analyzed with Pearson's or Spearman's correlation coefficients. *P*-value of < 0.05 was considered statistically significant.

Results

40 eyes of 23 patients with lipoid proteinosis and 40 eyes of 20 healthy subjects were included in the study (2 patients were excluded because of noncooperation to the EDI-OCT, and one patient was excluded because of retinal disease and low vision). The mean ages were 15,68 ± 5,98 years (range: 6 to 25; male/female ratio: 11/9) and 16,48 ± 5,69 years (range: 7 to 26; male/female ratio: 10/10), in the study and control groups, respectively. No statistical difference was found regarding age, gender, SE, AL, and IOP ($P > 0.05$) (Table 1). The mean subfoveal, temporal, and nasal choroidal thickness measurements were 414,13 ± 53.88 µm, 359.97 ± 64.75 µm and 322.10 ± 56.74 µm in the study group, respectively; 341.60 ± 42.01 µm, 329.55 ± 41.30 µm, 295.44 ± 43.07 µm in the control group, respectively. Choroidal thickness of all three regions in patients with lipoid proteinosis was statistically higher than that in the healthy subjects ($P < 0.05$) (Table 2). The foveal thickness was 233.76 ± 15.75 µm in patients with lipoid proteinosis and 232.18 ± 19.32 µm in the healthy subjects; no statistically significant difference was found between the two groups. When the correlation between age and choroidal thickness was analyzed, no significant correlation was observed between age and choroidal thickness (r = -0.111, $P = 0.662$ in the study group; r = 0.018, $P = 0.944$ in the control group).

Table 1
Demographic and ocular characteristics of the groups

	Study	Control	*P values*
Eye	40	40	
Age (years)	15,68 ± 5,98 (6–25)	16,48 ± 5,69 (7–26)	0.640
Sex (male / female)	11/9	10/10	0.759
SE (diopters)	0.19 ± 0.45	0.23 ± 0.40	0.703
AL (mm)	22.95 ± 0.79	23.29 ± 0.97	0.199
IOP (mm Hg)	14,30 ± 2.52	14,85 ± 2.57	0.278

Table 2
Mean choroidal thickness (CT) and central foveal thickness (CFT) measurements and *P* values

	Study	Control	*P values*
Subfoveal CT	414,13 ± 53.88 (254–557)	341.60 ± 42.01 (276–442)	0,000
Temporal CT	359.97 ± 64.75 (254–537)	329.55 ± 41.30 (265–436)	0,017
Nasal CT	322.10 ± 56.74 (207–414)	295.44 ± 43.07 (212–372)	0,024
CFT	233.76 ± 15.75 (205–259)	232.18 ± 19.32) (212–305)	0.697

Discussion

Lipoid proteinosis is a genodermatosis running a chronic benign but progressive course up to early adulthood.[14] The disease severity may vary from individual to individual. Presentation is usually in early childhood, but the diagnosis can be at any age.[15] Only several hundreds of cases have been reported to date; however, the disease is more common in the area where our hospital is located due to the large number of consanguineous marriages.[16] Ophthalmologists usually examine patients for a pathognomonic sign of the disease, called moniliform blepharosis which may be, albeit not typically, the first sign.[17, 18] Other rare reported ocular findings in the literature are loss of lashes, madarosis, trichiasis, glaucoma, increased central corneal thickness, conjunctival nodules, drusen, nasolacrimal duct obstructon.[13]

In some ocular and systemic diseases, choroidal thickness may determine whether the disease is an active phase or atrophic phace.[11, 19] In lipoid proteinosis, although thickening of Bruch's membrane and hyaline depositions in the choroidal vessels were described in a few cases, no study to date has described choroidal thickening.[13, 15] To our knowledge, this is the first and the largest case-control clinical study to evaluate the choroidal thickness in patients with lipoid proteinosis. The findings of the present study demonstrated that patients with lipoid proteinosis had a significantly thicker choroid than that of the healthy subjects. The choroid was thicker in all quadrants from the nasal to temporal regions. Hyaline deposition, which is the main pathology of the disease, may account for our findings. The thickening of the choroid had no effect on visual acuity in the patients; however, early deterioration in vision may occur in the elderly due to prolonged insult to the choroidal vasculature by hyaline and subsequent atrophy. In the study, our patients were younger than 25 years old; because of that, we could not observe whether long-term disease causes thinning of the choroid or not.

