Association of Retinal Artery and Other Inner Retinal Structures With Distribution of Tapetal-like Reflex in Oguchi’s Disease

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PURPOSE. To report novel ophthalmoscopic features of patients with Oguchi’s disease, and to describe how they may be related to the unusual tapetal-like fundus appearance.

METHODS. Twenty-one eyes of 11 patients who were diagnosed with Oguchi’s disease were investigated. Genetic screening of seven cases showed homozygous mutations in the SAG gene (c.926delA). The retinal appearance was retrospectively assessed in the fundus photographs, and the optical coherence tomographic (OCT) and fundus autofluorescence (AF) images.

RESULTS. In 11 eyes of 7 patients, clearly demarcated dark regions without tapetal-like reflex were observed in the midperipheral retinal regions. In the dark regions, OCT showed lower reflectances in the photoreceptor layer but the AF images had normal reflectances. In nine eyes of six patients, the dark regions were partially demarcated by retinal arteries but not by veins. In nine eyes of five patients, the extent of the dark regions either increased or decreased during the course of the disease process, and these changes were not due to the state of adaptation or a posterior vitreous detachment. In all eyes, the peripheral retinal arteries but not veins had either high or low reflective regions along one side.

CONCLUSIONS. Although the alterations of the outer retinal layers are believed to be most responsible for the abnormal tapetal-like reflex in patients with Oguchi’s disease, these ophthalmoscopic features cannot be explained solely by the abnormality of the outer retina. Our findings suggest that the appearance of tapetal-like reflex is strongly affected by alterations of structures in the inner retinal layers.

Keywords: Oguchi’s disease, tapetal-like reflex, Mizuo-Nakamura phenomenon, SAG gene, fundus photograph

Oguchi’s disease is an unusual form of congenital stationary night blindness and is characterized by a golden or grayish-white tapetal-like reflex of the fundus.1 This unusual reflex disappears only after a long period of dark-adaptation.2 Mutations in the arrestin gene (s-antigen; SAG, OMIM 181031)3 or the rhodopsin kinase gene (g protein–coupled receptor kinase 1; GRK1, OMIM 180381)4 have been identified as the causative genes. Most Japanese patients have mutations in the SAG gene.5–7

Oguchi4 described the abnormal fundus appearance of the first patient (22-year-old man) in 1907. He reported that the retinal reflex in the periphery appeared finely marbled just as if it was covered by hoarfrost. The degree of abnormality increased gradually toward the periphery. The choroidal vessels could not be observed except in the far periphery. The peripheral retinal vessels appeared much clearer than in the normal retina but the tips of the vessels appeared darkened. The vessels appeared elevated above the background just like the veins of a leaf, and the peripheral vessels had high reflectivity along one side.

These characteristic ophthalmoscopic findings were reported more than 100 years ago, and the origin of unusual fundus reflex has been investigated by various methods: histopathological assessments,8,9 intraretinal injection of potassium chloride,10 surgical removal of the vitreous,11 scanning laser ophthalmoscopy,12 optical coherence tomography (OCT),13–16 and adaptive optics scanning light ophthalmoscopy.15 In spite of all of these studies, the underlying mechanism of the tapetal-like reflex has not been definitively determined.

We have carefully examined the fundi of 11 patients with Oguchi’s disease, and found that there are ophthalmoscopic features that have not been reported. Our findings suggest that the inner retinal structures, including the vitreoretinal interface, retinal nerve fiber layer (RNFL), and retinal arteries, contributed to the appearance of tapetal-like reflex. These
findings provide important insights on the origin of the unusual fundus reflex in eyes with Oguchi’s disease.

**Patients and Methods**

This was a retrospective case series performed at the National Institute of Sensory Organs, Tokyo, Japan, and in the Department of Ophthalmology, Keio University, Tokyo, Japan. An informed consent was received from all of the subjects for the tests after an explanation of the procedures to be used. In addition, permission was obtained to use their medical data for research. The procedures used adhered to the tenets of the Declaration of Helsinki, and approval to perform this study was obtained from the Review Board/Ethics Committee of the National Institute of Sensory Organs and Keio University.

