Fundus Autofluorescence in Autosomal Dominant Occult Macular Dystrophy

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Objective: To characterize fundus autofluorescence (FAF) images of eyes with autosomal dominant occult macular dystrophy (OMD).

Methods: All patients received a comprehensive ophthalmologic examination for diagnosis of OMD. We evaluated the FAF images in 13 eyes of 7 patients with autosomal dominant OMD by confocal scanning laser ophthalmoscopy with excitation at 488 nm and emission more than 500 nm.

Results: The FAF images showed unspecific weak foveal hyperfluorescence in 4 eyes of 2 patients; one showed a thin hyperfluorescence in the temporal fovea bilaterally and the other showed weak hyperfluorescence in the fovea bilaterally. The optical coherence tomographic images showed abnormalities of the photoreceptor inner segment–outer segment line and cone outer segment tip line in all patients. However, 5 patients had normal FAF images regardless of morphological abnormalities of the photoreceptor.

Conclusions: Fundus autofluorescence is a useful method to acquire additional information of photoreceptor/retinal pigment epithelium function in eyes with OMD. Fundus autofluorescence will be also helpful for the differential diagnosis of eyes with OMD vs eyes with other dystrophies that have a distinctive FAF pattern.


OCCULT MACULAR DYSTROPHY (OMD) is an inherited macular dystrophy with a progressive decrease of visual acuity but with essentially normal fundus and fluorescein angiograms (FAs).1,2 Patients with OMD have normal full-field electroretinograms (ERGs), but the focal macular ERGs (FMERGs) and multifocal ERGs are abnormal.1-5 The latter findings are the key for diagnosing OMD. Occult macular dystrophy is inherited as an autosomal dominant trait1,2,3; however, patients with sporadic disease have been also reported.6,7 Optical coherence tomography (OCT) in eyes with OMD showed abnormalities in the foveal structure.8,9 Recently, a loss of the cone photoreceptor outer segments and defects in the junction of the photoreceptor inner segment–outer segment line were demonstrated in patients with sporadic OMD.10,11 The most characteristic finding in eyes with OMD that differentiates it from other retinal diseases is the normal-appearing fundus even in the advanced stages. It is conceivable that this normal-appearing fundus has been attributed to well-preserved retinal pigment epithelium (RPE) function.

Lipofuscin is derived from the phagocytosed photoreceptor outer segments and normally accumulates in the RPE.12,13 Fundus autofluorescence (FAF) recorded with a confocal scanning laser ophthalmoscope can provide information about the distribution of lipofuscin in the RPE of the eyes noninvasively.14 By being able to detect the lipofuscin mainly at the RPE level, FAF could be a useful method to detect and characterize the lipofuscin distribution in a wide variety of inherited and acquired retinal diseases even when fundus changes are not or have not been clearly shown by routine ophthalmoscopy and FA.15-30

To our knowledge, the FAF findings in autosomal dominant OMD have not been published, although there are 2 case reports that describe the FAF findings in sporadic OMD.30,31 However, some of the cases diagnosed with sporadic OMD may have different etiologies because the causative gene of OMD is unknown and eliminating acquired diseases such as age-related macular degeneration is very difficult.

The purpose of this study was to characterize the FAF images in patients with autosomal dominant OMD and to determine whether the FAF images can help in evaluating the photoreceptor turnover of eyes with OMD. To accomplish this, we...
investigated the FAF images of 13 eyes in 7 patients who had been diagnosed with autosomal dominant OMD.

**METHODS**

We studied 13 eyes of 7 patients diagnosed with OMD. All of the patients had a family history of OMD and were diagnosed with autosomal dominant OMD. All of the patients were being studied at the National Institute of Sensory Organs, Tokyo, Japan. An informed consent was obtained after a full explanation of the procedures. All studies were conducted in accordance with the Declaration of Helsinki.

There were 2 men and 5 women whose ages ranged from 47 to 80 years (mean, 51.0 years). One eye was excluded because it had an idiopathic epiretinal membrane. The ophthalmological examinations included best-corrected visual acuity, D, diopters; ERG, electroretinogram; fI/ERG, full-field ERG; FH, family history; FMERG, focal macular ERG; ellipses, not examined; IOL, intraocular lens; IS-OS, inner segment–outer segment junction; mfERG, multifocal ERG; OCT, optical coherence tomography, OMD, occult macular dystrophy; +, present; −, absent.

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Abbreviations: AD, autosomal dominant; BCVA, best-corrected visual acuity; D, diopters; ERG, electroretinogram; fI/ERG, full-field ERG; FH, family history; FMERG, focal macular ERG; ellipses, not examined; IOL, intraocular lens; IS-OS, inner segment–outer segment junction; mfERG, multifocal ERG; OCT, optical coherence tomography, OMD, occult macular dystrophy; +, present; −, absent.

