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CLINICAL INVESTIGATION

Three cases of acute-onset bilateral photophobia

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Abstract

Purpose To report the findings in 3 cases of bilateral negative electroretinograms (ERGs) with acute onset of photophobia.

Study design Retrospective case series.

Methods The medical charts of the 3 patients were reviewed.

Results A 43-year-old woman, a 68-year-old woman, and a 41-year-old woman were referred to Nagoya University Hospital. Their main symptom was bilateral acute photophobia. None of the patients had any systemic diseases or specific medical history. The decimal best-corrected visual acuity (> 0.8) and Humphrey visual fields (mean deviation > -3 dB) were relatively well preserved in all 3 patients. The optical coherence tomography (OCT) and fundus autofluorescence findings were essentially normal. Fluorescein angiography showed mild leakage in 1 patient but no abnormality in the other 2 patients. However, the ERGs of the 3 patients had the features of abnormal ERGs found in patients with incomplete congenital stationary night blindness (CSNB). Exome analyses found no pathogenic variants related to known CSNB-related genes. The symptoms and ERGs of the 3 patients have not progressed or recovered after a relatively long follow-up period.

Conclusion The ERG characteristics of 3 patients with bilateral photophobia were similar to those of incomplete CSNB, suggesting post-phototransductional abnormalities. The symptoms and genetic analyses indicated the possibility of an acquired condition rather than a hereditary retinal disease.

Keywords Acquired retinal disease · Incomplete-type congenital stationary night blindness · Negative-type ERG · Post-phototransduction abnormality

Introduction

Full-field electroretinography (ERG) has been used to diagnose inherited and acquired retinal diseases. A selective reduction of the b-wave with a normal or minimally reduced a-wave leading to a negative-type ERG or electronegative ERG often indicates dysfunction of the post-phototransduction pathways. Bilateral negative ERGs are usually detected in hereditary retinal diseases, such as complete- or incomplete-type congenital stationary night blindness (CSNB) [1], X-linked juvenile retinoschisis [2], and Duchenne muscular dystrophy [3]. These diseases are related to dysfunction of post-phototransduction due to genetic mutations.

The characteristics of our 3 patients resemble those of patients with incomplete CSNB, and thus reviewing the characteristics of CSNB will be helpful in analyzing the results of our 3 cases. Complete CSNB is due to postsynaptic defects in retinal ON bipolar cell signaling, and the retinal OFF bipolar cell pathway is intact [1]. Complete CSNB

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is caused by variants of the genes coding for proteins located on retinal ON bipolar cells. Incomplete CSNB is due to defects of the synapses from the photoreceptors to both the ON and the OFF bipolar cell pathways. Incomplete CSNB is caused by mutations in the CACNA1F (MIM: 300110) and CABP4 (MIM: 608965) genes that code for proteins localized to the photoreceptor synaptic terminals. CACNA1F$^{-/-}$ and *Cabp4*$^{-/-}$ mouse retinas have abnormal photoreceptor synaptogenesis with ectopic synapses originating from rod bipolar and horizontal cells that extend into the outer nuclear layer [4, 5].

Because of the absence of distinctive morphologic changes shown on ophthalmoscopy and optical coherence tomography (OCT), the differentiation of complete from incomplete CSNB can be best made by full-field ERGs conforming to the protocol of the International Society for Clinical Electrophysiology of Vision (ISCEV) [6]. In both types of CSNB, ERGs with the bright flash under the scotopic condition (dark-adapted [DA] 3.0 and 10.0) have a negative waveform. However, in incomplete CSNB, rod-specific ERGs (DA 0.01) are present but of subnormal amplitude. In addition, the amplitudes of the 30-Hz flicker and the single-flash photopic ERGs (light adapted [LA] 3.0) are markedly reduced. On the other hand, in complete CSNB, rod-specific ERGs (DA 0.01) are undetectable, whereas the 30-Hz flicker ERGs and single-flash photopic ERG (LA 3.0) have distinctive waveforms [7, 8].

Bilateral negative ERGs can also be associated with acquired diseases as in melanoma-associated retinopathy (MAR). MAR is a rare disease with retinal ON bipolar dysfunction that is caused by an autoantibody against a protein expressed by retinal ON-bipolar cells [9–13]. However, the concept of acquired diseases with negative ERGs that resemble incomplete CSNB has not been reported, although some unilateral cases have been reported [14, 15].