Twenty-one eyes of 11 patients (4 men and 7 women, age 12–79 years) who were diagnosed with Oguchi’s disease were studied (Table). The left eye of patient 7 was excluded from the analysis because the fundus photographs were of poor quality. In all eyes, the fundus had a diffuse or localized golden tapetal-like reflex which is pathognomonic for Japanese cases of Oguchi’s disease. The full-field scotopic ERGs were non-recordable after 30 minutes of dark-adaptation. The mixed rod-cone bright-flash responses had an electronegative shape with reduced a-wave and severely reduced or absent b-wave. The photopic ERGs were normal. These ERG findings are typical of Oguchi’s disease. The visual acuity was normal in all of the patients except patient 10 who had untreated senile cataracts.

Genetic analyses were performed in seven patients, and all had the same homozygous mutation in the SAG gene (c.926delA), which is frequently found in Japanese patients with Oguchi’s disease.5–7

Photographs of the posterior pole to the equator were taken with fundus cameras (TRC-50X, TRC-50IA, and TRC-50DX type IA; Topcon, Tokyo, Japan), and the characteristic features, such as distribution patterns of tapetal-like reflex and appearance of the retinal vessels, were retrospectively assessed independently by two experienced ophthalmologists (YK and KT). In cases in which the conclusions were different, discussions were held until both examiners agreed.

Optical coherence tomography images were obtained in the light-adapted condition by spectral-domain OCT (Cirrus HD-OCT, version 6.5; Carl Zeiss Meditec, Dublin, CA, USA) and by swept-source OCT (DRI OCT-1 Atlantis; Topcon) after pupil dilation. Fundus autofluorescence (AF) images were obtained in the light-adapted condition with a confocal scanning laser ophthalmoscope (HRA 2; excitation light, 488 nm; barrier filter, 500 nm; field of view, 55°; Heidelberg Engineering, Heidelberg, German) following pupil dilation.

**Results**

**Dark Regions Demarcated by Retinal Arteries**

Under room-light conditions of the outpatient clinic, a tapetal-like reflex was observed in all of the cases, but its distribution was not homogeneous over the entire retina. In 11 eyes of 7 patients, there were clearly demarcated dark regions without a tapetal-like reflex (Fig. 1, arrows; Table). These dark regions were located along or posterior to the equator in all 11 eyes. In nine eyes of six patients, the dark regions were partially demarcated by retinal arteries but not by veins (Fig. 2, arrows). In the dark regions, the retina appeared slightly depigmented compared with that of healthy Japanese individuals. The depigmentation was observed in patients both with and without myopia and did not seem to be associated with myopic changes (Table). Choroidal vessels could be clearly seen only in the dark regions (Fig. 2).

**Optical Coherence Tomography and Fundus AF Imaging**

The OCT images showed that the reflectance of the photoreceptor layer was much higher in the region with tapetal-like reflex than in the dark region, as previously described (Fig. 3). Regions with tapetal-like reflex had higher reflectivity of the photoreceptor inner segment ellipsoid (ISe) line and of the layer of photoreceptor outer segment above the RPE. There were no apparent structural abnormalities in either the inner or outer retinal layers or choroid (Fig. 3A). In the AF images, there were no demarcated lesions corresponding to the dark regions in the fundus photograph (Fig. 3B, asterisks).

**Expansion and Contraction of Dark Regions**

In nine eyes of five patients (patients 1, 2, 3, 4, 11), fundus photographs had been serially taken over several years, and we compared the changes in the tapetal-like reflex. In the right eye of patient 1, the dark region in the superior-temporal retina was replaced by the tapetal-like reflex from the periphery that expanded toward the center (Fig. 4A). In the left eye of patient 2, the dark region in the nasal retina was replaced by a tapetal-like reflex of the periphery that expanded toward the center, and the dark region was not present at the age 22 years (Fig. 4B). In the right eye of patient 3, the region with tapetal-like reflex in the inferior retina was replaced by a dark region that expanded from the center toward the periphery. Thus, the dark regions gradually expanded in this eye (Fig. 4C). In the right eye of patient 1, the regions with and without the tapetal-like reflex interlaced, and the dark regions either expanded or contracted depending on the retinal locations during the follow-up period (Fig. 4D). In total, only an expansion of the dark regions was observed in three eyes of two patients, and only a contraction of the dark regions was observed in three eyes of two patients. In three eyes of two patients, both expansion and contraction of the dark regions was observed depending on the retinal locations (Table). None of these patients noticed either an improvement or reduction of nyctalopia after the distribution pattern changed.