We also considered that the choroidal thickening in lipoid proteinosis may be as a result of the inflammatory response to hyaline material. The authors bring some information about the evidence of inflammation in lipoid proteinosis. Abtahi et al. reported a case with bilateral uveitis and LP. They theorized that inflammatory response to the deposition of hyaline material in the uveal tract may be the reason for the development of uveitis in lipoid proteinosis.[20] Aksoy and An, evaluated inflammatory markers in the disease and it was found that the neutrophil/lymphocyte ratio, which can be used as an inflammatory biomarker in some diseases such as diabetes mellitus and psoriasis vulgaris, was statistically higher than that of healthy control group.[21] In another study, It was found that oxidant parameters of blood in lipoid proteinosis were higher than those of the healthy control group.[22] In the light of these studies, we thought that a possible inflammatory response to hyaline may contribute to thickening of the choroid in patients with lipoid proteinosis.

Choroidal thickness of patients should be interpreted with caution as it may be affected by many factors such as age, refractive errors, disease duration, and axial length as well.[23] The same person may have up to 100 mm asymmetry between right and left eyes.[23] One study found that the Choroidal thickness decreases with age, but decreases much faster in old age than in relatively younger people; however, in another study, It was found no statistically significant difference in choroidal thickness between the pediatric population (313 μm) and adults (306 μm).[24, 25] There was a zero correlation between age and choroidal thickness both in lipoid proteinosis group and healthy subjects. In a study comparing choroidal thickness between sex, It was found that men have significantly thicker choroid than women; however, some other studies did not find any differences.[25, 26] Likewise, we found similar mean choroidal thickness values between males and females [male, 404.05 ± 41.77 μm, female 423.20 ± 62.53 μm in the study group (P = 0.271); male 334.10 ± 32.77 μm, female 348.50 ± 48.86 μm in the control group (P = 348)]. The mean age of subjects in the control group was 16,48 ± 5,69 years. In the study conducted by Read and colleagues (mean age 13 ± 1.4 years), subfoveal choroidal thickness in non-myopic eyes was found 359 μm.[27] Another study included 1323 healthy children, with the age of 11 and 12, SFCT was 369 μm in males and 348 μm in females.[26] Our value of the control group (341μm) was in concert with the literature.

Our study has some limitations. First, our study included patients younger than 25 years, so that choroidal thickness of older patients remains unanswered. Second, analysis of medium and large choroidal vessel separately may be essential in discussing the pathophysiology of some diseases; we calculated just the total thickness of the choroid, not considering the large and medium choroidal vessels separately nor did we perform revolutionary technology of OCT-based angiography which may shed light on our understanding of pathogenesis of choroidal thickening in lipoid proteinosis by showing choroidal microvascular network.[28, 29] Large case-control studies in patients with different disease duration are necessary but are difficult due to the low incidence of the disease.

In conclusion, choroidal thickness was significantly higher in patients with lipoid proteinosis than that of healthy subjects. Hyaline deposition and ensuing inflammation may account for our findings. Additional studies to understand more completely the tenets of our results are necessary.

Declarations

Funding:

None

Conflicts of interest:

None

Availability of data and material:

All data generated or analysed during this study are included in this article

Code availability:

none

Ethics approval:

The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee (approval number: HRU/20.16.13).

Consent to participate:

Informed consent was obtained from the participants or their parents.