The purpose of this report is to present our findings for 3 patients who complained of acute-onset photophobia in both eyes and who all had ERGs that resembled those of bilaterally incomplete CSNB.

Patients and methods

This was an observational study of 3 patients who presented with acute photophobia. The procedures used were approved by the institutional review board of the Nagoya University Graduate School of Medicine (no. 2010-1067-4). Signed informed consent was obtained from the patients, and all procedures conformed to the tenets of the Declaration of Helsinki.

The medical charts of the 3 patients were reviewed. The patients had undergone comprehensive ophthalmologic examinations at Nagoya University Hospital including visual acuity measurements (decimal units), dilated ophthalmoscopy, spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering), and fundus autofluorescence imaging (FAF; 200Tx, Optos). In addition, full-field ERGs (UTAS, LKC Technologies) were recorded according to the ISCEV standard protocol. Focal macular ERGs (ER-80, Kowa) were elicited by a stimulus spot of 15 degrees in diameter with a luminance of 30 cd/m^2 on a background luminance of 3 cd/m^2, according to previous reports [16, 17]. En face images of the fovea were obtained from patient 1 by means of a flood-illuminated adaptive-optics (AO) fundus camera (rtx1, Imagine Eyes), as previously described in detail [18–21]. Blood samples were collected for genetic analysis. Whole-exome sequencing was done according to the published protocol of the National Institute of Sensory Organs (NISO). A customized analysis protocol for the Japanese population was used for variants filtration [22].

Results

Case 1

Patient 1 was a 43-year-old woman who was referred to the Nagoya University Hospital in 2014 because of sudden onset of photophobia and night blindness in both eyes. The ophthalmologist at the primary hospital had suspected MAR because of negative-type ERGs in both eyes. The patient did not report any specific ocular or systemic diseases or use of any type of medication. She had no family history of inherited retinal disease.

The initial examination showed that her best-corrected visual acuity (BCVA) was 1.2 in each eye. Her refractive error (spherical equivalent) was -2.0 D for both eyes. Goldmann perimetry did not show any constriction of the visual fields. Humphrey perimetry showed no scotoma, with a mean deviation of -0.5 dB in each eye. The findings of an arrangement test of the Farnsworth Panel D-15 and a test with plates of the Standard Pseudoisochromatic Plates-Part 2 (SPP-2) were normal. The fundus (Fig. 1a), FAF, and fluorescein angiography (FA) (Fig. 1b) findings were normal. Optical coherence tomography showed a normal retinal structure with a clearly visible ellipsoid zone (EZ) and a partially visible cone interdigitation zone (CIZ; Fig. 1c, d). An AO montage image of the patient's macula detected a well-defined cone photoreceptor mosaic (Fig. 1e–h). The cone density map showed normal distribution of the cones for an area of about 4 degrees in diameter (Fig. 1i). The findings from these retinal images obtained at our hospital were all within normal limits.

Full-field ERGs were recorded according to the ISCEV standard protocol. The DA ERGs elicited by a 0.01-cd.s.m^{-2}

