Case Report

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Oguchi's disease: two cases and literature review

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Abstract

Oguchi's disease is a rare form of congenital stationary night blindness, associated with light-dependent golden fundus discoloration. In this report, we describe two cases of Oguchi's disease, both of which had two characteristic features: congenital stationary night blindness and fundoscopic manifestation of the Mizuo–Nakamura phenomenon. In both patients, fundus examination revealed a metallic sheen throughout the retina, which disappeared after 2.5 hours of dark adaptation, suggestive of the Mizuo–Nakamura phenomenon. The characteristic electroretinogram (ERG) changes (i.e., un-recordable rod response and reductions of maximal response, oscillatory potentials, and flicker response) in these patients confirmed the clinical diagnosis of Oguchi's disease. Furthermore, we discuss the results of our literature search for evidence concerning the diagnosis and pathogenesis of this rare disease. Further studies regarding the genes involved in phototransduction and light adaptation are needed to determine the pathogenesis of this rare disease.

Keywords

Oguchi's disease, congenital stationary night blindness, Mizuo–Nakamura phenomenon, electroretinogram, fundus discoloration, phototransduction, light adaptation

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Introduction

Oguchi's disease is an autosomal recessive hereditary disorder involving a rare form of congenital stationary night blindness, which is associated with light-dependent golden fundus discoloration and a clinical feature known as the Mizuo–Nakamura phenomenon (i.e., disappearance of golden or silver-gray metallic sheen in the retina after

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prolonged dark adaptation).[1,2] Affected patients exhibit reduced or no rod function, combined with normal cone function, on electroretinogram (ERG) examinations.[1] To our knowledge, there is limited available literature regarding Oguchi's disease, and the majority of affected patients have been identified in Japan.[3] Most patients are offspring of consanguineous marriages. In this report, we describe two patients with Oguchi's disease and discuss the results of our literature search for evidence concerning the diagnosis and pathogenesis of this rare disease.

Case report

Case 1

A 19-year-old man was referred to the retina center of the eye hospital for further fundus examination, following the discovery of abnormal fundus color during pre-LASIK examinations. He complained of night blindness that had begun in early childhood. There was no history of consanguineous marriages in his family. His family medical history was unremarkable and his physical examination findings were normal. Ophthalmic examination showed a best-corrected visual acuity of 20/16 with a correction of −2.50 diopters in both eyes. Visual field and color vision findings were normal; anterior segment examination results were also normal in both eyes. Dilated fundus examination revealed a metallic sheen throughout the retina in both eyes (Figure 1). Retinal vessels were dim purple, thus producing marked contrast. There were dark shadows near the vessels and a murky gray plaque with unclear boundaries in the peripheral fundus. After 2.5 hours of dark adaptation, both fundus and vessels had regained normal color, confirming the presence of the Mizuo–Nakamura phenomenon. The golden yellow metallic fundus color returned after exposure to light for 30 minutes. ERG was performed in accordance with the standards of the International Society for Clinical Electrophysiology of Vision; the results

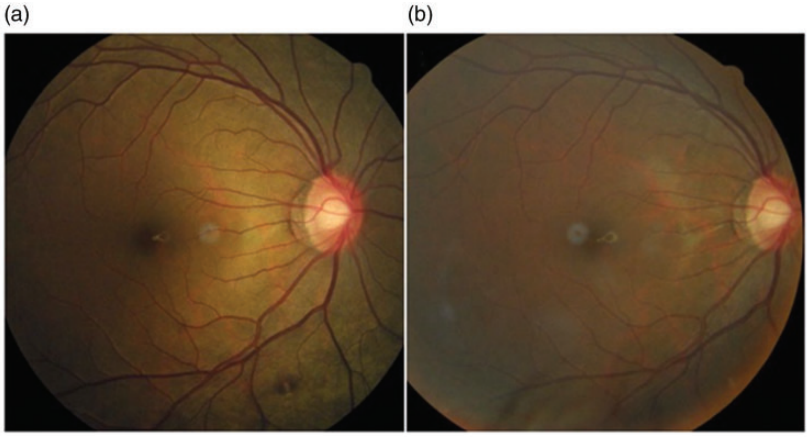

Figure 1. Fundus photography of the patient in case 1 before (a) and after (b) dark adaptation. (a) Fundus findings were characteristic of Oguchi's disease with an abnormal metallic sheen throughout the retina before dark adaptation. Dark shadows were evident near the vessels and a murky gray plaque with unclear boundaries was present in the peripheral fundus. (b) After 2.5 hours of dark adaptation, the fundus and vessels returned to normal color.

showed that rod response was unrecordable (i.e., a straight line), maximal response amplitudes significantly decreased, and oscillatory potentials and flicker response mildly decreased compared with the normal limit, although the cone response was normal. Based on the typical Mizuo–Nakamura phenomenon and abnormal ERG changes, the clinical diagnosis was Oguchi's disease. However, the patient's family rejected genetic testing. At the 1-year follow-up, the patient's best-corrected visual acuity, fundus examination, and ERG findings were generally stable.

