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Mizuo–Nakamura phenomenon in X-linked retinoschisis

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ABSTRACT

Purpose: To determine whether the Mizuo–Nakamura phenomenon, which is an important diagnostic sign of Oguchi's disease, also occurs in patients with genetically proven X-linked retinoschisis (XLRS).
Methods: We examined three patients with a clinical and genetic diagnosis of XLRS and one patient who was clinically diagnosed with Oguchi's disease, with an emphasis on the Mizuo–Nakamura phenomenon. We obtained color fundus photographs, especially in the fully dark-adapted state, using the non-mydriatic mode on a digital retinal camera and infrared observation monitor to avoid the bleaching effects caused by the viewing light, which alters the fundus color in a short time.
Results: The Mizuo–Nakamura phenomenon was observed in all patients with molecularly proven XLRS, similar to that in the patient with Oguchi's disease. The sets of photographs were obtained in the light- and dark-adapted states using our newly devised techniques needed to witness the Mizuo-Nakamura phenomenon.
Conclusions and Importance: The Mizuo–Nakamura phenomenon was identified in three patients with genetically proven XLRS. To the best of our knowledge, this study provided the first genetic evidence of the Mizuo–Nakamura phenomenon in a patient with molecularly proven XLRS without the causative genetic abnormalities for Oguchi's disease. Our findings suggest that XLRS is responsible for the Mizuo–Nakamura phenomenon and its presence in XLRS is not a rare exception but may be a consistent manifestation of XLRS.

1. Introduction

The Mizuo–Nakamura phenomenon[1] is a term used to describe reversible changes in the fundus color from a gold leaf-like reflex under light conditions to the normal orange–red color after full dark adaptation, which is typically seen in Oguchi's disease.[2] and is a rare inherited form of stationary night blindness. This apparently normal fundus color, as seen under full dark adaptation, returns to its original state shortly after exposure to the examination light. X-linked retinoschisis (XLRS), a rare form of inherited retinal dystrophy, typically presents as foveal retinoschisis in a "spoke-wheel" configuration.[3] A glistening silver–gray reflex resembling Berlin's edema[3] seen over the retina is also an important diagnostic sign, especially in older patients who have lost typical foveal retinoschisis and developed atypical atrophic macular degeneration.[4,5] This study examined the changes in the fundus color of these patients by focusing on the Mizuo–Nakamura phenomenon. We identified the Mizuo–Nakamura phenomenon in three patients with molecularly proven XLRS, as was seen in the patient with Oguchi's disease. The Mizuo–Nakamura phenomenon was considered to be solely related to XLRS, as one of the patients with XLRS did not have G-protein-coupled receptor kinase 1 (*RHOK*) or S-antigen visual arrestin (*SAG*) variants, which are the causative gene abnormalities in Oguchi's disease. The purpose of this study was to provide support for the notion that the presence of the Mizuo–Nakamura phenomenon in XLRS is not a rare exception but a uniformly observed characteristic of this condition.

2. Materials and methods

This study was conducted in accordance with the tenets of the Declaration of Helsinki. The Kanazawa University Hospital Human Research Review Board approved the study protocol (approval number: Visual Science 252). We obtained both written and verbal informed consent from all patients for participation and publication of their data. Data from two of the patients presented in our study (patients 2 and 3) were reported in another study that described pathogenic variants in the *XLRS1* gene.[6]

Three patients with XLRS and one patient with Oguchi's disease underwent complete ophthalmologic examination, including