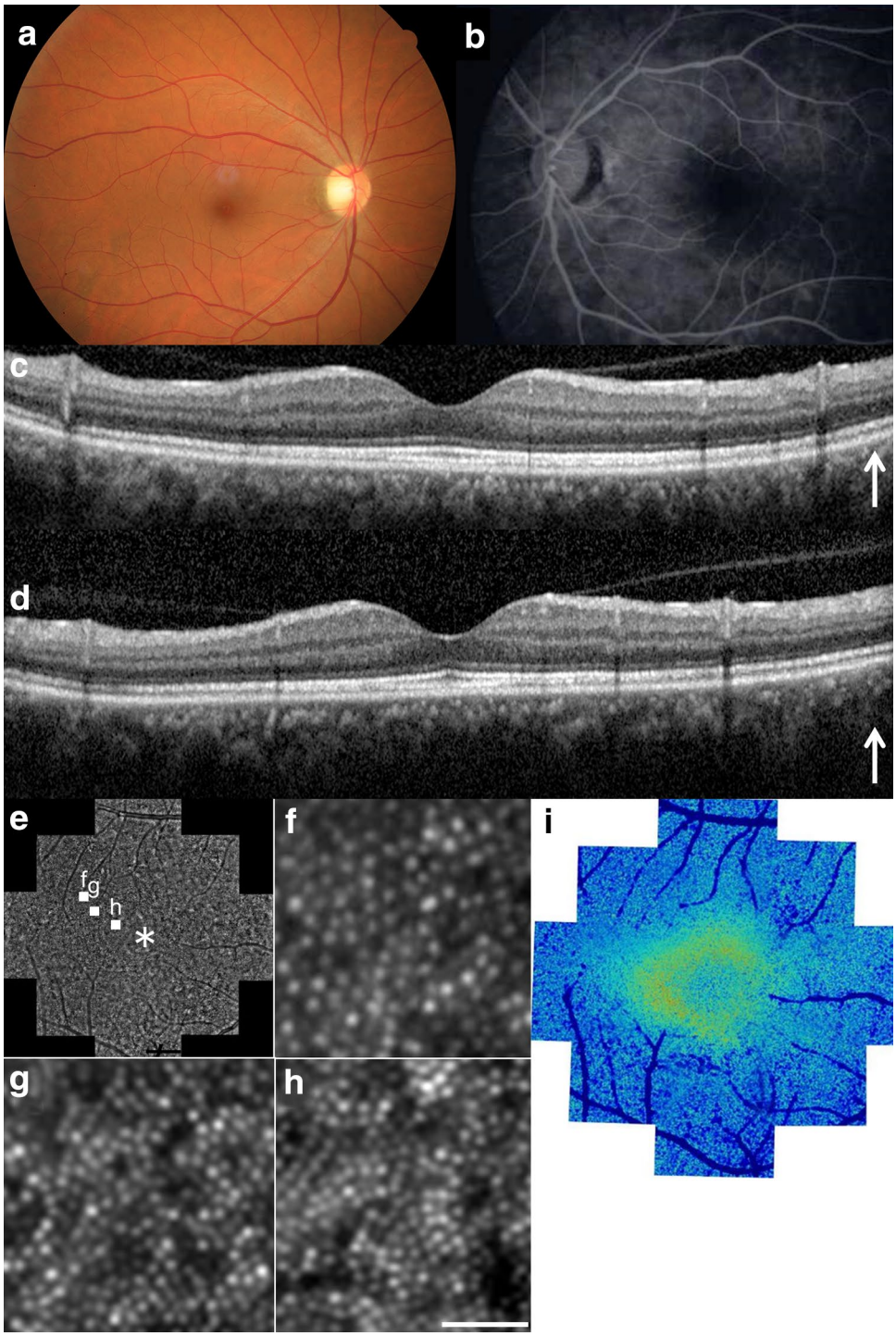

Fig. 1 Results of fundus photography, fluorescein angiography, spectral domain optical coherence tomography (SD-OCT), and adaptive optics fundus imaging in case 1. The **a** fundus photograph (right eye) and **b** fluorescein angiogram (left eye) show no abnormalities. The vertical cross-section SD-OCT images (**c**, right eye; **d**, left eye) show an intact ellipsoid zone (EZ) and cone interdigitation zone (CIZ). **e** AO fundus image montage of the right eye of case 1. The magnified images of the white square in the AO image (**e**) are shown in **f**, **g**, and **h**. The magnified images in **f**, **g**, and **h** correspond to 3, 2, and 1 degrees from the fovea (white asterisk), respectively. Scale bar: 30 µm. A cone mosaic pattern is clearly visible, and the cone density map shows a normal distribution (**i**)

flash were completely extinguished (Fig. 4). The DA-3.0 and DA-10.0 ERGs had negative waveforms with normal a-waves (Fig. 4). These results suggested normal rod photoreceptor function but abnormal post-photoreceptor responses. The LA-3.0 ERG and 30-Hz flicker ERG were markedly reduced; however, the a-wave of the LA-3.0 ERG was recordable (Fig. 4). The results of the LA-3.0 (cone) ERGs and 30-Hz flicker ERGs indicated the possibility of either a loss of cone function or an impairment of the post-phototransduction responses of the ON and OFF bipolar cell pathways. However, the normal cone mosaic in the AO fundus camera and normal structure in the OCT images in addition to the relatively well-preserved a-wave of the LA-3.0 (cone) ERG suggested an abnormality in the synaptic transmission to the ON and OFF bipolar cell pathways. These results suggest a similar pathophysiology to that of

incomplete CSNB. The amplitudes of the b-waves of the focal macular ERGs were about one-half of those of healthy controls, and the implicit time of the b-wave was 50 ms, which is markedly delayed when compared with that of the normal limits (40–43 ms; Fig. 4). The presence of the focal ERGs accounted for the preservation of the BCVA, and the delay of the b-wave suggested a disturbed neural transmission between the photoreceptors and bipolar cells.

