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Clinical features and visual function in a patient with Fish-eye disease: Quantitative measurements and optical coherence tomography

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ABSTRACT

Purpose: We describe a case of fish-eye disease (FED) where the clinical features and visual function were investigated using anterior segment optical coherence tomography (OCT) and quantitative measurements.

Observations: A 36-year-old Japanese woman with FED presented with bilateral corneal opacities and visual complaints. Both contrast sensitivity and straylight were measured and OCT imaging was performed. Contrast sensitivity and straylight measurements revealed remarkably decreased visual function, despite good visual acuity. OCT demonstrated homogenously hyper-reflective corneal opacification, and a normal total corneal thickness.

Conclusions and Importance: The findings from this case suggest that OCT is useful for analyzing the clinical features of FED, and that the quantitative measurement of visual function furthers the understanding of vision-related symptoms in FED, despite good visual acuity.

1. Introduction

Bilateral corneal opacity is a hallmark clinical feature of Fish-eye disease (FED), which was first reported by Carlson et al.[1] The dense corneal opacification is slowly progressive and causes severe visual impairment beginning as early as 15 years of age.[2] FED is a rare autosomal recessive disorder and known as a partial disease of lecithin–cholesterol acyltransferase (LCAT) deficiency.[3,4] It is thought that cholesterol is deposited in the corneal stroma because patients with FED cannot esterify free cholesterol contained in high-density lipoprotein (HDL) particles. Transparency is a fundamental optical property of the cornea, and the accumulation of free cholesterol can decrease corneal transparency and impair visual function. If the visual impairment becomes severe, penetrating keratoplasty may be considered as a treatment option.[5] Thus far, the quantification of decreased visual function in FED has not been reported.

Here we report a case involving a 36-year-old woman with FED whose clinical features and visual function were investigated using anterior segment optical coherence tomography (OCT) and quantitative measurements of contrast sensitivity and straylight.

2. Case report

A 36-year-old Japanese woman with bilateral corneal opacities and a suspected lipid metabolism disorder was referred to the Department of Ophthalmology. Analysis of fasting serum demonstrated an extremely low HDL cholesterol level (1.0 mg/dl), a low low-density lipoprotein cholesterol level (16.0 mg/dl), and a high free cholesterol to esterified cholesterol ratio (74.0 mg/dl to 1.0 mg/dl). LCAT activity was attenuated (99 U; standard value, 235–550 U) when determined using the Sekisui Medical Anasolv LCAT kit (SEKISUI MEDICAL CO., Tokyo, Japan); however, renal function was preserved (no proteinuria). On the basis of these findings, the patient was diagnosed with FED.

The patient reported several vision-related symptoms, including hazy vision, photophobia and visual impairment in darkness. Because of severe photophobia, she often experienced difficulty in opening her eyes. She had pale blue eyes in her early teens. Her maternal great-grandfather also had bilateral corneal opacifications, and there was no relevant history in her paternal family. She reported no other relevant ophthalmological history and was not taking any medications. Her best-corrected visual acuity measured using a standard visual acuity test with Landolt rings was 20/12.5 in the right eye and 20/20 in the left eye. Slit-lamp examination revealed a diffuse, cloudy opacity involving