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measurement of best-corrected visual acuity (BCVA) and intraocular pressure, slit-lamp biomicroscopy, fundus examination following pupil dilation, spectral-domain optical coherence tomography (OCT), color fundus photography in the light and fully dark-adapted states, fluorescein angiography, and autofluorescence imaging. Full-field electroretinograms (ERGs) were recorded according to the standards of the International Society for Clinical Electrophysiology of Vision.[7] Genetic analysis was performed using polymerase chain reaction amplification and Sanger sequencing at RIKEN. Photographing the Mizuo–Nakamura phenomenon using an ordinary fundus camera can be difficult, owing to the bleaching effects that arise while focusing the observation light on the fundus, which alters the normal dark-orange fundus color to a golden tapetal-like reflex within a short time.[8] The non-mydriatic mode of a digital retinal camera (CX-1: Canon Inc., Tokyo, Japan) was used to acquire the fundus photographs in the fully dark-adapted state in order to visualize the Mizuo–Nakamura phenomenon. We captured the same retinal area before and after dark adaptation using the internal eye fixation target. The non-mydriatic mode permits the acquisition of fundus photographs without the use of illumination for observation, which bleaches the pigments and alters the adaptation status. Fully dark-adapted fundus photographs of the desired areas can be obtained using the infrared observation monitor of the camera, thus eliminating the influence of the viewing light while aiming and focusing on the fundus. We acquired a sufficient number of repetitions of full dark adaptation to obtain complete panoramic fundus photographs in this state, considering the influence of the flash of the camera.

3. Results

3.1. Patient 1

The proband was an 18-year-old man who was referred to Wakabayashi Eye Center owing to suspected Oguchi's disease in 2009. The BCVA was 0.5 in the right eye and 0.6 in the left eye. The peripheral visual field was normal. The fundus exhibited a silver–gray or gold-leaf-like reflex in the widely posterior polar eyeground extending beyond the vascular arcade (Fig. 1A) under normal room light conditions. Spoke-wheel-shaped retinoschisis was observed in the fovea. The glistening gold-leaf reflex disappeared and turned to the orange–red color of the apparently normal fundus (the Mizuo–Nakamura phenomenon) (Fig. 1B) on the fundus photographs obtained after 1 h of full dark adaptation, similar to Oguchi's disease. OCT revealed foveal retinoschisis between the inner nuclear layer and outer plexiform layer confined to a small area at the foveola (Fig. 1C). Slightly reduced amplitudes were observed on the 30-Hz flicker ERG, light-adapted 3.0 ERG, and dark-adapted 0.01 ERG (Fig. 2). The dark-adapted 3.0 ERG revealed a typical "negative" configuration (Fig. 2). The *XLRS1* pathogenic variant of 102R/W[9] was identified in this patient without the presence of *RHOK* or *SAG* variants. Therefore, patient 1 was considered to have only XLRS and not Oguchi's disease. The Mizuo–Nakamura phenomenon in the posterior polar area appeared less prominent at reexamination after 1 year than that at the initial examination (data not shown). OCT performed at this time depicted the progression of retinoschisis, spreading to a wider area in the posterior eyeground.

3.2. Patient 2

The patient was a 23-year-old man with retinoschisis whose case was previously reported[6] when he was 11 years old. This patient had an R197P pathogenic variant in the *XLRS1* gene.[6] The BCVA was 0.4 in both eyes. OCT revealed retinoschisis in the macula. The silver–gray reflex was not apparent in the posterior polar area; however, we could clearly observe it outside the vascular arcade (Fig. 3A). We obtained panoramic photographs of a wide area of the apparently normal orange–red colored fundus, which corresponded to the silver–gray reflex in the light state (Mizuo–Nakamura phenomenon) (Fig. 3A and B) using three repetitions of 1 h of full dark adaptation to avoid the bleaching influences of the flash.

3.3. Patient 3

This patient was a 37-year-old man with retinoschisis whose case was previously reported[6] when he was 25 years old. This patient had a frameshift pathogenic variant of 195 del T in the *XLRS1* gene.[6] The BCVA was 0.3 in the right eye and 0.02 in the left. The fundus was widely atrophic owing to long-term disease progression, and the silver–gray reflex was not observed in the posterior polar area; however, a faint silver glistening area was observed in the midperipheral retina in the light condition (Fig. 4A). After 1 h of full dark adaptation, the posterior polar area did not exhibit any color change; however, the part of the midperipheral retina corresponding to the area of the silver–gray reflex in the light state changed to a normal-appearing fundus color (Fig. 4B). The Mizuo–Nakamura phenomenon was discernible in this patient, considering the changes in color before and after dark