To exclude the possibility that the changes in distribution of the dark regions were due to the adaptation status, we examined how the borders of dark regions changed during light-adaptation in patient 1. After 3 hours of dark-adaptation, the tapetal-like reflex was not detected in the entire retina, the Mizuo-Nakamura phenomenon, but the reflectivity of the retina did not become homogeneous (Fig. 5A). After light-adaptation, the tapetal-like reflex reappeared, and the dark regions became clearly visible in the same location. The borders between the regions with and without tapetal-like reflex are indicated by the white arrows in Figure 5B. Their locations did not change during the course of the light-adaptation, which would indicate that the changes in distribution of the dark regions were not due to the adaptation state.

**High and Low Reflective Regions Along Peripheral Arteries**

As described by Oguchi1 in 1907, the peripheral vessels had either high or low reflective regions running along the vessels (Fig. 6). We also found that there were other characteristic
### Summary of the Cases

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Numbers in parentheses indicate ages at initial and final examination. F, female; L, left; M, male; NE, not examined; R, right; SE, spherical equivalent; +, observed in the fundus photograph; −, not observed in the fundus photograph.
FIGURE 1. Fundus photographs of eyes with Oguchi’s disease showing clearly demarcated dark regions. The dark regions without tapetal-like reflexes are located along or posterior to the equator (arrows) in patient 1 (A, B), patient 2 (C, D), patient 3 (E), and patient 11 (F).
FIGURE 2. Dark regions demarcated by retinal arteries. The locations of the retinal arteries are shown by white dots in the right columns. The dark regions are partially demarcated by retinal arteries but not by veins (arrows), in the right eye of patient 1 (A), the left eye of patient 1 (B), the left eye of patient 2 (C), and the left eye of patient 3 (D).
features in the reflectance of the retinal vessels. The highly reflective regions were observed only along one side of the arteries but not along the veins (Fig. 6A, arrowheads). They had the same color as the tapetal-like reflex and appeared different from the strong vascular reflexes commonly observed in children. The highly reflective regions along the arteries disappeared after 3 hours of dark-adaptation.

The low reflective regions were observed either along one side or both sides of the arteries but not along the veins (Fig. 6B, arrowheads). Following 3 hours of dark-adaptation, the dark regions became undetectable due to the disappearance of the tapetal-like reflex in the surrounding regions. The highly reflective regions along the retinal arteries were observed in all of the 21 eyes of 11 patients, and those along the retinal veins were observed in only one eye of patient 4 (Table). The low reflective regions along arteries were observed in 19 eyes of 10 patients, and those along veins were not observed in any eyes (Table).

There were other unusual findings related to the retinal arteries. In the left eye of patient 4, both highly and lowly reflective regions were observed at the same location of a peripheral artery (Fig. 6C, left). In the left eye (Fig. 6C, middle) and right eye (Fig. 6C, right) of patient 3, the dark regions were observed along the peripheral arteries but were slightly separated from the vessels (arrowheads in Fig. 6C, middle and right). The same findings were observed in both eyes of patient 4.

**Dark Regions Along RNFL**

In the right eye of patient 4, there was a dark region without tapetal-like reflex that ran parallel to the RNFL bundle (Fig. 7, left). Following prolonged dark-adaptation, the tapetal-like reflex decreased, and the border of the dark region completely disappeared (Fig. 7, middle). This dark region was not observed in the fundus photographs 3 years and 6 months later in this eye (Fig. 7, right).

**Swept-Source OCT**

High-contrast vitreous images were obtained by swept-source OCT from the eyes of patient 1 (Fig. 8). The vitreous was...
homogeneously distributed over the dark regions, and a posterior vitreous detachment could not be observed. There were no apparent abnormalities in the vitreoretinal interface observed along the border between the tapetal-like reflex and dark regions (Fig. 8, arrows).

