Original Article

Clinical Findings in Four Siblings with Genetically Proven Oguchi Disease

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Abstract

Purpose: To assess the clinical findings in normal daylight status and 3 h of dark-adapted status in family members with Oguchi disease (OD).

Methods: Four siblings with OD and their parents were included in this case series. The presence of disease was confirmed with genetic analysis and comprehensive clinical evaluation. Corrected distant visual acuity (CDVA), automated visual field analysis (VFA), optical coherence tomography (OCT), OCT angiography (OCTA), colored fundus photography, fundus autofluorescence (FAF), fundus fluorescein angiography (FFA), electroretinography (ERG), and dark adaptation test (DAT) results were obtained in normal daylight status. On the next day, after 3 h of dark adaptation, the patients were re-evaluated. The findings obtained in normal daylight status and 3 h dark-adapted status were compared.

Results: The mean age of the four sibling subjects was 15.25 ± 2.2 years. All subjects had 20/20 CDVA and normal VFA. There was no abnormality in OCT and OCTA in normal daylight status and 3 h of dark-adapted status. Colored fundus photographs showed characteristic golden-yellow colored reflex in the mid-peripheral retina in normal daylight status, and discoloration in 3 h of dark-adapted status. In FAF and FFA, no abnormal pattern was observed in normal daylight status and 3 h of dark-adapted status. ERG showed rod function alterations and normal cone function. DAT showed delayed rod adaptation and normal cone adaptation. ERG and DAT findings remained unchanged after 3 h of dark adaptation.

Conclusion: After 3 h of dark adaptation, golden-yellow fundus color returns to normal in patients with OD; however, rod function alterations and normal cone function in ERG, as well as delayed rod adaptation and normal cone adaptation in DAT remain unchanged.

Keywords: Dark adaptation, Electroretinography, Fundus, Mutation, Oguchi disease

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Introduction

Congenital stationary night blindness (CSNB) refers to a group of disorders characterized by infantile onset of nyctalopia and non-progressive retinal dysfunction that can be inherited as X-linked recessive, autosomal recessive, or autosomal dominant traits.[1] CSNB is caused by mutations in genes that involve the phototransduction cascade or the retinal signal pathway from photoreceptors to bipolar cells.[1] CSNB does not usually show fundus abnormalities, except for myopic changes; however, there are two other variants of CSNB with distinctive fundus abnormalities: fundus albipunctatus and Oguchi disease (OD).[2]

OD is inherited in an autosomal recessive manner.[2] Two causative genes have been described for OD: S-arrestin or S-antigen gene (*SAG*) and rhodopsin kinase or G protein-coupled receptor kinase 1 (*GRK1*) gene.[3] Patients

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with OD may have night blindness, but normal color vision and visual acuity. The characteristic clinical finding in OD is a golden-yellow or diffuse gray-white fundus discoloration. After at least 3 h of dark adaptation, normal fundus appearance and normal rod function would be reobtained.[2]

In the literature, there are few reports on the clinical findings of OD because the disease is extremely rare. The aim of this study is to comprehensively report ocular findings of subjects with OD in normal daylight status and 3 h of dark-adapted status.

Methods

This case series includes four Turkish siblings referred to the retina clinic of a tertiary referral center. The presence of OD was revealed with genetic analysis. The subjects underwent a comprehensive ophthalmological evaluation, and the results were recorded. The research protocol adhered to the Declaration of Helsinki, and the protocol was approved by the local research ethics committee. Written informed consent was obtained from all the study participants. This study is registered in the Australian New Zealand Clinical Trials Registry (No. ACTRN 368991).

The siblings are from a consanguineous marriage, and their healthy parents had fourth-degree relatives (first-degree cousins). For genetic analysis, genomic DNA was obtained from peripheral leukocytes (10 mL of whole blood) of the siblings and parents by ammonium acetate extraction (AppliChem GmbH, Gatersleben, Germany). DNA samples were quantified with a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Inc., Wilmington, NC, USA) before polymerase chain reaction (PCR). All exons of the OD-related genes *SAG* and *GRK1* were amplified with PCR, purified with Wizard SV Gel and PCR Cleanup system (Promega Corporation, Madison, WI, USA), and sequenced with BigDye Terminator v3.1 Cycle Sequencing Kit (Thermo Fisher Scientific, Inc., Wilmington, NC, USA). Sorting Intolerant from Tolerant (SIFT; http://sift.bii.a-star.edu.sg/) and Polymorphism Phenotyping v2 (PolyPhen-2; http://genetics.bwh.harvard.edu/pph 2/) were used for bioinformatic analysis.