The visual fields were determined by Goldmann perimetry and the Humphrey Visual Field Analyzer (model 750; Carl Zeiss Meditec, Inc, Dublin, California). The Swedish interactive threshold algorithm standard strategy was used with program 30-2 of the Humphrey Visual Field Analyzer.

The OCT images were recorded using a Fourier-domain OCT (HD-OCT; Carl Zeiss Meditec) in all patients except patient 4, who was examined with a time-domain OCT (TD-OCT; Carl Zeiss Meditec).

Full-field ERGs were recorded using an extended testing protocol incorporating International Society for Electrophysiology of Vision standards. The ERGs were used to assess the retinal function under both scotopic and photopic states.

The FMERGs were recorded with a commercially available FMERG system (ER80; Kowa Company, Tokyo, Japan, and Mayo Company, Nagoya, Japan) using a bipolar contact lens electrode (Burian-Allen ERG Electrode; Hansen Ophthalmic Laboratories, Iowa City, Iowa). The stimulus and background lights were generated by light-emitting diodes and had maximal spectral emissions of 440 to 460 nm and 550 to 580 nm, respectively. The luminances of the stimuli and background were 115.7 cd/m² and 8.0 cd/m². The duration of the stimulation was 100 milliseconds. The responses were amplified and filtered by digital band-pass filters from 5 to 200 Hz (Neuropack µ, MEB 9102; Nihonkoden, Tokyo). Five hundred responses were summed with a stimulus frequency of 5 Hz.

The multifocal ERGs were recorded with the Visual Evoked Response Imaging System (EDI, San Mateo, California) using a Burian-Allen ERG electrode. The visual stimuli consisted of 61 hexagonal elements with an overall subtense of approximately 60°. The luminance of each hexagon was independently modulated between black (3.5 cd/m²) and white (138.0 cd/m²) according to a binary m-sequence at 75 Hz. The surround luminance was set at 70.8 cd/m².

The FAF images were recorded with a confocal scanning laser ophthalmoscope (model HRA/HRA2; Heidelberg Engineering, Dossenheim, Germany) after the pupil was dilated, and the recordings followed the protocol of Smith et al. This instrument uses a blue laser light at 488 nm for illumination and a barrier filter at 300 nm to limit the fluorescence to the autofluorescent struc-
The radiant power through the pupil was 180 µW, which gave a retinal irradiance of 227 µW/cm² for a field of 30° square. The acquisition time was 15 to 30 seconds. The scanned FAF images were recorded as JPEG files that were 512 × 512 pixels. The gain setting was 94% and each image was the average of 9 raw scans.

**RESULTS**

The diagnosis of OMD was made by the following findings: bilateral involvement, gradually decreasing visual acuity, normal ophthalmoscopic findings, normal FA, normal scotopic and photopic full-field ERGs, and absence or decrease of the amplitude of the FMERGs. All of our patients had the inheritance pattern of autosomal dominant as expected for OMD. Because FA was not performed in patients 2 and 5, we were careful in diagnosis and used the information of the other families who had already been diagnosed with OMD.

The clinical characteristics of the 7 patients are shown in the **Table**. The mean interval from the onset of the subjective visual decrease to the time of examination was 11 years with a range from 3 to 22 years. The best-corrected visual acuities ranged from 20/200 to 20/40. The spherical equivalent refractive error ranged from −9.38 to +2.25 diopters. Five eyes were pseudophakic. All patients had a central scotoma except for patient 3 who had both a central scotoma and a superior nasal visual field defect due to glaucoma. The FMERGs and multifocal ERGs were reduced in all patients within the 5° to 15° central region (Table). The OCT images showed an irregularity of the inner segment–outer segment line and loss of the cone outer segment tip line at the fovea in all patients.

Of 13 eyes of 7 patients, 4 eyes of 2 patients showed FAF abnormalities at the fovea and 9 eyes of 5 patients showed no abnormalities in the FAF images. The 4 eyes had hyperfluorescent lesions and none of the eyes had hypofluorescent lesions.

