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Familial Pathologic Myopia, Corneal Dystrophy, and Deafness: A New Syndrome

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Background: Numerous syndromes with myopia and hearing loss have been described up to now. We present a family with pathologic myopia, corneal dystrophy, and deafness distinct from these syndromes.

Cases: Ten patients in the same Turkish family were evaluated by ophthalmologic, audiologic, physical, radiologic, genetic, serologic, and biochemical examinations.

Observations: Ophthalmic examination indicated that all the cases had myopia, 7 of them had pathologic myopia, 1 had intermediate, and 2 had mild. Four of the patients with pathologic myopia had corneal dystrophy that was bilaterally manifest as white opacities in the posterior stroma near Descemet's membrane in an axial distribution; 1 of these 4 patients also had a tilted disc. Otolaryngologic examination revealed conductive hearing loss in 3 cases, mixed hearing loss in 2, and sensorineural hearing loss in 1. The results of karyotypic analyses of all cases were normal. The pedigree analysis showed the disease was inherited through successive generations as an autosomal dominant trait. The results of biochemical, serologic, and radiologic investigations were normal. The same pathophysiologic process in all cases seemed to account for the myopia, the corneal dystrophy and the deafness.

Conclusions: To our knowledge, this type of case has not been reported in the literature. Therefore, we named this syndrome "familial pathologic myopia, corneal dystrophy and deafness." **Jpn J Ophthalmol 2001;45:612–617**

Key Words: Corneal dystrophy, hearing loss, pathologic myopia, tilted disc, syndrome.

Introduction

There are a number of syndromic and nonsyndromic diseases that cause hearing and visual impairment.[1] The medical literature contains numerous reports of oculosystemic syndromes that list myopia as one of the associated features. Some of these associations are real, and the others are anecdotal. Recognizing these syndromes in a patient with myopia and hearing loss may help to direct the patient to appropriate medical follow-up and treatment.[2] The dysgeneses, dystrophies, and degeneration of the cornea account for a broad spectrum of ocular abnormalities, ranging from clinical curiosities to sight-threatening anomalies.[3] We herein describe a family with pathologic myopia, corneal dystrophy, and hearing loss. To our knowledge, there has been no case described in the literature with only these particular features.

Materials and Methods

A male patient with decreased visual acuity and hearing loss was examined, followed by 9 additional patients from the same family (4 female and 5 male) with similar problems. The patients were evaluated by ophthalmologic, audiologic, physical, radiologic, genetic, and biochemical examinations.

The following ophthalmologic examinations were conducted: visual acuity with and without glasses, intraocular pressure with applanation tonometer, anterior chamber angle with Goldmann triple-mirror lens, and

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slit-lamp biomicroscopic examinations. Fundus examination was done with direct and indirect ophthalmoscopy, and with 90 D lens after full mydriasis to look for degenerative changes in the retina. The axial length was measured by using A-scan biometry five times in succession, and then the mean value was used for axial length.

After the patients were examined audiologically, pure tone audiograms were performed in a soundproof room, using an Interacoustics Audiometer. Pure tone thresholds, short increment sensitivity index and tone decay were obtained from 250 to 8000 Hz at octave intervals, both by air and bone conduction. Narrow band masking was used where indicated. Acoustic reflex, middle ear tympanometry and compliance were investigated using a tympanometer. Fistula test was elicited by placing a pneumatic otoscope in the ear canal and transmitting positive and negative pressures to the drum. Caloric tests were also obtained. Because otosclerosis was suspected, exploratory tympanotomy was performed, in another center, in the right ear of one female case from this family.

Computed tomographic examination of the temporal bone and plain radiography of cranium, vertebral column, pelvis, elbow, and knee were performed for each patient. Conventional cytogenetic and pedigree analyses were done. Serology for syphilis and all routine biochemical tests were performed.

Results

General Systemic and Ophthalmologic Examination

Clinical and ophthalmological findings for all cases are given in Table 1. Myopia was observed in all 10 patients, of whom 7 had pathologic myopia, 1 had intermediate myopia, and 2 had mild myopia. Visual acuity was prominently decreased in 7 of the 10 patients.