In normal daylight status, the subjects underwent ophthalmological examinations, including the corrected distant visual acuity (CDVA) with Snellen chart, color vision with Ishihara pseudoisochromatic test plate (Kanehara Trading Inc., Tokyo, Japan), intraocular pressure (IOP) measurement with Goldmann applanation tonometry, and anterior segment evaluation. Automated visual field analysis (VFA) (Humphrey Field Analyzer, Carl Zeiss Meditech, Inc., Dublin, CA, USA) was performed using the 24-2 Swedish interactive threshold algorithm fast strategy with a Goldmann size III stimulus on a 3.5-apostilb background. The test was repeated if necessary, and acceptable results were obtained with high-reliability indices (fixation errors <20%, false positives <15%, and false negatives <%15). The pupils were then dilated with topical tropicamide 0.5% (Tropamide, Bilim Ilac Sanayi ve Ticaret AS, Istanbul, Turkey). Macular configuration and thickness were examined using spectral domain optical coherence tomography (SD-OCT) (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Heidelberg, Germany) (20 × 20 with 49 sections, ART 15). Foveal avascular zone area and vessel density quantifications were evaluated with 6.0 × 6.0 scan size (mm) using the Angio-Vue OCT angiography (OCTA) device (version 2017.1.0.151 of the RTVue XR Avanti, Opto-Vue, Inc., Fremont, CA, USA). Colored fundus photographs and fundus autofluorescence (FAF) images were acquired using a scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Heidelberg, Germany). Fundus fluorescein angiography (FFA) was performed on the same system. Prearterial, arterial, arteriovenous, venous, and recirculation phases were observed, and images were taken. Full-field electroretinography (ERG) (MonPack 3, Metrovision, Perenchies, France) measurements were performed according to the International Society for Clinical Electrophysiology of Vision standards. The ERG amplitudes and latencies after dark adaptations were compared to the baseline values, and the changes >30% were considered statistically significant.[4] Dark adaptation test (DAT) was performed using the same device (MonPack 3, Metrovision, Perenchies, France). All results of ophthalmological evaluations were noted.

On the next day, the subjects were seated for 3 h in a completely dark room that was protected from daylight with entirely opaque curtains. After sitting for 3 h in the darkroom, colored fundus photography, FAF, SD-OCT, OCTA, FFA, ERG, and DAT were re-evaluated, respectively. The patients were not exposed to light between the examinations. Results of re-evaluations were also noted, and qualitative results obtained in normal daylight status and 3 h of dark-adapted status were observationally compared. The most representative and best quality figures obtained from the patients were given for each examination to demonstrate the clinical findings.

Results

The mean age of the two male and two female siblings is 15.25 ± 2.2 years (range, 12–19). None of the subjects had systemic diseases, nor had any undergone surgery.

According to the results of the gene analysis, a novel missense mutation, *GRK1* c.923T>C, was found in all siblings. This mutation was demonstrated by amino acid alignment analysis to be in a phylogenetically conserved region and resulted in an amino acid change from leucine to proline at position 308. This novel mutation resides in the catalytic domain of the *GRK1* gene and is shared with autosomal recessive transmission among all family members. The mutation was homozygous in all siblings and heterozygous in their 41-year-old mother and 44-year-old father, neither of whom have any ocular complaints. No other mutations were found in the *GRK1* gene in the siblings.

In normal daylight status, all subjects had 20/20 CDVA without refractive correction, and they recognized all symbols in the

Ishihara plate. The mean IOP of the subjects was 16.34 ± 3.2 mmHg (range, 11–20). All eyes were phakic, and slit-lamp anterior segment evaluations revealed normal findings.