**DISCUSSION**

We examined the medical records of 11 cases of Oguchi’s disease and found funduscopic findings that have not been reported. In the midperipheral region of the fundus, there...
were clearly demarcated dark regions without tapetal-like reflex where the retina, RPE, and choroid had normal layered structures in the OCT images (Figs. 1, 3). The dark regions were partially demarcated by retinal arteries but not by the veins (Fig. 2). The distribution of the dark regions either expanded or contracted during the course of the disease process, and these changes could not be simply explained by the state of adaptation or the presence of a posterior vitreous detachment (Figs. 4, 5).

The peripheral retinal vessels had either highly or lowly reflective regions, and these were observed only along arteries and not along veins (Fig. 6). There was a dark region without tapetal-like reflex, whose location coincided with that of the RNFL bundle (Fig. 7).

The mechanism causing the tapetal-like reflex has not been definitively determined. The results of histopathological studies suggested the existence of an abnormal layer between the photoreceptor and the RPE and the presence of fuscin bodies in the RPE.8 The presence of pigment granules in the nerve fiber layer also has been reported in another study.9 The histopathological investigations, however, have not determined the origin of tapetal-like reflex.

De Jong et al.10 suggested that an increase in the concentrations of extracellular K⁺ produced the tapetal-like reflex because it resembled spreading depression of electric activity in the retina. They suggested that the increased extracellular concentration of potassium was caused by defective Müller cells and led to the tapetal-like reflex in both X-linked retinoschisis and Oguchi’s disease. Considering the genetic origin of Oguchi’s disease in the outer retina, however, the above explanations do not seem reasonable.

Kuroda et al.11 presented a case of Oguchi’s disease in which the tapetal-like reflex disappeared following vitrectomy for the treatment of a rhegmatogenous retinal detachment. They concluded that surgical damage to both the inner limiting membrane and Müller cells led to the release of K⁺ into the vitreous cavity. This then led to a decrease in the concentration of K⁺ in the extracellular space and disappearance of the tapetal-like reflex.11 However, this phenomenon occurred under very pathological conditions after vitreous surgery and could not explain the changes in the distribution patterns of the dark regions that occurred spontaneously.

The results of recent imaging studies have suggested that alterations of the photoreceptor layer is associated with the presence of the tapetal-like reflex. The alterations of the OCT images of the photoreceptor layer corresponded with the changes in the coloration of the fundus, which would suggest that the regions around the photoreceptor outer segments are the sites of the abnormal coloration.13–15 This is supported by the causative mutation in the SAG gene, which encodes S-arrestin, a photoreceptor protein.

Using a helium-neon laser (633 nm) scanning laser ophthalmoscope (SLO), Usui et al.12 found diffuse, fine, white particles in the deep layers of the retina that were not detected
in healthy subjects. The appearance of these particles coincided with the appearance of the tapetal-like reflex. They suggested that the particles were located in the outer retina or RPE, and could be the cause of the abnormal fundus appearance in Oguchi’s disease.

The changes in the reflectance of the rod photoreceptor mosaics in the adaptive optics SLO also suggested that the photoreceptor layer contributed to the tapetal-like reflex.\cite{15}

In our cases, the regions without tapetal-like reflex corresponded with the regions of decreased reflectivity in the photoreceptor layer (i.e., layer between Is e and RPE in the OCT images) (Figs. 3A, 8A, 8B). As in previous studies, the photoreceptor layer is considered to be the most likely origin of the tapetal-like reflex in Oguchi’s disease. The results from the AF imaging indicated that there were no local metabolic abnormalities in the RPE in the areas with and without tapetal-like reflex (Fig. 3B).

There were, however, several findings of the retinal appearance that could not be explained solely by the abnormalities of the photoreceptor layer. The first was the contribution of retinal arteries that demarcate the dark regions without tapetal-like reflex (Fig. 2). The second was the highly or lowly reflective regions along the retinal arteries (Fig. 6). Third was the region without tapetal-like reflex whose distribution coincided with that of the RNFL bundle (Fig. 7). These findings suggest that the inner retinal layers can affect the appearance of the tapetal-like reflex.