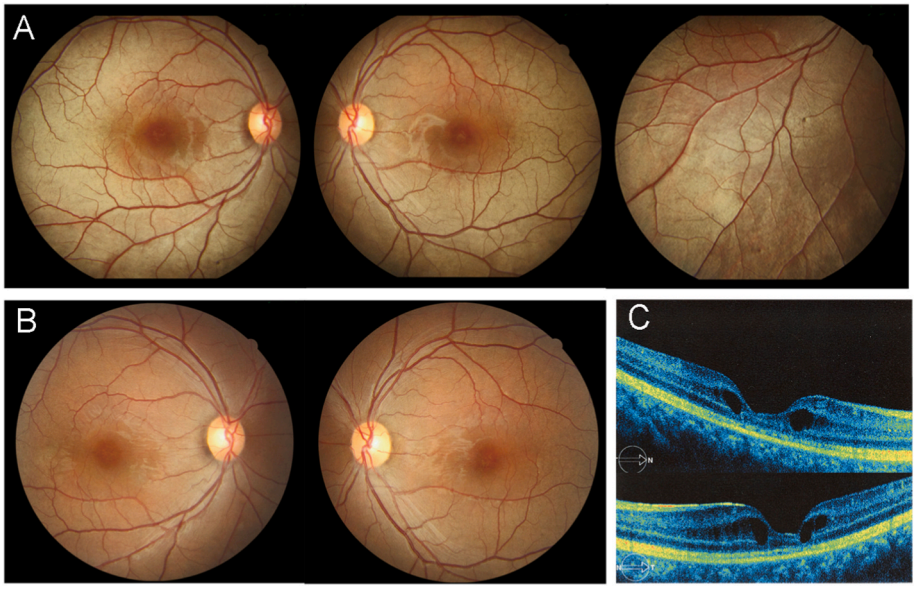

Fig. 1. Fundus images of Patient 1. A) Fundus photographs show a silver–gray or gold-leaf-like reflex in the posterior polar eyeground and midperipheral retina, except the foveola in both eyes in the light state. B) After full dark adaptation, the fundus returned to the apparently normal orange–red color (the Mizuo–Nakamura phenomenon). C) Optical coherence tomography shows foveal retinoschisis between the inner nuclear layer and outer plexiform layer. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