Case 2

An 18-year-old man (unrelated to the patient in case 1) visited the same hospital's retina center with the complaint of long-term night vision difficulties. This patient's family had no history of consanguineous marriages or night blindness. His best-corrected visual acuity was 20/20 in both eyes with a correction of −8.50 diopters in the right eye and −8.25 diopters in the left eye. Visual field and color vision findings were normal; additionally, anterior segment examination findings were normal in both eyes. Mydriatic fundus examination (Figure 2) revealed dark shadows and a murky gray plaque with unclear boundaries along peripheral arteries. Similar to the patient in case 1, the abnormal fundus color was entirely replaced by the normal red color after dark adaptation for 2.5 hours; the golden yellow metallic color returned after light adaptation for 30 minutes. ERG examination findings were similar to the results described for

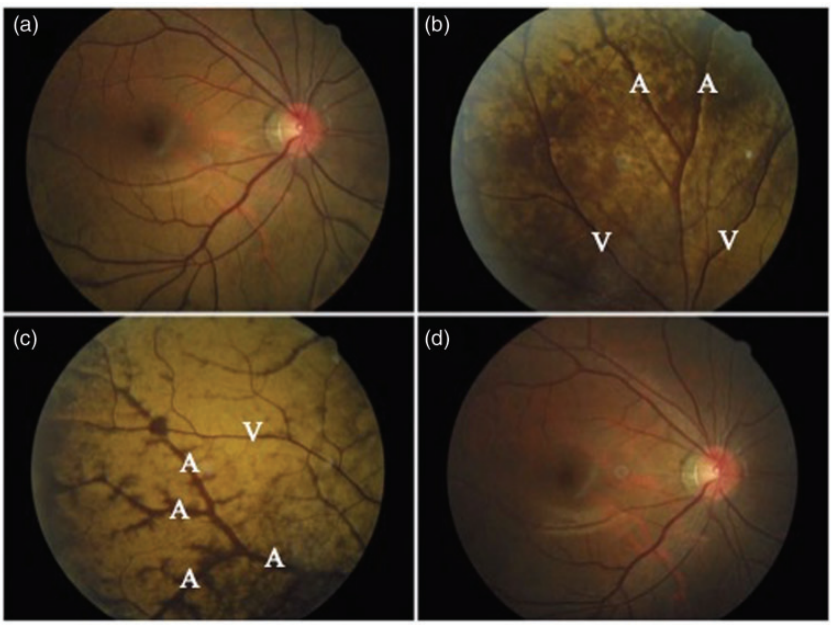

Figure 2. Fundus photography of the patient in case 2 before (a–c) and after (d) dark adaptation. (a–c) Before dark adaptation, a golden yellow metallic color was evident throughout the retina. (b, c) Dark shadows and a murky gray plaque with unclear boundaries were evident along peripheral arteries. (d) The fundus color was entirely replaced by normal red color after dark adaptation for 2.5 hours.
A, artery; V, vein.

the patient in case 1. After 2.5 hours of dark adaptation, the amplitudes of maximal response, flicker response, and (especially) rod response were markedly enhanced. This patient's family also rejected genetic testing. At the 6-month follow-up, the patient's vision, fundus examination, and ERG findings were similar to the results during his first visit.

Discussion and Conclusions

Both patients in this report had two typical characteristics: congenital stationary night blindness and the Mizuo–Nakamura phenomenon during fundoscopic examination. The Mizuo–Nakamura phenomenon comprises a golden or gray-white metallic sheen in the fundus; the fundus appears normal after prolonged dark adaptation.[1] Moreover, the characteristic ERG changes (i.e., un-recordable rod response and reductions of maximal response, oscillatory potentials, and flicker response) confirmed the clinical diagnosis of Oguchi's disease.

In patients with Oguchi's disease, light sensitivities often improve following extended dark adaptation.[4] In particular, dark-adaptation studies usually demonstrate a normal cone response and an extremely prolonged rod response;[4] the dark adaptation threshold may be normal after 4 hours of dark adaptation. In our patients, we found that rod response, maximal response, oscillatory potentials, and flicker response all decreased, but the cone response was generally normal. The amplitudes of maximal response, flicker response, and (especially) rod response were enhanced after dark adaptation in the patient in case 2, implying that his rod photoreceptors could achieve normal sensitivity to dim light.