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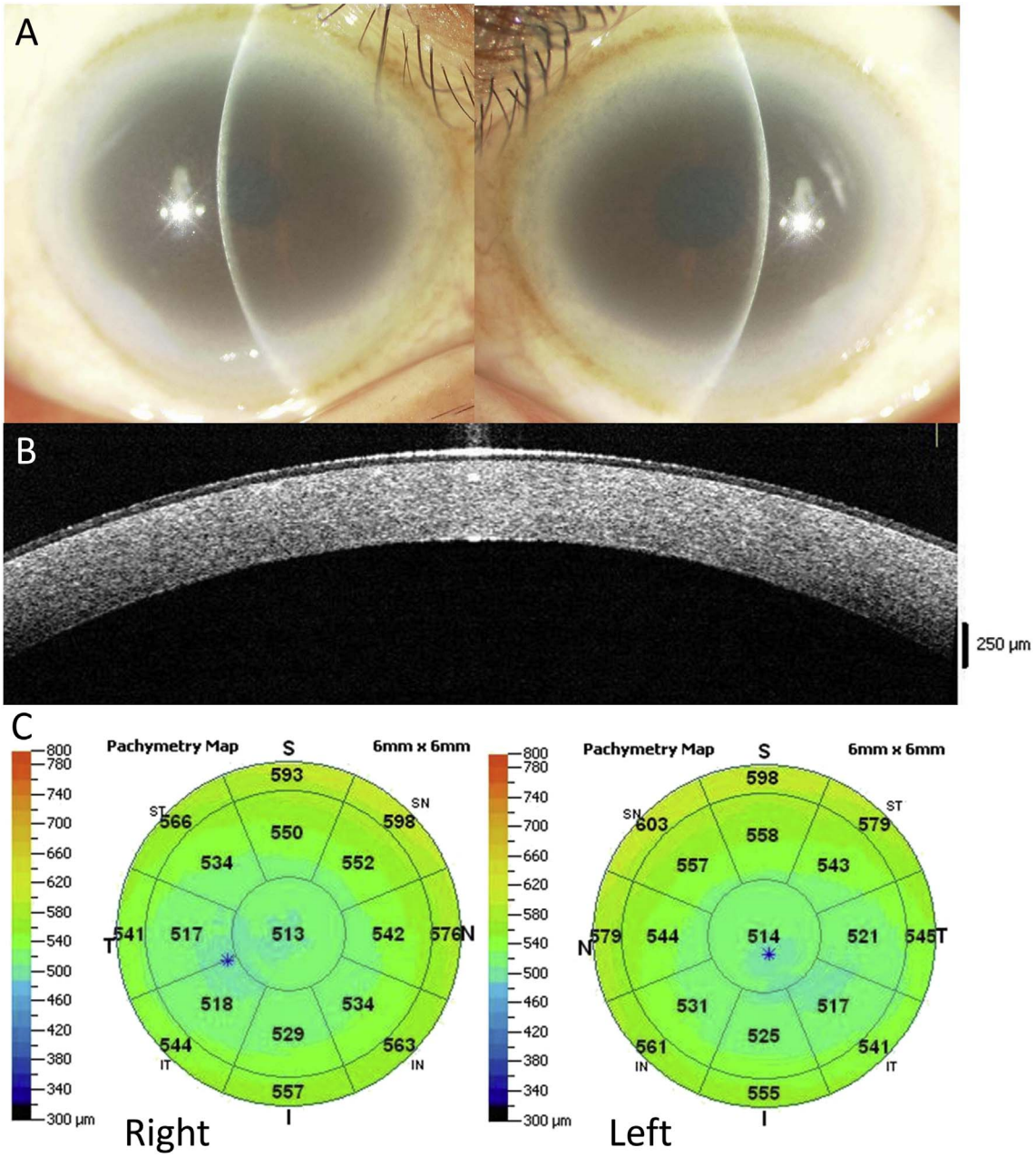

Fig. 1. Findings of ophthalmological examinations for a 36-year-old Japanese woman with fish-eye disease.
(A) Slit-lamp examination shows bilateral, diffuse corneal clouding.
(B) Fourier-domain optical coherence tomography (OCT) image of the right eye shows a homogeneously hyper-reflective corneal stroma.
(C) Corneal thickness mapping on a Fourier-domain OCT image shows a normal total corneal thickness (513 µm; right eye, 514 µm; left eye).

the entire cornea in both eyes. The peripheral cornea showed the maximum involvement, with no distinct lucid interval (Fig. 1A). No corneal vascularization was observed, and there were no other abnormal findings in the anterior or posterior segment of both eyes.

2.1. Visual function assessment

Contrast sensitivity and straylight were measured to quantify visual function. Contrast sensitivity was measured using a standard test chart (CSV-1000E chart; Vector Vision Co., Greenville, OH), which presents vertical sine wave gratings at four spatial frequencies. Each spatial frequency includes eight different contrast levels. In our patient, contrast sensitivity was decreased relative to the normal range in both eyes (Fig. 2). Straylight was measured using a straylight meter (Oculus GmbH, Wetzlar, Germany). Straylight measurements can quantify light scattering that results in a veil of straylight over the retinal image, which can lead to hazy vision or increased glare hindrance. The amount of straylight was expressed as the logarithm of the straylight parameters (log[s]); greater values indicate more straylight and more glare sensitivity. Straylight values for both eyes (2.09 log[s] for right, 2.18 log[s] for left) were remarkably increased by ten times when compared with those reported for normal eyes of age-matched individuals (approximately 0.9 log[s]).[6]

2.2. OCT

Fourier-domain OCT (RTVue-100; Optovue, Inc., Fremont, CA) revealed that the entire corneal stroma in both eyes was homogenously hyper-reflective (Fig. 1B). Thickness mapping for the total cornea demonstrated a central corneal thickness of 513 and 514 µm in the right