Four patients had bilateral corneal dystrophy manifested as white opacities in the posterior stroma near Descemet's membrane, in an axial distribution. Within the opacities, there were also vertical, horizontal, and partially oblique clear spaces, creating an appearance of squares and triangles at the level posterior to the stroma (Figures 1A and 1B).

In addition to optic nerve myopic changes, one of the dystrophic patients had a tilted disc. One patient had had a cataract operation following eye trauma 35 years previously. Another patient with pathological myopia but without corneal dystrophy had been operated on for retinal detachment 25 years previously. The anterior segments of all cases were found to be normal by slit-lamp biomicroscopic examination. No abnormality in the iridocorneal angle was detected by Goldmann triple-mirror lens examination, and the intraocular pressure was normal.

In the fundus examination, thinning of retina, pigment epithelial atrophy and myopic crescent were detected in the family members with pathologic myopia. These cases with pathologic myopia showed such peripheral changes as choroideal atrophy and posterior vitreous detachment. One case also had posterior staphyloma.

Otolaryngologic Examination

There was conductive hearing loss in 3 of the patients, mixed type in 2 and sensorineural in one. Hearing loss was asymmetrical in 4 of the patients. No patients had middle ear effusion or other diseases causing hearing impairment, and they showed normal tympanogram and acoustic reflexes. None of the patients complained of vertigo, tinnitus, diplacusis, or intolerance of loudness.

The earliest evidence of the syndrome was ocular involvement. The onset of visual manifestations was in the first decade of life, and hearing impairment appeared in the second decade. Hearing loss was also noted in the patients with severe pathologic myopia and corneal dystrophy. There was no pathologic finding in the right ear of the one family member who had undergone exploratory tympanotomy, which explained the hearing loss. The results of the fistula and caloric tests were normal in all the patients.

Genetic Examination and Laboratory Investigations

Cytogenetic analysis revealed no specific structural or numerical chromosome aberrations in any of the patients. Pedigree analysis indicated that this syndrome was autosomal dominantly inherited, as shown in Figure 2. The findings of all routine biochemical and serologic tests were found to be normal. Family members, including individuals affected with the syndrome, had normal life span and intelligence.

Discussion

We report on a family with pathologic myopia, corneal dystrophy, and hearing loss. To date, numerous syndromes with myopia and hearing loss have been described. All these syndromes include skeletal, cranial, and arthritic anomalies as well as myopia and hearing loss. Table 2 summarizes the differences and the simultaneous presence of myopia and hearing loss in these patients with similar syndromes in previous reports.[4–11]

Our patients showed neither joint enlargement nor

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Table 1. Clinical and Ophthalmological Findings in Family Members Studied

Patient No.	Sex	Age (y)	Best Corrected Visual Acuity*	Myopia (D)†	Corneal Dystrophy	Hearing Level (dB)‡	Metz Recruitment	Axial Length (mm)
1-AK	Male	55	R: 3 fcm	−23.00	+	56 M	+	R:31.5
			L: 3 fcm	−24.00	+	54 M	+	L:31.6
2-AI	Female	53	R: 2 fcm	−25.00	+	60 C	+	R: 31.2
			L: 1 fcm	−25.00	+	65 C	+	L: 31.9
3-MK	Male	51	R: 0.4	−12.00	+	55 SN	+	R: 28.2
			L: 0.4	−9.00	+	50 SN	+	L: 27.9
4-SK	Male	47	R: 0.6	−8.00	−	15	−	R: 24.5
			L: 0.7	−8.50	−	15	−	L: 24.3
5-EG	Female	44	R: 2 fcm	−16.00	−	60 C	+	R: 31.6
			L; 1 fcm	−19.00	−	60 C	+	L: 31.4
6−EK	Male	36	R: 2 fcm	−17.00	+	90 M	+	R: 34.6
			L: 3 fcm	−18.00	+	90 M	+	L: 34.1
7-HK	Male	30	R: 0.1	−14.00	−	40 C	+	R:28.6
			L: 0.1	−12.00	−	37 C	+	L: 27.8
8-UK	Male	21	R: 0.8	−8.00	−	10	−	R: 24.8
			L: 0.9	−7.50	−	12	−	L: 24.6
9-SK	Female	20	R: 1.0	−1.00	−	10	−	R: 24.6
			L: 1.0	−1.50	−	10	−	L: 24.3
10-AG	Female	13	R: 1.0	−1.25	−	10	−	R: 24.4
			L: 1.0	−1.25	−	10	−	L: 24.3