None of the candidate variants for incomplete CSNB, including CACNA1F and CABP4, was detected by whole-exome sequencing analysis. Six other heterozygous variants were detected in the genes reported in Retnet (https://sph.uth.edu/retnet/home.htm), ie, *ADGRA3, CC2D2A, CNGB3, ERCC6, TLR4,* and *TMEM126A*. However, from the inheritance pattern and clinical presentation, these gene variants did not seem to be related to this patient's condition. We have followed this patient for 4 years, and her signs and symptoms have remained essentially unchanged.

Case 2

Patient 2 was a 68-year-old woman who was referred to Nagoya University Hospital in 2015 with acute-onset photophobia and night blindness in both eyes. Cataract surgeries had been performed on both eyes at the primary hospital, but her symptoms had not changed. She did not report any symptoms of autoimmune disease or use of any medication. She did not have a family history of inherited retinal disease.

At the initial examination, her BCVA was 0.8 in each eye. Her refractive error (spherical equivalent) was -2.5 D for both eyes. Humphrey perimetry did not show any constriction of the visual fields, and the mean deviation was -0.5 dB for the right eye and -2.5 dB for the left eye. The Farnsworth Panel D-15 results were within normal limits. The fundus appeared normal, but FA showed mild leakage from the disc and vessels in both eyes, indicating slight inflammation (Fig. 2a, b). However, blood tests did not show any abnormality that could explain this inflammation. Optical coherence tomography showed a normal retinal structure with clearly visible EZ and CIZ (Fig. 2c, d).

The full-field and focal ERGs resembled those of case 1 (Fig. 4). The retinal imaging and ERG results also suggested a similar pathogenesis to that of case 1. One heterozygous missense variant in CABP4 (NM_001300895:exon6:c.G506A:p.R169H) was detected by whole-exome sequencing analysis. CABP4 is one of the causative genes of incomplete CSNB. The allele frequency of the *CABP4* variant (c.G506A:p.R169H) in the general population was 0.00001592 according to GenomAD (http://gnomad.broadinstitute.org/), and the variant