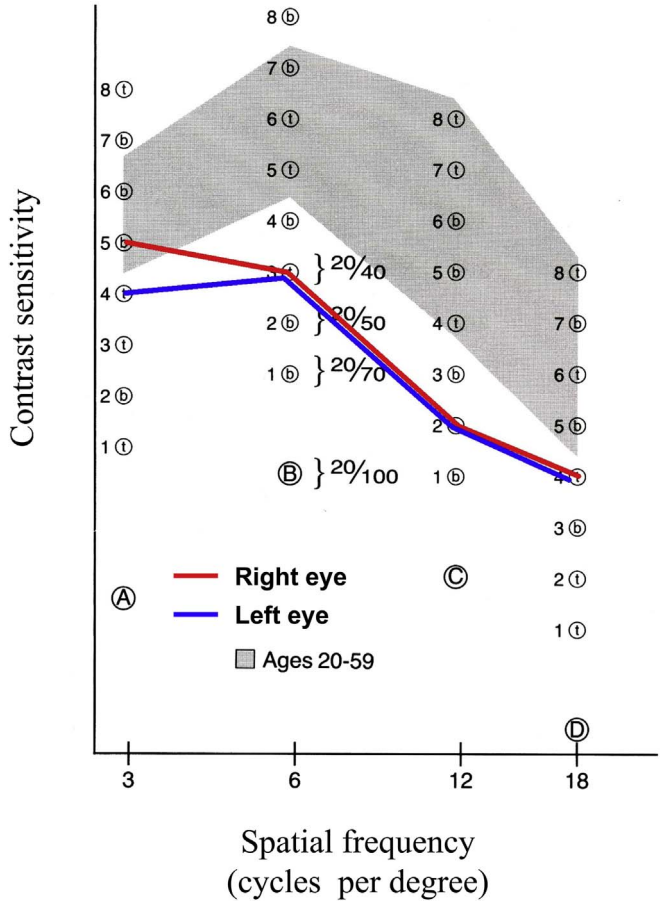

Fig. 2. Decreased contrast sensitivity in both eyes of a 36-year-old Japanese woman with fish-eye disease.
Each spatial frequency is presented at eight contrast levels. The highest contrast level that the patient could detect at each spatial frequency was determined to plot the curve. The grey area shows the normal range of contrast sensitivity for individuals aged 20–59 years. The red line indicates the right eye and the blue line indicates the left eye. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

and left eyes, respectively (Fig. 1C).

3. Discussion

We report a case involving a 36-year-old woman with FED whose clinical features and visual function were investigated using anterior segment OCT and quantitative measurements.

LCAT converts free cholesterol to cholesteryl esters, and a spherical α-HDL particle is formed by the migration of cholesteryl esters into its hydrophobic core. There are two kinds of related autosomal recessive disorders that cause a genetic deficiency in LCAT: complete LCAT deficiency and FED. Serum HDL-C concentrations are extremely low in these patients. Patients with complete LCAT deficiency develop corneal opacification, anemia, and progressive renal dysfunction. Patients with FED exhibit corneal opacification, but not the anemia and renal disease. In patients with FED, LCAT activity is generally conserved via apoB-containing lipoproteins and FED is recognized as a milder form of LCAT deficiency.[3] Diffuse corneal opacification is a phenotype that is usually observed in patients with genetic disorders of HDL metabolism, such as FED, LCAT deficiency, Tangier disease and apo A1 and C3 deficiency. Several reports have described the clinical ocular features of FED.[4,5,7–9] However, we are not aware of any report describing quantitative OCT of the cornea and assessment of visual function in eyes with FED.

In the present case, OCT demonstrated obvious corneal opacification and provided corneal thickness measurements. Several studies have evaluated the corneal thickness in patients with FED and LCAT deficiency using various techniques (Table 1).[2,5,7–9] For reference, recently reported thicknesses of the total cornea in normal eyes are also shown, regardless of previously reported differences between OCT and ultrasound pachymetry.[10–13] In the present case, the total corneal thickness was in the normal range relative to the reported values for normal eyes. While Koster et al. reported a French patient with FED whose cornea appeared thick on slit-lamp examination,[7] Tateno et al. reported a Japanese patient with FED whose central corneal thicknesses were 507 and 510 μm.[5] The total corneal thickness values for our Japanese patient were similar to those reported by Tateno et al.[5] Thus, differences in the total corneal thickness can be partly attributed to ethnic differences. With regard to the corneal thickness in patients with LCAT deficiency, Barchiesi et al. first reported a normal total corneal thickness using slit-lamp examination.[2] Later, it was reported that the total corneal thickness in patients with LCAT deficiency was more than 600 μm when measured using ultrasound pachymetry (623–629 μm according to Viestenz et al.[8] and 610–615 μm according to Palmiero et al.[9]). Reports regarding the corneal thickness in patients with FED, including our report, are scarce. The total corneal thickness seems to be normal or increased in both LCAT deficiency and FED. Further investigations including both patients with FED and those with LCAT deficiency would be helpful to clarify the association between LCAT activity and the corneal thickness.