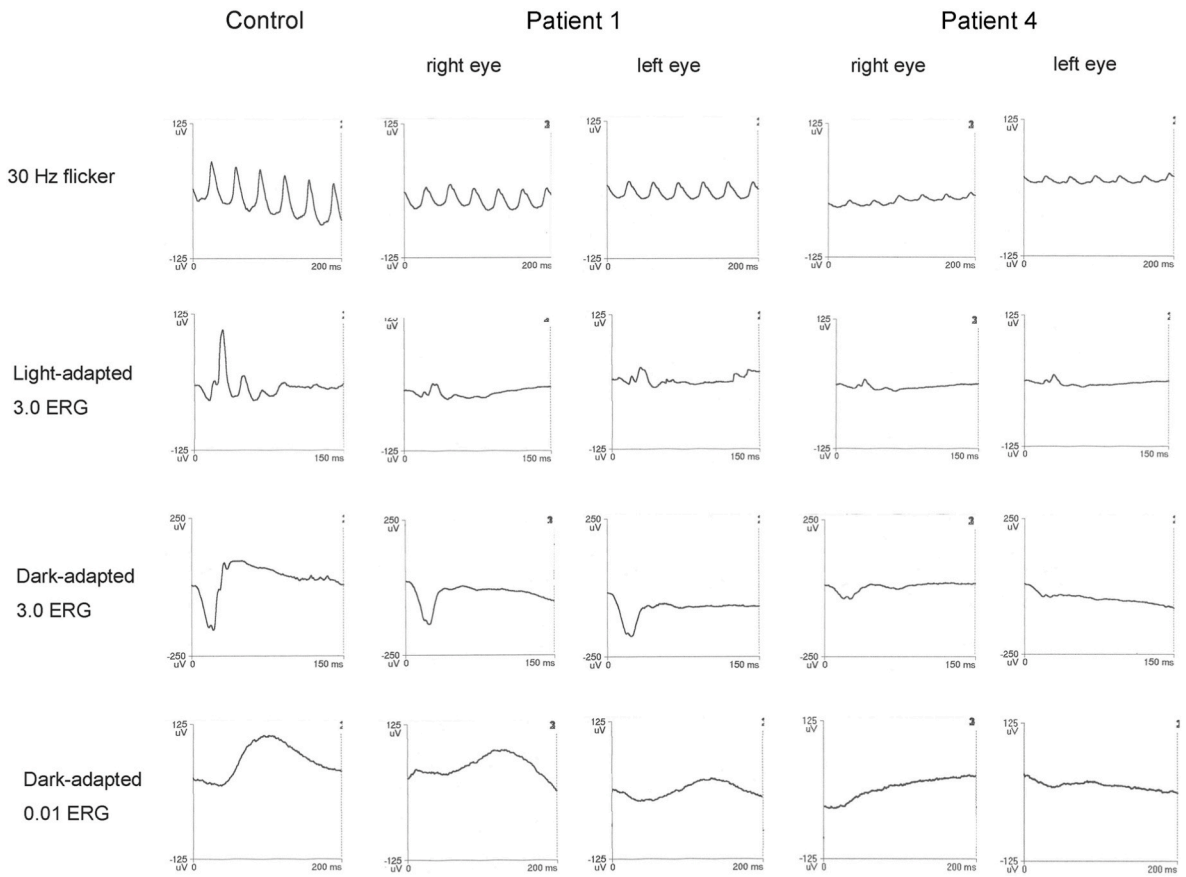

Fig. 2. Full-field electroretinograms for Patients 1, 4 and a control subject. In Patient 1, all amplitudes of the 30 Hz flicker ERG, light-adapted 3.0 ERG, dark-adapted 3.0 ERG, and dark-adapted 0.01 ERG are slightly reduced, and the dark-adapted 3.0 ERG show a typical "negative" configuration (b/a ratio<1.0). In Patient 4, all amplitudes of the 30-Hz flicker ERG, light-adapted 3.0 ERG, dark-adapted 3.0 ERG and dark-adapted 0.01 ERG are markedly reduced, and the dark-adapted 3.0 ERG also depicts a waveform with a "negative" configuration (b/a ratio<1.0).
ERG: electroretinography.

adaptation. OCT revealed a large cavity in the macula (Fig. 4C).

3.4. Patient 4

The patient was a 72-year-old man with Oguchi's disease who visited Wakabayashi Eye Center in 2013 with a chief complaint of blurred vision due to cataract. His visual acuity was 0.4 in the right eye and 0.9 in the left. He had difficulty with night vision, which had not progressed since childhood. The fundus showed a typical gold-leaf-like reflex with a dilated dark red retinal vein silhouetted against the reflex in the posterior polar eyeground and outside the vascular arcade under the normal room light condition (Fig. 5A). The glistening gold-leaf reflex disappeared, and the fundus returned to its normal color (Fig. 5B) (i.e., the Mizuo–Nakamura phenomenon) on the fundus photographs obtained using the non-mydriatic mode of the fundus camera before and after 1 h of full dark adaptation (which was exactly the same procedure as that used in the patients with XLRS). The foveal OCT appeared normal (Fig. 5C). All amplitudes of the 30-Hz flicker ERG, light-adapted 3.0 ERG, dark-adapted 3.0 ERG and dark-adapted 0.01 ERG (Fig. 2) were reduced, and the dark-adapted 3.0 ERG exhibited the characteristics of a "negative" configuration (Fig. 2). The diagnosis of Oguchi's disease could not be genetically proven because the patient refused DNA analysis; however, the diagnosis of Oguchi's disease in this patient was obvious based on his clinical history and ophthalmologic findings.