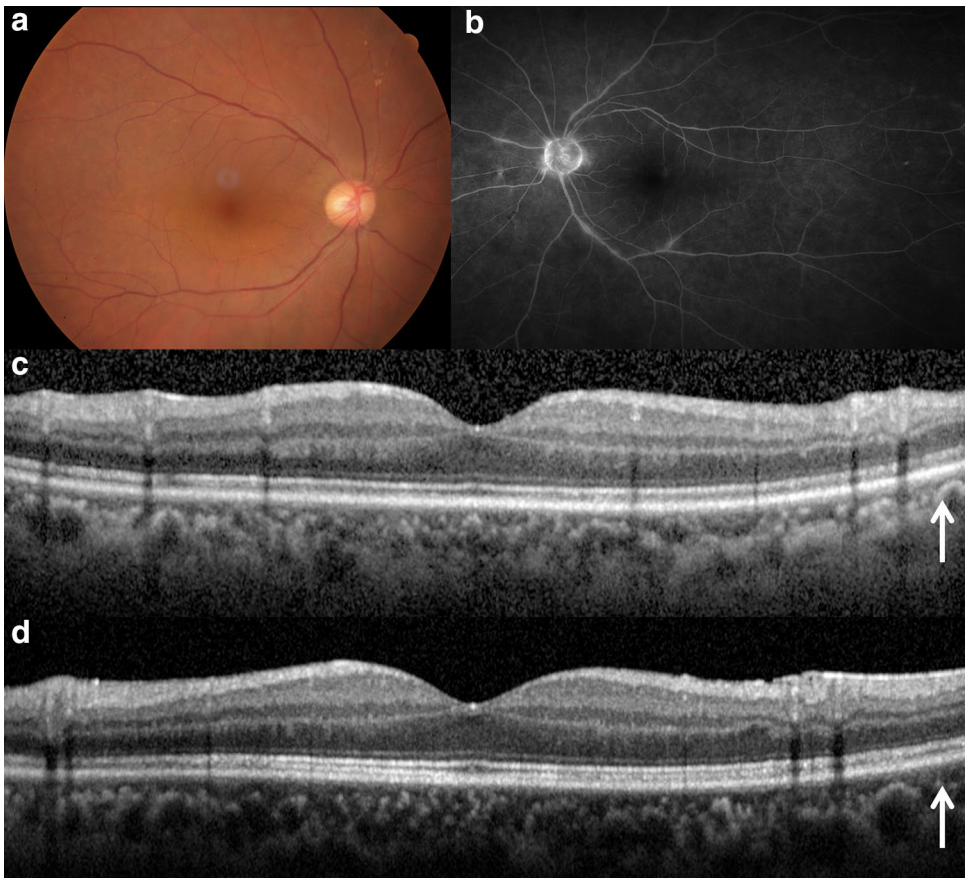

Fig. 2 Fundus photograph, fluorescein angiogram, and spectral domain optical coherence tomographic (SD-OCT) images of case 2. **a** Fundus photograph (right eye) shows no abnormality and **b** fluorescein angiogram (left eye) shows mild leakage from the optic disc and vessels. Vertical cross sections of the SD-OCT images (**c**, right eye; **d**, left eye) show an intact ellipsoid zone (EZ) and cone interdigitation zone (CIZ)

was not detected in the Human Genetic Variation Database (http://www.hgvd.genome.med.kyoto-u.ac.jp/) nor in the Integrate Japanese Genome Variation Database (https://ijgvd.megabank.tohoku.ac.jp/). In silico bioinformatic analyses were performed to predict the pathogenicity of the identified variants. The variant in CABP4 was predicted to be pathogenic by Protein Variation Effect Analyzer (PROVEAN), a software prediction program. However, the Sorting Intolerant from Tolerant (SIFT) and PolyPhen2 software programs did not predict this variant to be pathogenic.

Six other heterozygous variants were detected as candidates in the genes reported in Retnet, ie, *C2orf71, CRB1, LAMA1, MAK, NPHP4, RAX2, and WDR19*. However, from the inheritance pattern and clinical presentation, we judged that these gene variants did not account for the patient's condition.

We have followed this patient for 3 years, and her signs and symptoms have remained essentially unchanged.

Case 3

Patient 3 was a 41-year-old woman who was referred to Nagoya University Hospital in 2007 with acute-onset photophobia in both eyes. She had undergone scleral buckling surgery for a retinal detachment in the right eye in 2004. She had no family history of inherited retinal diseases. She did not report any specific ocular or systemic diseases or use of any medications.

At the initial examination, her decimal BCVA was 1.0 in both eyes. Her refractive error (spherical equivalent) was -7.25 D for the right eye and -8.0 D for the left eye. Humphrey visual field tests did not show any visual field defects. The fundus images showed changes associated with high myopia (Fig. 3a) and the scar resulting from the treatment for the retinal detachment in the right eye. Fluorescein angiography showed no leakage (Fig. 3b). The OCT images showed a dome-shaped macula due to high myopia, but the retinal layers were preserved and the ellipsoid zone was clearly visible (Fig. 3c, d).

The full-field DA-0.01 ERGs were present but reduced, and the DA-3.0 and DA-10.0 ERGs had negative waveforms.