To the best of our knowledge, Oguchi's disease is caused by disruptions in the inactivation steps of rod phototransduction. Thus far, causative mutations have been identified in the genes encoding arrestin (s-antigen; SAG) and rhodopsin kinase (G protein-coupled receptor kinase 1; GRK1).[2,5] Both SAG and GRK1 proteins deactivate rhodopsin, thus stopping the phototransduction cascade. Mutations in the genes encoding these proteins causes rhodopsin molecules to remain in a photoactivated state for an extended duration.[5] The SAG gene encodes a major protein of the outer retinal segment.[6] Mutations in the SAG gene(e.g., 926delA, R193X, R175X, and R292X) are reportedly associated with Oguchi's disease.[1] Waheed et al.[7] reported that a homozygous nonsense mutation (c.916G>T; p.Glu306*) in the SAG gene could cause Oguchi's disease in patients whose unaffected relatives had heterozygous or nonmutated genes. Recently, the c.517delC, p.P96LfsX28 mutation was identified in exon four of the SAG gene in patients with Oguchi's disease type 1.[8]The GRK1 gene encodes rhodopsin kinase, which plays an essential role in the phosphorylation of rhodopsin in rod cells. Mutations in the GRK1 gene, such as c.1607_1610delCGGA and c.923T>C, are presumably related to Oguchi's disease.[6,9] The findings thus far indicate that both SAG and GRK1 gene mutations can cause the Oguchi's disease phenotype. A homozygous or compound heterozygous mutation in the SAG gene on chromosome 2q37.1 (2,3) is associated with Oguchi's disease type 1, while Oguchi's disease type 2 is caused by a mutation in the GRK1 gene on chromosome 13q34.[8] A progressive rod-cone degeneration, retinitis pigmentosa (RP), has also been observed in patients with recessive mutations in SAG.[10] Similar mutations were previously found in siblings with different phenotypes, namely Oguchi's disease and RP.[10] Maw et al.[11] reported that patients with Oguchi's disease developed progressive pigmentary retinal degeneration. However, the natural histories of SAG-associated Oguchi's disease and RP

remain unclear; long-term follow-up investigations are needed to define the courses of these diseases and determine whether affected patients undergo phenotypic transition from Oguchi's disease to RP.

Thus far, the etiopathogenesis of the Mizuo–Nakamura phenomenon remains unknown. It is presumably caused by an excess of extracellular potassium in the retina because of a reduced potassium scavenging capacity in retinal Muller cells.[12] In addition to Oguchi's disease, the Mizuo–Nakamura phenomenon and similar fundoscopic manifestations have been observed in conditions such as RP, X-linked retinoschisis, and cone-rod dystrophy.[12–14] Generally, Oguchi's disease is described as stationary night blindness, whereas RP is considered progressive night blindness. Patients with X-linked retinoschisis exhibit splitting within inner retinal layers.[13] In these patients, fundus examinations reveal foveal schisis, peripheral schisis, and the Mizuo–Nakamura phenomenon.[13] Foveal schisis is present in all patients with X-linked retinoschisis, while peripheral schisis is present in fewer than 50% of affected patients.[13]Finally, cone-rod dystrophy is an inherited progressive retinal disorder, characterized by a loss of visual acuity, disturbance in color vision, and a central scotoma.[15] In some patients with cone-rod dystrophy, fundoscopic manifestation of bull's eye maculopathy is evident.[14] Notably, affected patients can exhibit cone dystrophy with no or mild rod dystrophy on ERG.[14]

Thus far, no treatment for Oguchi's disease has been found. Therefore, the diagnostic signs are important to recognize. Here, we described two affected patients, with the aim of helping ophthalmologists to more closely monitor this disease.

In conclusion, the clinical diagnosis of Oguchi's disease is based on congenital stationary night blindness and the Mizuo–Nakamura phenomenon. Additionally, reduced or no rod functions with normal cone functions on ERG examinations are distinctive characteristics in patients with Oguchi's disease. If necessary, this disease may be documented based on genetic testing. However, the etiopathogenesis of the Mizuo–Nakamura phenomenon remains unknown. Further studies concerning the genes involving phototransduction and light adaptation, including SAG and GRK1 genes, are needed to elucidate the pathogenesis of this rare disease.

Ethics statement

This case report was not required to be reviewed by the ethics review committee because it discusses the diagnosis and pathogenesis of a rare disease; no exploratory treatment was performed. Written informed consent was obtained from each patient for the publication of this case report and any accompanying images. A copy of each written informed consent is available for review by the Editor-in-Chief of this journal.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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