4. Discussion

The Mizuo–Nakamura phenomenon has been previously reported in XLRS,[8,10,11] however, the patients in these reports were rarely genetically proven to have XLRS,[8,10,11] and there was no genetic evidence that a patient with genetically proven XLRS who showed the Mizuo-Nakamura phenomenon did not have Oguchi's disease.[11] Unless a patient with genetically proven XLRS tests negative for variants of the genes associated with Oguchi's disease, the comorbidity of XLRS with Oguchi's disease remains a matter of debate because the Mizuo–Nakamura phenomenon is a pathognomonic characteristic of Oguchi's disease. We provided the first genetic evidence that a patient with molecularly proven XLRS, who did not have the causative gene abnormalities for Oguchi's disease, presented with the Mizuo–Nakamura phenomenon, indicating that the phenomenon was solely related to XLRS in this patient.

Based on our experience with Patient 1 who presented with a typical and widespread manifestation of the Mizuo–Nakamura phenomenon, we formulated the hypothesis that a silver–gray reflex in XLRS turns to the normal fundus color after full dark adaptation. We demonstrated the typical fundus color changes of the Mizuo–Nakamura phenomenon in the silver–gray reflex in Patient 2 (Fig. 3A and B) using our new procedure, which can be employed for the objective evaluation of this phenomenon. The glistening silver–gray reflex over the retina is a common diagnostic sign observed in most patients with XLRS[3]; thus, this finding strongly supports the notion that the presence of the Mizuo–Nakamura phenomenon in XLRS is not a rare exception but may be a consistent manifestation of XLRS. The three patients described in the study represented the evolution of XLRS from the early (Patient 1), middle (Patient 2), and advanced (Patient 3) stages. Therefore, we believe that further examinations of a larger number of patients in the