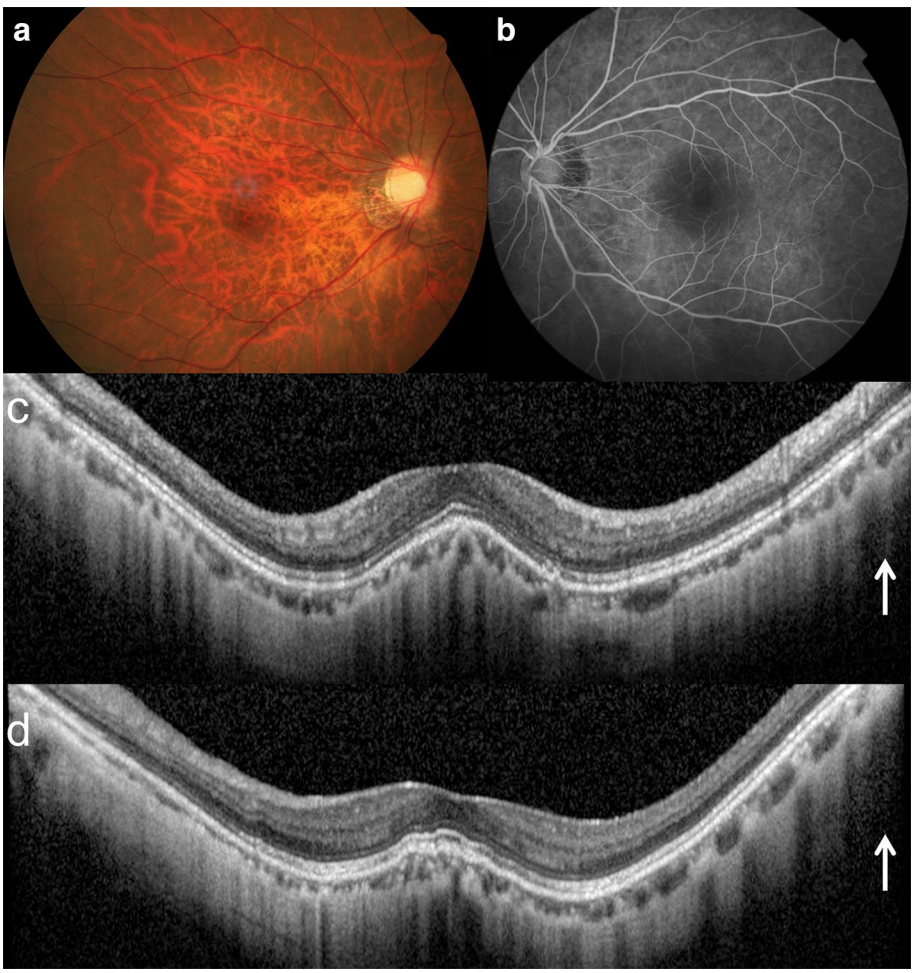

Fig. 3 Fundus photograph, fluorescein angiogram, and spectral domain optical coherence tomographic (SD-OCT) images of case 3. **a** The fundus photograph (right eye) shows high myopic changes and **b** the fluorescein angiogram (left eye) shows no abnormalities. Vertical cross sections of the SD-OCT images (**c**, right eye; **d**, left eye) show a dome-shaped macula in both eyes but an almost intact ellipsoid zone (EZ)