No scotoma was observed in their visual field, and all indices were within normal limits for their age. There was no difference in SD-OCT findings obtained in normal daylight status and 3 h of dark-adapted status, and normal macular configuration was seen in both conditions [Figure 1]. Foveal avascular zone area and vessel density quantification in OCTA were normal in normal daylight status [Figure 1], and findings persisted after 3 h of dark adaptation. In normal daylight status, colored fundus photographs of siblings showed a characteristic golden metallic reflex in the mid-peripheral retina. Neither vascular attenuation nor retinal degeneration was seen throughout the retina, and no maculopathy was observed. After 3 h of dark adaptation, the Mizuo–Nakamura phenomenon was

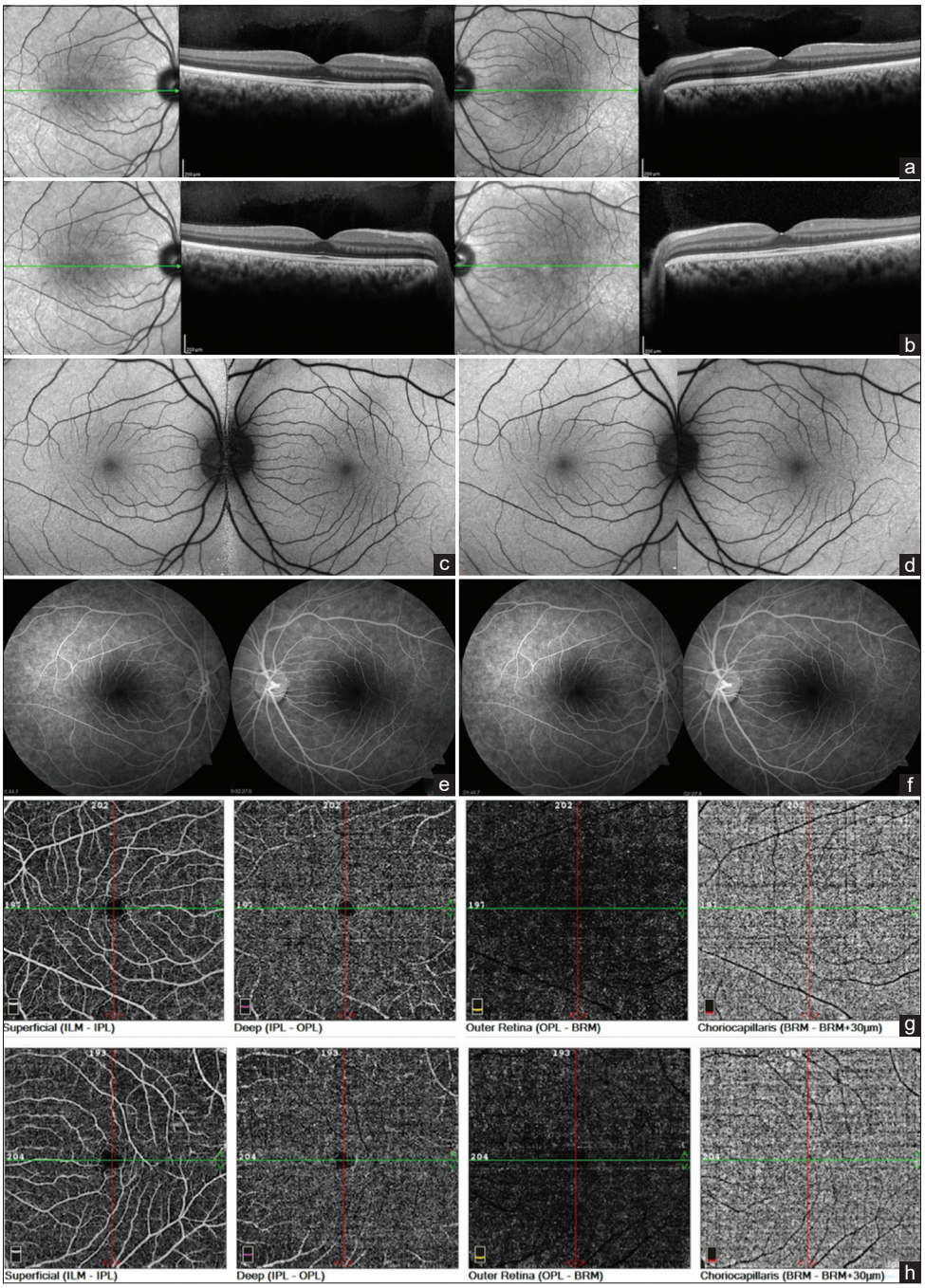

Figure 1: Normal macular configuration in spectral domain optical coherence tomography images (a) in normal daylight status, and (b) in 3 h dark-adapted status. Normal fundus autofluorescence findings (c) in normal daylight status, and d) in 3 h dark-adapted status. Normal fluorescein angiography images: (e) in normal daylight status, and (f) in 3 h dark-adapted status. Normal foveal avascular zone area and vessel density quantification in 6.0 × 6.0 scan size (mm) optical coherence tomography angiography images in normal daylight status (g) in the right eye, and (h) in the left eye

demonstrated: The fundus color changed to normal throughout retina after 3 h of dark adaptation [Figure 2]. In FAF and FFA, no abnormal pattern was observed in normal daylight status and 3 h of dark-adapted status [Figure 1]. The full-field scotopic 0.01 ERG showed undetectable a- and