Consent for pablication:

Informed consent was obtained from the all authors

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Figures

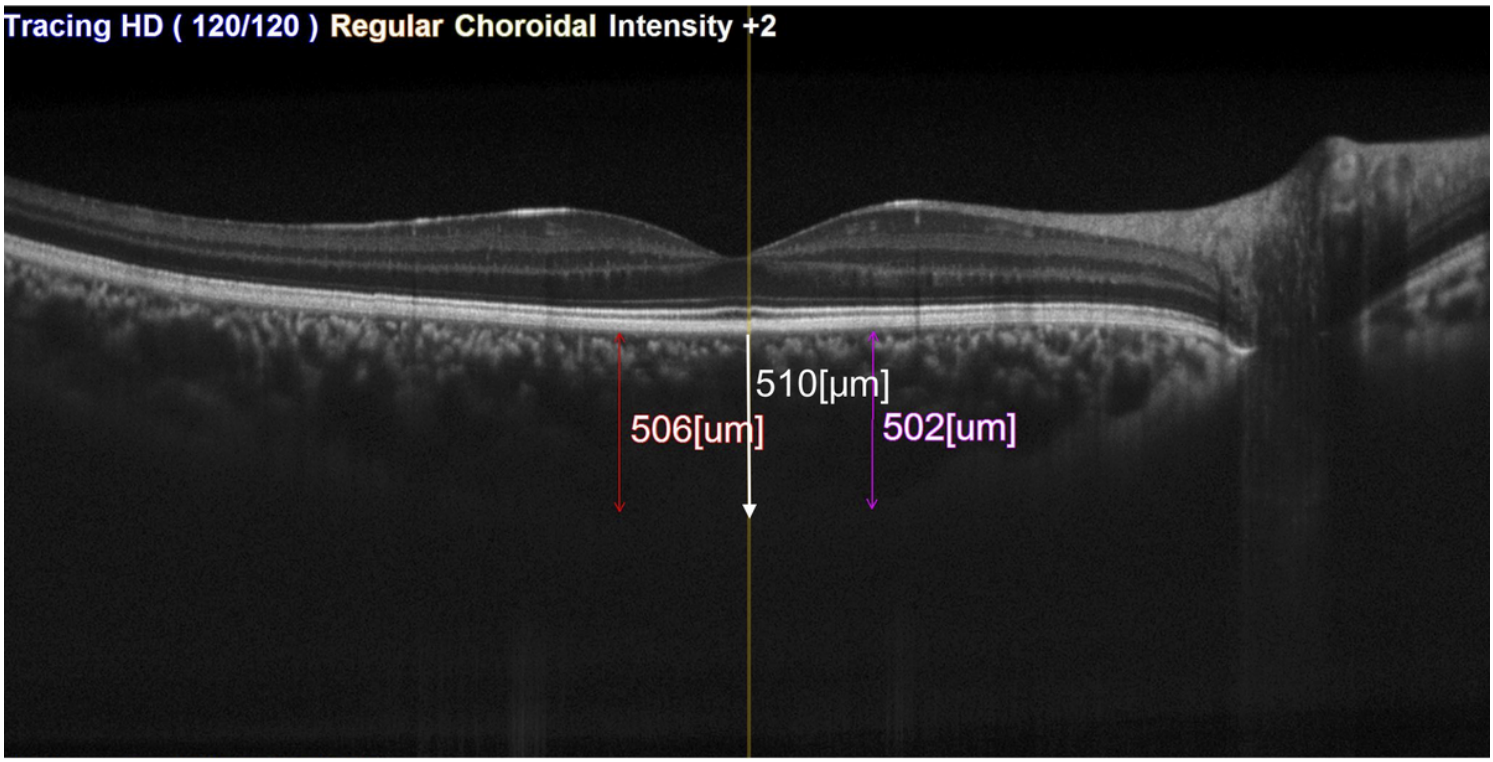

Figure 1

Subfoveal (white), temporal (purple) and nasal (red) choroidal thickness measurements by Enhanced depth imaging optical coherence tomography in a patient with lipoid proteinosis