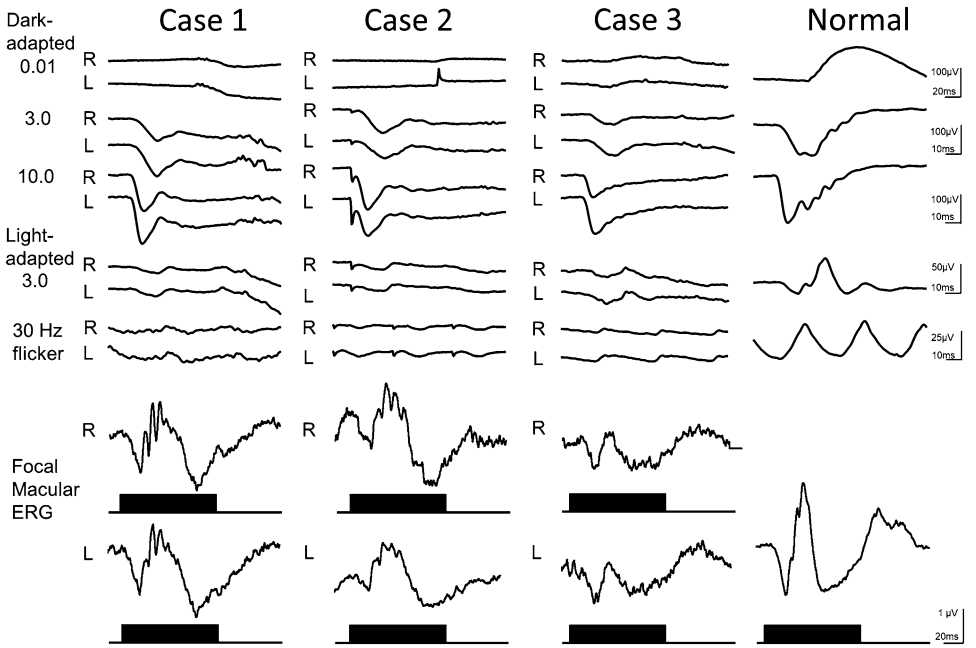

Fig. 4 Full-field ERGs recorded under conditions conforming to the guidelines of the International Society for Clinical Electrophysiology of Vision Standards, and focal macular ERGs elicited by a 15-degree stimulus spot with a 100-ms stimulus duration. The ERGs of cases 1, 2, and 3 and a healthy control (right) are shown. The ERGs of the right and left eyes have similar features in all the cases. The dark-adapted (DA)-0.01 ERGs are extinguished in cases 1 and 2 and severely reduced in case 3. The DA-3.0 and DA-10.0 ERGs have negative waveforms for all 3 cases. The light-adapted 3.0-ERG and the 30-Hz flicker ERG are markedly reduced. The focal macular ERGs are prominent, although those of case 3 are reduced owing to high myopia. However, the waveforms of the focal macular ERG differed from those of the control, and the b-waves became wider and the implicit time of the b-wave was delayed

The LA-3.0 ERG and 30-Hz flicker ERG were markedly reduced. The amplitudes of the ERGs of the right eye were smaller than those of the left eye, although the waveforms were similar. These smaller ERG amplitudes might have been caused by the retinal damage caused by the earlier retinal detachment in the right eye. Compared with the ERGs in cases 1 and 2, the DA-0.01 and LA-3.0 b-waves were relatively well preserved in case 3 (Fig. 4). The amplitudes of the focal ERGs were reduced when compared with those of cases 1 and 2, presumably due to high myopia (Fig. 4). However, the implicit time (48 ms) was delayed when compared with that of healthy controls (40–43 ms). The original diagnosis for this patient was cone-rod dystrophy with a normal fundus, but the diagnosis was later changed to acquired post-phototransduction dysfunction of the retinal ON and OFF bipolar cells.

None of the candidate variants for complete and incomplete CSNB was detected by whole-exome sequencing analysis. Eleven other heterozygous missense variants were detected in the genes reported in Retnet, including *ARHGEF18, C2orf71, C3, CLUAP1, DMD, EYS, HARS, INPP5E, TSPAN12, SAG,* and *USH1C*. However, from the inheritance pattern and clinical presentation, we judged that these gene variants could not account for the patient's condition.

We have followed this patient for 10 years, and her signs and symptoms have remained essentially the same.

Discussion

We have described 3 patients who each presented with sudden onset of photophobia in both eyes and who each had negative-type ERGs. These 3 patients had some signs in common: sudden-onset bilateral photophobia, minimal reduction in the BCVA, and neither progression nor recovery of the ERGs or symptoms after a relatively long follow-up period.

The properties of the full-field ERGs were somewhat similar to those of incomplete CSNB, ie, negative-type ERG, severe reduction of the b-waves elicited by scotopic dim flashes, and severely reduced cone and flicker ERGs. A prolonged implicit time with distinct focal macular ERG b-waves was also a common finding. These findings in common suggested a similar pathogenesis in the 3 patients. Although we have not evaluated the characteristics of the focal macular ERGs in patients with incomplete CSNB in detail, it has been reported that the amplitude of the P1 component of multifocal ERGs in the central region was normal, while those of the more peripheral locations were reduced

in patients with incomplete CSNB [23]. These findings are comparable to those of the focal macular ERGs of our 3 patients. The similarity of the properties of the ERGs in our 3 patients to those with incomplete CSNB suggests a signaling defect involving both the ON and the OFF bipolar pathways. Attempts to record the ON–OFF ERGs elicited by long-duration stimuli from these 3 patients were not successful because of eye movements due to dizziness caused by the bright stimuli.

The signs and symptoms of the 3 patients corresponded with the properties of the ERGs. The photophobia appeared to be related to the reduced cone and 30-Hz flicker ERGs, and the relatively preserved focal macular ERGs accounted for the preserved visual acuity. The night blindness in cases 1 and 2 might be related to the absence of DA-0.01 ERGs, while the absence of night blindness in case 3 might be related to the preserved DA-0.01 ERG.

Compared with the phenotypes of patients with incomplete CSNB, those of our 3 patients differed in several ways: our patients had relatively preserved visual acuity, while that of incomplete CSNB patients is moderately reduced, with a decimal visual acuity of about 0.5. The chief complaint of our patients was photophobia, which is a minor complaint in patients with incomplete CSNB.