b-waves in normal daylight status. The scotopic 3.0 ERG showed a negative configuration a-wave with a significantly reduced amplitude and a nearly absent b-wave. The ERG findings obtained in 3 h of dark-adapted status were almost identical. DAT showed a normal cone adaptation curve and delayed dark adaptation, with a biphasic rod curve at approximately 3 h in normal daylight status and 3 h of dark-adapted status.

Discussion

OD is a kind of CSNB, a group of non-degenerative and non-progressive retinal disorders characterized by the deficient vision in the dark.[1] This rare disease is inherited as an autosomal recessive trait. In a European study, all of the reported patients had mutations in *GRK1*. However, most Japanese patients with OD have another causative gene, *SAG*.[5] In subjects included in this study, a novel missense mutation, *GRK1* c.923T>C, was identified in affected members of a consanguineous Turkish family. This novel mutation was reported previously.[6]

The siblings in this study had normal best corrected visual acuity, color vision, and IOP. Hayashi *et al*.[7] reported that automated visual field examination showed significant paracentral field defects in a case with retinal pigment epithelium atrophy. However, Yoshii *et al*.[8] did not observe visual field defects in patients with OD. In this study, the subjects had no structural fundus abnormality, and the automated VFA for all subjects with OD were within normal limits.

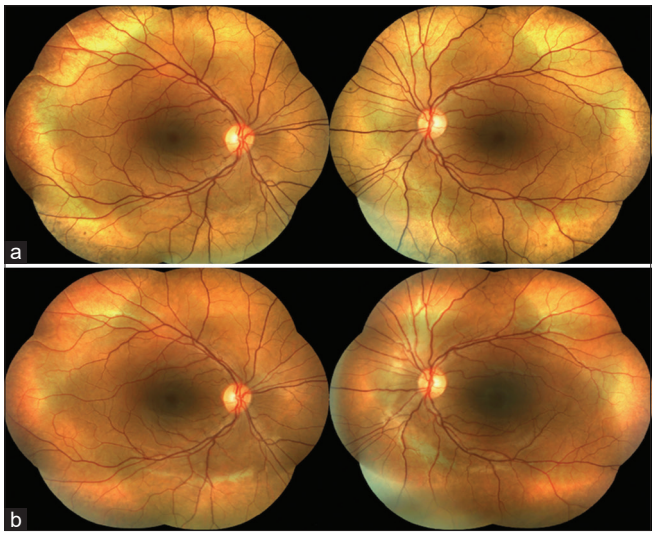

Figure 2: The Mizuo–Nakamura phenomenon: (a) mid-peripheral golden colored fundus photographs in normal daylight status, and (b) normal colored fundus photographs after 3 h of dark adaptation