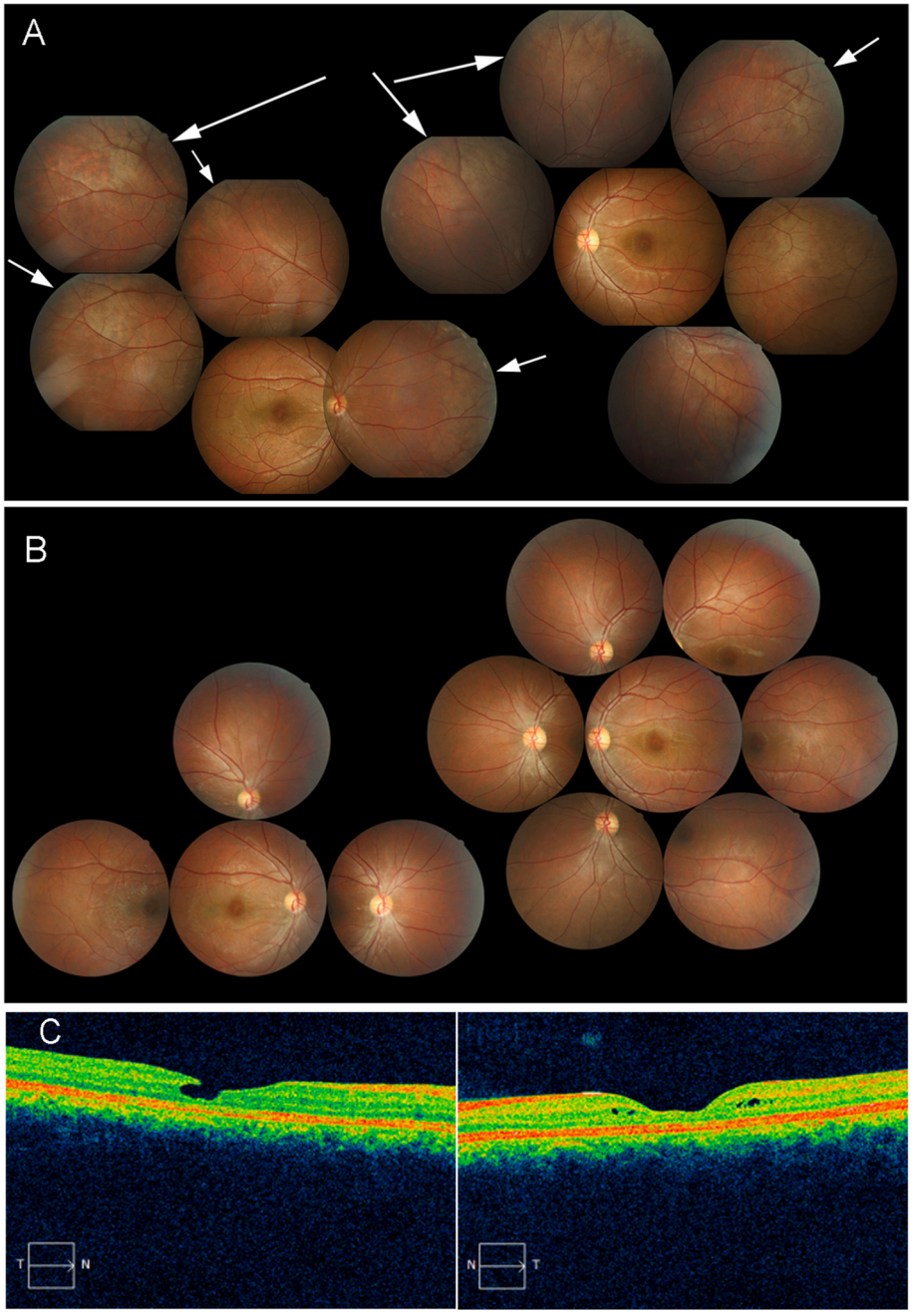

Fig. 3. Fundus photographs and optical coherence tomography of Patient 2. A) In the light state, the silver–gray reflex is not apparent in the posterior polar area; however, it is clearly visible outside the vascular arcade (arrows). B) After a couple of repetitions under full dark adaptation to avoid the bleaching influences of the flash, panoramic photographs of a wide area of the orange–red normal-appearing fundus color were obtained especially in the left eye, corresponding to the area showing the silver–gray reflex in the light state. C) The right fovea showed a lamellar hole configuration (the left) and the left (the right) showed the thinning of the retina and small cavities in the retina. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

different stages of XLRS, followed by our new method of fundus photography, can elucidate the widespread existence of the Mizuo–Nakamura phenomenon in XLRS.

The Mizuo–Nakamura phenomenon is a qualitative, not quantitative, response. The most important step in the evaluation of the Mizuo–Nakamura phenomenon is the acquisition of fundus photographs depicting its normal color to establish the base color value under full dark adaptation. It is easy to acquire fundus photographs in the light state; however, they can be quite difficult to obtain in the dark-adapted condition, as noted earlier.[8] The non-mydriatic mode of the camera allowed us to acquire fundus photographs without using illumination for observation. The phenomenon can be identified by acquiring photographs of the area corresponding to the silver–gray reflex before and after dark adaptation. The retina was widely atrophic in Patient 3 and we could observe the silver–gray reflex in a few areas of the mid-peripheral fundus, and the posterior polar area no longer showed the silver–gray reflex because of disease progression in Patients 2 and 3. Therefore, the Mizuo–Nakamura phenomenon is observed in the posterior polar area only when macular involvement is confined to the foveola and limited to the early stage of the disease. One should focus on areas of the silver–gray reflex on indirect ophthalmoscopy and acquire photographs of these areas in the dark-adapted state using the non-mydriatic mode of the fundus camera to evaluate the Mizuo–Nakamura phenomenon in older patients with XLRS presenting with widespread degeneration.

The importance of the Mizuo–Nakamura phenomenon in XLRS is unclear, and its pathogenesis remains to be elucidated. The fundus color changes in our patients with XLRS and Oguchi's disease were observed using the same procedure before and after dark adaptation and showed considerably similar results. The gold-leaf-like reflex in both XLRS[12] and Oguchi's disease[13] disappeared after vitrectomy. The negative ERG waveform is seen in both XLRS[4] and Oguchi's disease.[14] and our study