Individuals with the complete type of CSNB usually have high myopia, but high myopia was detected only in patient 3, and the refractive errors did not seem to be related to the disease in our 3 patients.

Differential diagnosis

In our 3 patients, a differential diagnosis was needed from electronegative cone-rod dystrophy, which is reportedly caused by mutations in several genes [24–27]. Patients with cone-rod dystrophy have retinal degeneration that can be detected in fundus photographs and OCT images. Our patients did not have any structural changes shown in the OCT images and also did not have the gene variants accountable for electronegative cone-rod dystrophy. More specifically, patient 1 had normal cone distribution in the images obtained with the AO fundus camera in the macular region.

Another disorder that had to be included in the differential diagnosis is peripheral cone dystrophy because the cone ERGs of our patients resembled those reported in patients with peripheral cone dystrophy [28]. However, patients with peripheral cone dystrophy have normal or minimally reduced scotopic ERGs.

We performed whole-exome sequencing and evaluated the variants by means of in silico analysis. Pathogenic variants were not found in the known incomplete CSNB genes or in the genes shown in Retnet (https://sph.uth.edu/retnet/) according to the guidelines of The American College of Medical Genetics and Genomics (ACMG) (https://www.acmg.net/docs/standards guidelines for the interpretation of sequence variants.pdf). However, variants in known genes do not account for all cases of incomplete CSNB. We should consider the genetic abnormalities in *CABP4*, such as large deletion and intron variants, especially for case 2, which were not detected by whole-exome sequencing. Further analyses using whole-genome sequences to salvage the deep intronic/structural variants of CSNB-related genes could help in further clarification of the genetic diagnosis.

The major question was whether the characteristics of our cases were acquired or inherited. Because we did not have any ocular findings before the onset, we had to deduce the pathology from the patients' complaints. The acute onset of photophobia suggested an acquired condition. In addition, the patients reported distinctive changes in their eyesight after the onset; for example, they needed to wear sunglasses on sunny days and they had difficulties in seeing objects on a bright white background.

Negative ERG can occur in several acquired disorders including retinal ischemia and inflammation (eg, birdshot chorioretinopathy and diffuse unilateral subacute neuroretinitis) [2, 29, 30]. However, minimal abnormalities on FA and normal findings on OCT did not indicate these conditions. In addition, retinal ischemia and inflammation usually cause unilateral disturbances.

Bilateral negative ERG in acquired disease is found in MAR, which is a rare disease with retinal ON bipolar dysfunction. MAR is caused by an autoantibody against a protein expressed by retinal ON-bipolar cells [9–12]. However, antibody screening for the antitransient receptor potential melastatin 1 (TRPM1) antibody, which is one of the common antibodies in MAR [31], was negative for cases 1 and 2 (data not shown).

Autoimmune retinopathies, which are sometimes caused by autoantibodies to a systemic malignancy, might be postulated as a cause of our cases. The autoantibodies may disturb signaling from the photoreceptors to both ON and OFF bipolar cells. The antigen might be a protein located in the photoreceptor synaptic terminal, which would then be classified as a gene related to incomplete CSNB. The detection of an antiretinal autoantibody would help in the diagnosis of our cases, but autoantibodies can be present in normal human serum and they are difficult to identify [32].

In addition, we need to consider bilateral acute zonal occult outer retinopathy (AZOOR) [33]. The signs and symptoms of AZOOR include photopsia, enlarged blind spots, and visual field loss corresponding to a functionally altered outer retina. In our cases, the symptoms of photophobia, cone ERG abnormality, and minimal changes in the fundus and OCT [18] are features in common with those of AZOOR, but negative ERG and almost intact visual fields are not present in AZOOR. However, a similar

proposed etiology of AZOOR, autoimmune response or virus infection [33], should be considered.

In conclusion, we examined 3 cases of bilateral acute photophobia with negative ERGs. The minimal morphologic abnormalities and the ERG properties indicate a similar pathogenesis to that of incomplete CSNB, which is caused by disturbances of the signaling from the photoreceptors to both ON and OFF bipolar cells. Whole-exome analysis did not detect any pathogenic variants, and the acute photophobia seemed to suggest an acquired mechanism. To the best of our knowledge, no known disorders can explain these conditions. In cases of photophobia without the loss of visual acuity and normal retinal morphology, ERGs are essential for making the diagnosis.

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