* R: right, L: left, fcm: finger counting from meter (visual acuity assessed by Snellen chart).
† D: diopter.
‡ dB: decibel, M: mixed, C: conductive, SN: sensorineural.

abnormal joint mobility, and the skulls were normal. Physicomotor development, weight, height, and mental development were normal. The eye problem appeared in the first decade of their life, hearing loss in the second decade, and the increasing severity of both followed. In differential diagnosis, mucopolysaccharidosis is an important corneal involvement, in which there is corneal clouding.[10] In our patients, the corneal dystrophy did not affect their vision.

Although corneal dystrophy may be apparent at birth, it usually is initially seen later, in the first or second decade of life. Dystrophies show a hereditary pattern (usually autosomal dominant), are bilateral, symmetric, and may be progressive. They tend to affect the central cornea more than the periphery and to be avascular, and they usually are unrelated to any other local or systemic disease.[12]

Posterior crocodile shagreen is a bilateral con-

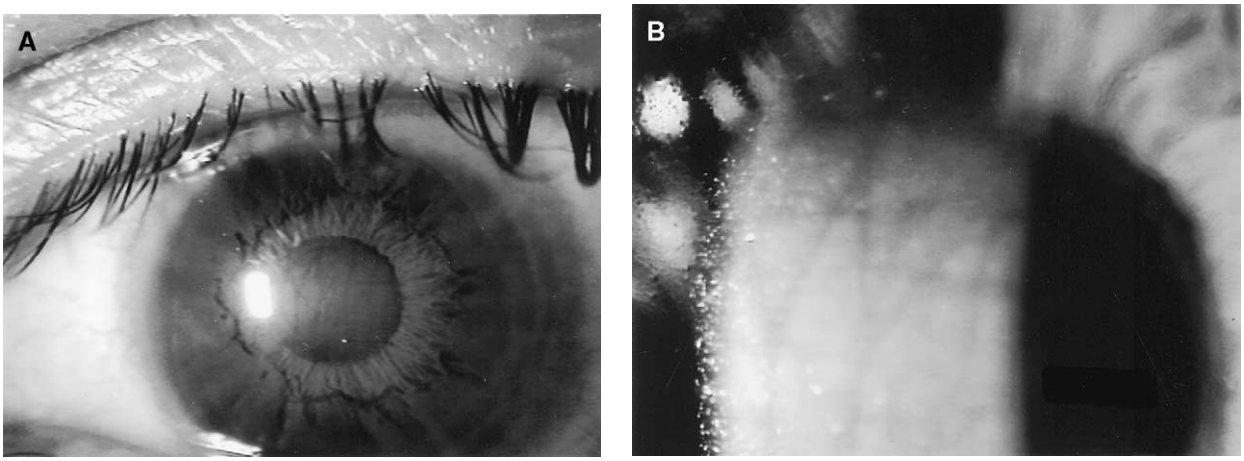

Figure 1. Corneal appearances in patient 6. White opacity and clear spaces, creating an appearance likened to square or triangle, in posterior stroma and near Descemet's membrane. A, anterior view. B, zoomed slit-lamp view.