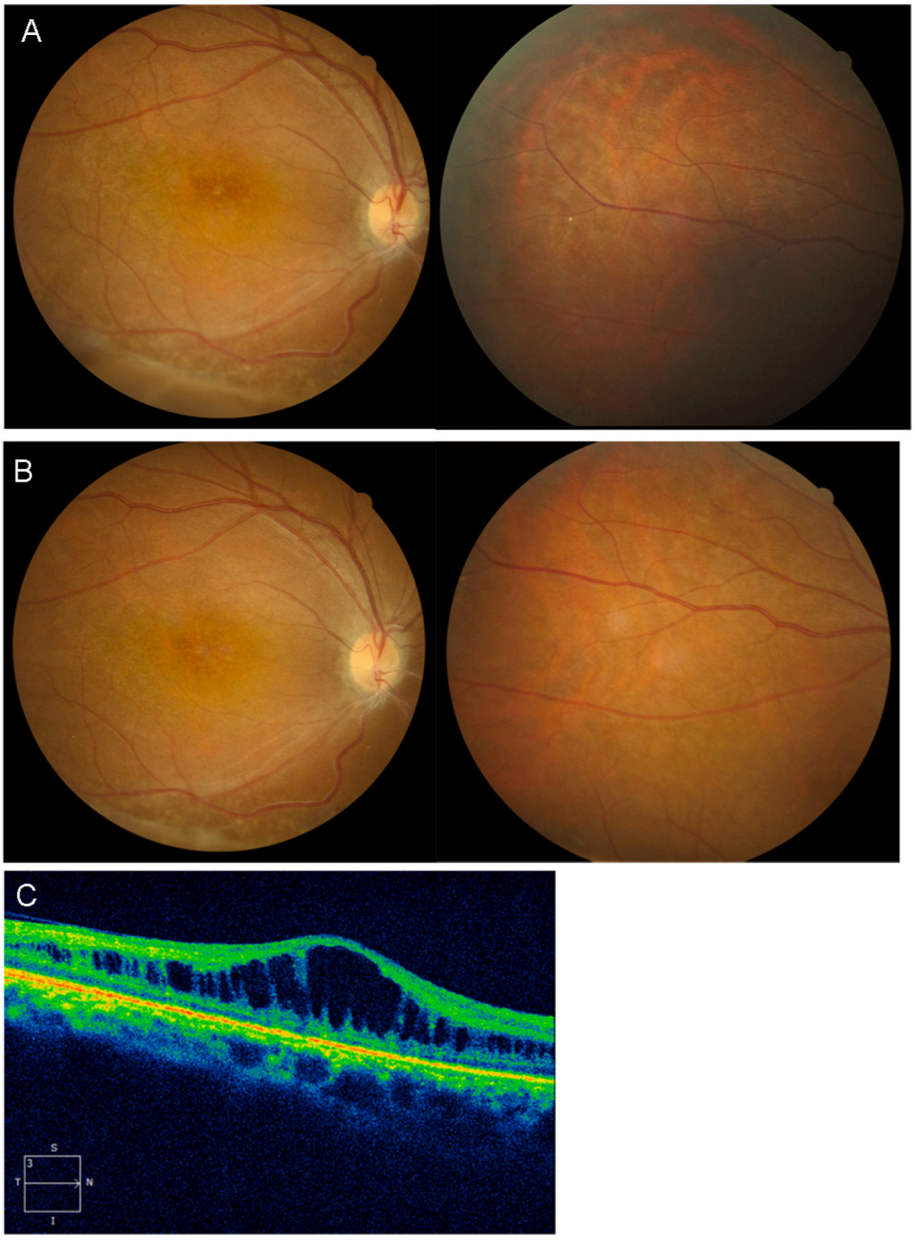

Fig. 4. Fundus photographs and optical coherence tomography of Patient 3. A) Although the silver–gray reflex is not seen in the posterior polar area, it is seen in the mid peripheral area. B) After full dark adaptation, a discernible change from the silver–gray reflex to the normal-appearing fundus color is seen in the midperipheral area. C) Optical coherence tomography shows a large cavity in the macula extending widely to the posterior polar area. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

demonstrated the Mizuo–Nakamura phenomenon in patients with XLRS and Oguchi's disease. These common characteristics between the two diseases are suggestive of similar underlying pathogenesis or etiology for the gold-leaf or silver–gray reflex and Mizuo–Nakamura phenomenon.