Previously, it was described that patients with FED exhibit visual impairment, while those with LCAT deficiency show no visual impairment.[4] Several reports have described that patients with FED have no or slight visual impairment when they are young, and that their vision deteriorates slowly, until they finally experience difficulties with distant vision, particularly that in darkness.[1,5,7] In our case, measurements of contrast sensitivity and straylight demonstrated impaired visual performance. Contrast sensitivity is important for visual function; it can

Table 1
Total corneal thickness in previous reports.

Disease	Author (year)	Total cornea (measuring method)
Normal	Ishibazawa et al. (2011)[10]	544 ± 34 μm (UP) 530 ± 33 μm (OCT)
	Chen et al. (2012)[11]	516.5 ± 27.6 μm (UP) 510.8 ± 28.6 μm (OCT)
	Şimşek et al. (2016)[12]	535.6 ± 35.2 μm (UP) 525.9 ± 33.2 μm (OCT)
	Scotto et al. (2017)[13]	537.4 ± 37.5 μm (UP) 535.8 ± 35.5 μm (OCT)
FED	Koster et al. (1992)[7]	thick (slit-lamp examination)
	Tateno et al. (2012)[5]	507-510 μm (unknown)
	The current case	513-514 μm (OCT)
LCAT deficiency	Barchiesi et al. (1991)[2]	normal (slit-lamp examination)
	Viestenz et al. (2002)[8]	623-629 μm (UP)
	Palmiero et al. (2009)[9]	610-615 μm (UP)

UP, ultrasound pachymetry; OCT, optical coherence tomography; FED, Fish eye disease; LCAT, lecithin-cholesterol acyltransferase.

influence reading fluency, computer task accuracy and reaction time, and orientation-mobility performance. Therefore, decreased contrast sensitivity may influence the quality of life in patients with FED.

Previous studies conducted in European drivers have established reference values of straylight for normal eyes.[14–18] Straylight in the various pathological conditions of the cornea have also been investigated previously.[19–30] In hereditary corneal dystrophies, there is variation in the increase in straylight depending on the type of disease.[19] In eyes with central crystalline dystrophy, straylight was markedly increased with relatively well-preserved visual acuity, while in eyes with posterior polymorphous dystrophy, straylight was not increased regardless of impaired visual acuity. Eyes with macular dystrophy and lattice dystrophy demonstrate an intermediate effect on straylight findings. A correlation between corneal guttae and stralylight was reported in patients with Fuchs' endothelial corneal dystrophy.[20] Moreover, in keratoconic eyes or dry eyes, an increase in straylight has been reported.[21–24] Several studies have assessed straylight in eyes after keratoplasty.[25–30] The effect of deep lamellar endothelial keratoplasty and penetrating keratoplasty on straylight values was small.[25] Both Descemet stripping endothelial keratoplasty and penetrating keratoplasty for Fuchs' endothelial corneal dystrophy improved stralylight postoperatively,[26–29] while another study showed greater straylight values after Descemet stripping endothelial keratoplasty compared to penetrating keratoplasty.[30] In the present case, because there were no other abnormal eye findings, it was assumed that the remarkably increased straylight was due to the massive diffuse corneal clouding. Patients may complain about increased straylight in different ways, including hazy vision, increased glare, loss of contrast and color and difficulty in against-the-light face recognition.[6] Therefore, measurements of contrast sensitivity and straylight can reveal the ‘real-world’ visual performance, which standard visual acuity measurements cannot detect.

Generally, ophthalmic consultation is requested by non-ophthalmic physicians for patients whose disease (usually systemic disease) is associated with ocular abnormalities. Most non-ophthalmic physicians recognize standard visual acuity as the only measurement of visual function. Thus, if standard visual acuity is not impaired, they may not be able to understand vision-related symptoms in patients with FED. In the present case, complaints such as hazy vision and photophobia could be explained by quantitative measurements of contrast sensitivity and straylight, which were helpful to explain the patient's impaired visual function to her non-ophthalmic physicians. In addition, because corneal opacity is the only distinct clinical manifestation of FED, demonstration of cross-sectional OCT and slit-lamp images would be helpful to explain the corneal opacity to the patient and non-ophthalmic physician.

4. Conclusion

In conclusion, the findings from this case suggest that OCT is useful for analyzing the clinical features of FED, and that the quantitative measurement of visual function furthers the understanding of vision-related symptoms in FED, despite good visual acuity.

Patient consent

Written consent to publish personal information and case details has been obtained from the patient.

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Conflicts of interest

None.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Appendix A. Supplementary data

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