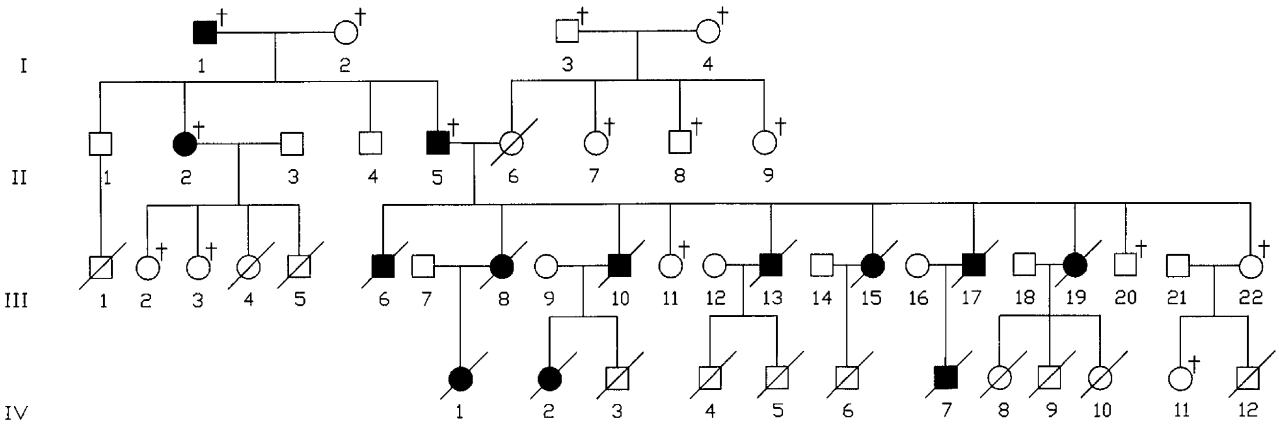

Figure 2. Pedigree chart of reported family, illustrating autosomal dominant trait. □: male, ○: female, ■: affected male, ●: affected female, /: examined, †: deceased.

dition marked by a series of small, grayish white, polygonal opacities separated by relatively clear spaces, creating an appearance that looks like crocodile leather. This pattern may be seen in either the anterior or posterior corneal layer and is usually prominent centrally. Vascularization does not occur, and only rarely are opacities dense enough to reduce vision.[12] Crocodile shagreen may be seen in the superficial or deep corneal stroma and is best seen by wide-slit oblique illumination. The superficial type is usually seen as an aging change, but either type may be familial and neither produces visual symptoms.[13]

Posterior crocodile shagreen is age-related and may be unilateral.[14] It should be noted that our patients with corneal dystrophy were 35 to 55 years old. This age range is not higher than that of patients with posterior crocodile shagreen. In addition, the features of this syndrome were seen bilaterally in all patients. We believe that in our patients, decreased vision was due to myopia and its effects on the retina rather than the corneal dystrophy.

In differential diagnosis, the association and causes of inflammatory corneal disease and hearing loss should be considered. Syphilis and Cogan's syndrome, presenting the above clinical findings, are of utmost importance. Syphilitic interstitial keratitis occurs usually between the ages of 5 and 25 years with acute bilateral ocular pain and severe blurring of vision. In the late phase, deep stromal opacities in front of Descemet's membrane, and nonperfused stromal ghost vessels are evident by direct- or retro-illumination.[15,16] Systemic physical findings of congenital syphilis include frontal bossing, overgrowth of maxillary bones, Hutchinson's teeth, early loss of teeth, saddle nose, rhagades and saber shins. In serologic testing, VDRL and FTA-ABS, and MHA-TP are positive for recent or active disease.[15] Cogan's syndrome is a rare disorder and begins at middle age with acute tinnitus, vertigo, sudden unilateral or bilateral sensorineural hearing loss, and recurring episodes of nonsyphilitic interstitial keratitis.[17–19] Our patients showed no systemic findings presenting in syphilis or Cogan's syndrome and no vascular changes or ghost vessels in the corneal lesions. The serologic tests for syphilis were not positive.

Keratitis, ichthyosis and deafness (KID) syndrome and Harboyan syndrome were also taken into consideration for differential diagnosis. The KID syndrome is a rare situation and includes keratitis and deafness in addition to the ichthyotic skin lesions. Neurosensory deafness is usually present at birth but is often recognized only later when speech development is delayed. The characteristics of the keratitis are vascularization, corneal ulceration, and pannus formation eventually resulting in blindness.[20] In the latter, the cornea has thickened, is edematous and has a total diffuse homogeneous whitish opacity, with progressive sensorineural hearing loss. It is proposed to have an autosomal recessive mode of inheritance.[21,22] In our patients, the lesions of the cornea and the genetic inheritance were found to be different from these situations. Furthermore, myopia was common in our patients.