5. Conclusions

In conclusion, we provided a new procedure for fundus photography needed to witness the Mizuo-Nakamura phenomenon, and we identified the phenomenon in all patients with genetically proven XLRS. To the best of our knowledge, we provided the first genetic evidence of the Mizuo–Nakamura phenomenon in a patient with molecularly proven XLRS without the causative gene abnormalities for Oguchi's disease. Our findings suggest that XLRS is responsible for the phenomenon; the presence of the phenomenon in XLRS is not a rare exception but may be a consistent manifestation of XLRS.

Patient consent

We obtained both written and verbal informed consent from all patients for participation and publication of their data.

Financial Support

No funding or grant support.

Authorship

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

Data availability statement

The data generated in this study are available upon reasonable request.

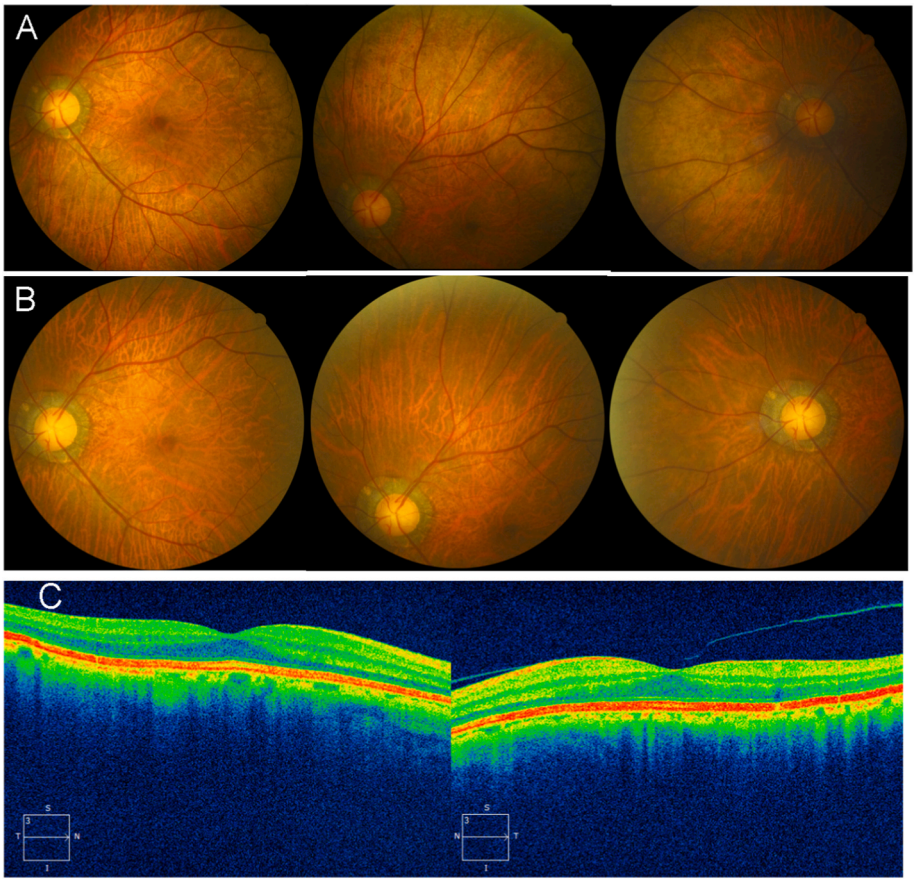

Fig. 5. Fundus photographs and optical coherence tomography in Patient 4 (Oguchi's disease). A) The gold-leaf reflex is seen in the posterior polar area and outside the vascular arcade. B) After full dark adaptation, the fundus returned to the normal-appearing fundus color (Mizuo–Nakamura phenomenon). We obtained the photographs using the same procedure as that used in all the XLRS cases in this study. C) Optical coherence tomography reveals a normal macula. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Declaration of competing interest

No conflicting relationship exists for any author.

Acknowledgments

None.

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