The results of our examination on patient 1, a typical case of OMD, are shown in **Figure 1**. The patient was a...
51-year-old man with a best-corrected visual acuity of 20/200 in both eyes. He complained of bilateral visual decrease and a blind spot in the central field for 3 years. He had an autosomal dominant inheritance pattern. His mother, patient 3, had the same symptoms. Ophthalmoscopy (Figure 1A) and FA (Figure 1B) showed that his macula was normal. Static perimetry detected a central scotoma bilaterally. Although all components of the full-field ERGs were slightly reduced because of the high myopia, they were not reduced enough to alter the diagnosis of OMD. The a- and b-waves of the FMERGs were abolished in amplitudes with prolonged implicit times in the responses elicited by 5°, 10°, and 15° stimuli (Figure 1D). The OCT images showed that the inner segment–outer segment line was disrupted at the fovea and the cone outer segment tip line was not present in the entire macular region (Figure 1E and F [arrow]). The FAF images had a thin hyperfluorescence in the temporal fovea of the right eye (Figure 1C [arrow]). The hyperfluorescence was annular; however, the border in the nasal area was not clear. All examination findings were bilaterally symmetrical. The FAF abnormalities were restricted to the fovea, sparing the foveola, while morphological abnormalities were present in the entire macula. The FAF images of patients 3, 4, and 5 and the OCT images of patient 3 are shown in Figure 3. The FAF images appeared normal, although the OCT images showed the same abnormality at the fovea as in patients 1 and 2 (Figure 3C [arrow]). There was a shadow of medial opacity in patient 3 (Figure 3).

**COMMENT**

We investigated the FAF images associated with photoreceptor outer segment turnover or RPE dysfunction in eyes with autosomal dominant OMD. Our results showed that FAF images had weak hyperautofluorescent changes at the fovea in 4 eyes of 2 patients and no abnormalities in 9 eyes of 5 patients. In general, the FAF images in OMD were not severely abnormal, which indicates that the FAF results can be used in the differential diagnosis of OMD from other macular dystrophies. It was very difficult to quantify the influence of aging on the FAF findings because (1) the observation period of each patient was very short and (2) the duration between the onset and the time of examination could not be determined accurately because OMD is a slowly progressive disease and the time of onset based on patients’ concern is not reliable. In addition, we could not completely eliminate the existence of macular pigments blocking the 488-nm autofluorescence, which could modify the autofluorescence from lipofuscin in the fovea. Estimation of the density of the macular pigment could be helpful for a more precise degree of autofluorescence derived from fluorophore in RPE.

Fundus autofluorescence was also valuable in assessing the condition of photoreceptor outer segment turn-
over in OMD. Weak hyperautofluorescent changes in the 2 patients implied an increased photoreceptor outer segment turnover, which could have been caused by photoreceptor death. On the other hand, in 5 patients, the functional and morphological damage in the photoreceptor was shown by the reduced FMERG amplitudes and OCT, even though FAF abnormalities were not identified. This inconsistency suggests that the degree of progression in the photoreceptor damage was so gradual that FAF images did not manifest the abnormalities in the photoreceptor outer segment turnover, such as a hyperautofluorescent lesion. Fundus autofluorescence could give us information regarding the degree of progression in OMD.

In the 4 eyes with abnormal FAF, OCT demonstrated abnormalities over the entire macula area, although the FAF abnormalities were restricted to the fovea. The localized hyperfluorescence in the FAF images may be because the photoreceptor outer segment turnover was not uniform at a particular stage of the disease progression. Hyperautofluorescence in the FAF images is prominent when the disease is progressing, such as in retinitis pigmentosa and geographic atrophy. Fundus autofluorescence measurements when the symptoms first appear might reveal some initial changes in the outer segment metabolism in OMD.

None of our patients with OMD showed decreased or absent FAF, which reflects RPE loss or atrophy. In ad-
dition, the appearance of the RPE in the OCT is always normal in the entire macular region, although damage to the photoreceptors was detected. This implies that the primary lesion of OMD is of the cone photoreceptors and the RPE is not damaged fatally even in the late stages. Autosomal dominant OMD is considered to be a central cone dystrophy. It is well known that the FAF images of eyes with other dystrophies show distinct patterns of FAF abnormalities. Retinitis pigmentosa shows a ring of high-density fluorescence and parafocal rings have also been observed in Leber congenital amaurosis. Best disease, X-linked retinoschisis, and cone-rod dystrophy have also been observed in Stargardt disease. RPE atrophy leads to a characteristic hypofluorescent appearance and flecks show distinct abnormalities in the FAF. Pattern dystrophy shows hypofluorescent lesions or patchy multiple hyperfluorescent/hypofluorescent lesions.

The FAF images of OMD did not have any pathognomonic abnormalities, unlike other dystrophies. Although patient 1 had a disconnected ringlike hyperautofluorescence at the fovea, it was definitely different from the shapes of other retinal dystrophies. This was probably because autosomal dominant OMD has distinctly different clinical characteristics from other dystrophies. We do not have sufficient information on the FAF pattern in sporadic cases of OMD and whether they have the same features as our patients. The FAF images allow differentiating autosomal dominant OMD from other retinal dystrophies that have distinctive FAF findings.

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