One has to think about the corneal dystrophy of François in differential diagnosis. In this condition, there are cloudy gray areas with indefinite structure and indistinct margins and the endothelium, epithelium, and visual acuity are unaffected.[23] In our patients, corneal dystrophy was found to be located near Descemet's membrane in the central part of the

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Table 2. Present Syndrome and Similar Syndromes: Similarities and Differences

Name	Inheritance*	Clinical Features	Differences
The present syndrome: Familial pathologic myopia, corneal dystrophy, and deafness.	AD	Myopia Pathologic myopia Corneal dystrophy Conductive hearing loss Mixed hearing loss Sensorineural hearing loss Positive Metz recruitment	
Marshall syndrome[4,5]	AD	Short stature Characteristic facial appearance Myopia Glaucoma Vitreoretinal degeneration Sensorineural deafness	Short stature Characteristic facial appearance Glaucoma Corneal dystrophy
Stickler syndrome[6,7]	AD	High myopia Glaucoma Chorioretinal degenerative changes Retinal detachment Articular disturbances Sensorineural deafness	Glaucoma Articular disturbances Corneal dystrophy
Weissenbacher-Zweymuller syndrome[8]		Disproportionate shortness Midface hypoplasia Cleft palate Skeletal abnormalities Hearing loss Degenerative myopia Glaucoma	Disproportionate shortness Midface hypoplasia Cleft palate Skeletal abnormalities Glaucoma Corneal dystrophy
Kniest syndrome[9]	AD	Dwarfism Joint stiffness Myopia Hearing loss (conductive and sensorineural)	Dwarfism Joint stiffness Corneal dystrophy
Muscupolysaccharidoses (Hurler, Hunter, Schie, Morquie, and other syndromes)[10]	AR XR (Hunter)	Dwarfism Corneal clouding Hepatosplenomegaly Skeletal deformities Vascular abnormalities Mental retardation Hearing loss (sensorineural, conductive, and mixed) Myopia	Dwarfism Corneal clouding Hepatosplenomegaly Skeletal deformities Vascular abnormalities Mental retardation Corneal dystrophy
Marfan syndrome[10]	AD	Conductive, mixed, and sensorineural hearing loss Extreme myopia Strabismus Cataract Retinal detachment	Strabismus Cataract Corneal dystrophy
Ehler-Danlos syndrome[11]	AD	Marfan syndrome findings + Skin fragility + Subcutaneous and intra-articular hemorrhage Angioid streaks	Strabismus, cataract Skin fragility Subcutaneous and intra-articular hemorrhage Angioid streaks Corneal dystrophy

*AD: autosomal dominant, AR: autosomal recessive, XR: X-linked recessive.

cornea. The clear spaces of corneal dystrophy produced different views. Although it is very similar to the posterior type of crocodile shagreen and dystrophy of François, pathologic myopia and deafness in the same family indicates that this entity is different from the previously reported syndromes.

The refractive status of the eye is based on the power of the cornea, the anterior chamber depth, the power

of the lens, and the axial length of the eye. As can be seen in Table 1, the myopia of our patients was related to the axial length of the eye. Most previous studies, however, used refraction instead of axial length to distinguish the type of myopia. Based on refraction, many of our patients had pathologic myopia.[24]

In corneal dystrophies, causes such as hyaline degeneration of collagen, primary amyloidosis of cornea, and localized mucopolysaccharidosis have been cited for the lesions.[25] Although many cases of myopia appear to be genetically determined, its precise pathophysiology and the influence of environmental factors in determining its development have yet to be elucidated.[24] It is known that myopia may occur if the sclera is affected by a connective tissue abnormality. Normal intraocular pressure may then cause stretching of the sclera and subsequent ocular expansion.[2]

The ocular and hearing abnormalities in diseases of connective tissue relate to a basic defect in connective tissue and impaired support of the ophthalmic and ear structures. Clinical features suggest that the genetic defect may have to be considered a disease of the surrounding mesenchymal tissue of the end-organs, such as the organ of corti, cornea, and sclera. The pathogenesis was thought to be a defect in collagen metabolism, as is the case in Stickler's syndrome. Laxity of ligamentum annulare and basillar membrane may cause hearing loss.

In conclusion, our patients showed a clinical picture that is very similar to posterior crocodile shagreen and the dystrophy of François for the corneal involvement. However, their syndrome is considered a distinct entity because of its associations with pathologic myopia and hearing loss. Therefore, we have named this syndrome "familial pathologic myopia, corneal dystrophy and deafness."

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