Most studies have reported interesting OCT findings in OD and suggest that photoreceptor structure changes in normal daylight status compared to prolonged dark-adapted status.[9-12] One study concluded that the rod outer segments were shortened in OD;[10] two others observed high-intensity areas in the outer segment (the normally hyporeflective space between the second and third bands of the outer photoreceptor complex).[9,11] Another study reported the disappearance of the inner and outer segments line under normal conditions with re-emergence after prolonged dark exposure.[12] Godara *et al*.[13] did not observe a difference in the outer segment length. Rather, they observed a pronounced increase in the relative intensity of the rods in the perifoveal image in normal conditions compared to the prolonged dark exposure condition.[13] SD-OCT in this study showed no prominent alterations in normal daylight status and 3 h of dark-adapted status, similar to the report by Godara *et al*.[13] This could be due to Mizuo–Nakamura phenomenon involvement only in the mid-peripheral retina and not in the posterior pole. If mid-peripheral retina SD-OCT images in normal daylight status and dark-adapted status could be compared, some findings could be more prominent. In addition to SD-OCT, no significant changes were observed in OCTA after 3 h of dark adaptation. To the best of our knowledge, the OCTA images in this study are the first OCTA demonstration in the literature in a subject with OD.

In OD, the most prominent characteristic clinical finding is a golden-yellow or diffuse gray-white fundus discoloration that disappears after prolonged dark exposure.[2] This condition is known as the Mizuo–Nakamura phenomenon.[2] In this study, when comparing findings obtained in normal daylight status and 3 h of dark-adapted conditions, the most prominent difference was the Mizuo–Nakamura phenomenon, which was more prominent in the mid-peripheral retina. This is not a novel clinical finding because some authors had previously reported mid-peripheral Mizuo–Nakamura phenomenon as a typical finding of OD.[14,15]

FAF is a non-invasive imaging modality that focuses on the fluorescent properties of pigments in the retina to generate images that help us view various disease processes from a different perspective.[16] It generates an image based on the distribution pattern of a fluorescent pigment called lipofuscin. Knowing the distribution pattern of lipofuscin in the normal retina is important in understanding a FAF image representing a retinal pathology.[16] FFA provides information about choroidal and retinal circulation, and normal FFA findings are achieved when retinal structure and circulation are normal. In the present study, FAF and FFA demonstrated no abnormality in normal daylight status and 3 h dark-adapted status. This cannot be considered an unusual clinical finding because both FAF and FFA examinations were reported as normal in OD if not masked with retinitis pigmentosa or other retinal dystrophies.[17-19]

In OD, there is an undetectable scotopic b-wave to a dim flash, and there may be an electronegative scotopic

response to a bright flash.[20] At the same time, there is significant a-wave reduction reflecting rod photoreceptor dysfunction.[20] Patients with OD also have a distinctive dark-adaptation curve. The early cone branch of the curve is normal with sensitivity plateaus at the cone level for approximately one to 2 h, at which point a rod-cone break occurs, and there is a subsequent recovery of full rod sensitivity over the next 1 to 2 h.[16] In this study, the a-wave of the mixed rod-cone ERG elicited by a bright flash was significantly reduced, and the full-field bright-flash ERG had a negative shape (b/a ratio <1). In addition, rod dark adaptation was markedly delayed, while that of cones was normal, as is typical of patients with OD. All these ERG and DAT findings persisted after 3 h of dark adaptation. Sergouniotis *et al*.[11] reported that partial ERG recovery can be observed with prolonged dark exposure for overnight, and one reason for these unchanged findings may be the 3-h limited dark exposure method of this study.

Most of the previous OD studies defined the ocular findings of OD. However, these studies focused on one or two parameters of ocular examinations. The most powerful aspect of this study is the presentation of a comprehensive clinical evaluation of subjects with OD in normal daylight status and dark-adapted status. On the other hand, the dark exposure time was limited for 3 h, and all re-evaluations were performed in the same day. A more prolonged dark exposure time performed separately for each examination could be a more ideal methodology.

The subjects reported in this study have a novel homozygous missense mutation of *GRK1* and Mizuo–Nakamura phenomenon. VFA, SD-OCT, OCTA, FAF, and FFA showed almost identical findings in normal daylight status and 3 h dark-adapted status. Scotopic and photopic ERG showed alterations in rod responses, and DAT showed delayed rod adaptation and normal cone adaptation. These findings did not change after 3 h of dark adaptation. The entire clinical evaluation was normal in the subjects' parents, who had a heterozygous *GRK1* mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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