As described in the first report by Oguchi,\cite{1} the intensity of the tapetal-like reflex varied depending on the direction of the observation light against the retina.\cite{17} A similar finding was

**FIGURE 6.** High and low reflective regions along the peripheral arteries. (A) Highly reflective regions are observed along the retinal arteries (arrowheads) but not along the veins. (B) Low reflective regions are observed along the retinal arteries (arrowheads) but not along the veins. (C) Both high- and low-reflectivity regions are observed at the same location of the retinal artery in the left eye of patient 4 (IC, left). The dark regions are observed along peripheral arteries, but located slightly apart from the vessels in the left eye (IC, middle) and right eye (IC, right) of patient 3. A, artery; V, vein.
reported for patients with X-linked retinoschisis. This is probably because the layer where the tapetal-like reflex originates has the properties of a plane mirror, namely, the angle of reflection equals the angle of incidence. If the incident angle is almost perpendicular to the retinal surface, strong tapetal-like reflex can be observed, but if it is not, the intensity of the reflex decreases. These reflective materials can be either layered structures or particles or chemical materials embedded in the outer segment discs, which are well-aligned structures parallel to the retinal surface. The Mizuo-Nakamura phenomenon can be explained by the disappearance of mirror-like reflective materials after prolonged dark-adaptation. The incident angle against the reflective materials, however, can be easily changed by the interfering retinal structures that have different refractive indices, such as a thickened vitreoretinal interface or vessel walls of retinal arteries or thickened RNFL. Changes in the distribution patterns of the tapetal-like reflex in Figure 4 can be more easily explained by the modulation of outer retinal reflex due to the inner retinal structures than by the local functional changes of the photoreceptors or RPEs per se. The increased or decreased reflectivity of the tapetal-like reflex may be due to the refractive structures that change the

![Figure 7](image_url)

**Figure 7.** A dark region running along the RNFL bundle can be seen in the nasal sector of the left eye of patient 4 (left). Prolonged dark-adaptation for 180 minutes reduced the tapetal-like reflex, and the border of dark region cannot be detected (middle). The dark region along the bundle of the RNFL disappeared during the 3 years and 6 months of follow-up (right). LA, light-adaptation; DA, dark-adaptation. Arrows indicate the same retinal locations in the nasal retina.

![Figure 8](image_url)

**Figure 8.** Optical coherence tomographic images across the regions with and without tapetal-like reflex. High-contrast vitreous images were obtained by a swept-source OCT. Horizontal line scan images in the superior portion of the right (A) and left (B) eyes in patient 1 are presented. The vitreous appears homogeneously distributed over the dark regions, and a posterior vitreous detachment cannot be observed. There were no abnormalities in the vitreoretinal interface along the border of the dark regions (arrows).
incident angle of the observation light. For example, vitreous traction on the retina can change during the natural course of the disease process, and this may change the reflection of the vitreoretinal interface, leading to the changes in distribution of the dark regions as observed in some of our cases (Fig. 2).

In addition, the direction and strength of the vitreoretinal traction may change during aging even before the posterior vitreous detachment is completed. This may explain the spontaneous changes in the distribution patterns of the dark regions in younger patients. The observations by OCT, however, could not detect either nonhomogeneous vitreous distribution or posterior hyaloid detachment locally along the border of the dark regions (Fig. 8). The interfering materials that can decrease the tapetal-like reflex may be too small and thin to be detected by current imaging techniques.

The decreased or increased reflectivity along arteries could be similarly explained (Fig. 6). Compared with the retinal veins, the retinal arteries are composed of additional muscle layers and appear more hyperreflective. Light passing beside the retinal arteries may be refracted and change the reflectance from the outer retina, although part of dark regions along the artery look too large to be simply explained by this change (Fig. 6C).

The alterations of the dark and tapetal-like reflex regions can be explained by changes in the refractive modulations in the inner retina. However, we could not find any metallic reflex in the dark regions even though we examined the retina from different directions (data not shown). The border between regions with and without tapetal-like reflex was always clear irrespective of the viewing angle. There must be another mechanism that changes the retinal reflectivity in Oguchi’s disease.

The tapetal-like reflex of the Mizuo-Nakamura phenomenon has been reported in other diseases, such as X-linked cone-rod dystrophy. X-linked retinoschisis, and also in carriers of X-linked RP. The underlying mechanism for this reflex has not been clearly determined by our case series, and the discussion we have made regarding possible mechanisms is very speculative. However, our results have given us important insights on the origin of this unusual fundus reflex.

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References