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CLINICAL CASE REPORT

Enhanced S-cone syndrome with preserved macular structure and severely depressed retinal function

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Abstract We present ophthalmic features and genetic analysis findings of a 44-year-old croatian patient with enhanced S-cone syndrome (ESCS). Complete ophthalmic examination, Ishihara colour vision test, dark adaptometry, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence imaging, Goldmann visual field and automated perimetry, full-field electroretinography (ERG), multifocal ERG, S-cone ERG and ON–OFF ERG were performed. Mutation screening of the *NR2E3* gene, which encodes a photoreceptor-specific orphan nuclear receptor, was performed with polymerase chain reaction amplification and direct sequencing. The patient has good visual acuity and normal colour vision. Fundus examination showed normal posterior pole and nummular pigment depositions at the level of the retinal pigment epithelium in the mid-periphery of the retina. The SD-OCT images showed normal macular structure and thickness. The ERG showed characteristic findings: photopic and scotopic responses to the same stimulus had a similar waveform and were dominated by short-wavelength-sensitive mechanisms. Mutation analysis revealed the known *NR2E3* mutation c.481delA (p.Thr161HisFsX18) and the novel *NR2E3* variant c.1120C > T (p.Leu374Phe). To the best of our knowledge, this is the only ESCS patient older than 40 years who phenotypically has preserved macular structure, good central visual acuity and severely depressed full-field ERG as well as the first reported patient with *NR2E3* mutation from Croatia.

Keywords Enhanced S-cone syndrome · ESCS · NR2E3 · Electroretinography · ERG

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Introduction

Enhanced S-cone syndrome (ESCS; OMIM 268100) is an autosomal recessive, slowly progressive, hereditary retinal disorder in which most of the cones are the short-wavelength-sensitive type (S-cones) [1, 2]. The patients lack rod function and have only very weak red- and green-cone function [1, 2]. Their ERG behaves like a greatly magnified blue-cone signal.

The syndrome is caused by mutations in the nuclear receptor subfamily 2 group E member 3 gene (*NR2E3*;

OMIM 604485) mapped on 15q22.32, which encodes a retinal orphan nuclear receptor that regulates the proper differentiation and maturation of rod and cone photoreceptors, in an intricate regulatory network including the cone-rod homeobox and the neural retina leucine zipper transcription factors [3–5].

Clinical findings of ESCS include congenital night blindness, progressively decreasing visual acuity, characteristic electroretinographic features showing both photopic and scotopic responses of a similar waveform, and characteristic fundus alterations.

Here, we report a 44-year-old female patient with ESCS who is compound heterozygous for the known *NR2E3* mutation c.481delA (p.Thr161HisFsX18) and the novel *NR2E3* variant c.1120C > T (p.Leu374Phe). The patient had good visual acuity, normal macular structure and severely depressed retinal function.

Materials and methods

Ophthalmological examination included best corrected visual acuity (BCVA), Goldmann applanation tonometry, slit-lamp and dilated fundus examination. Visual field analysis included Goldmann and Octopus automated perimetry (program tG2, TOP strategy). Colour vision test was performed with Ishihara 15-number plate edition. Spectral-domain optical coherence tomography (SD-OCT) of macula was performed with SOCT Copernicus (Optopol, Poland). Fundus autofluorescence imaging was performed with Topcon TRC-50IX fundus camera (Topcon Corporation, Tokyo, Japan) with fluorescein barrier filter after pupil dilation with 1 % tropicamide (Mydriacyl®). Dark-adapted threshold was measured after 45 min of dark adaptation to an 11° white test light shown centrally or 7° below fixation (Goldmann-Weekers dark adaptometer).

Full-field and multifocal electroretinograms (ERGs) were recorded from both eyes following the standards of International Society of Clinical Electrophysiology of Vision (ISCEV) [6, 7]. The recording electrode was a HK-loop, placed in the fornix of the lower eyelid [8]. The silver-chloride reference electrode was placed on the ipsilateral temple, and the ground electrode was positioned on the forehead. The pupils were dilated with 1 % tropicamide (Mydriacyl®). Full-field electroretinogram was performed using a Ganzfeld stimulator of the RETI port unit (Roland Consult, Wiesbaden, Germany). Dark-adapted ERG responses (rod response, maximal response and oscillatory potentials) were obtained after 20 min of dark adaptation and light-adapted responses (cone response and 30 Hz flicker) after 10 min of light adaptation to the background luminance of 22 cd/m^2. The strength of standard flash (maximal response, oscillatory potentials, cone response and 30 Hz flicker) was 2.4 cd s/m^2, and the strength of attenuated dark-adapted flash (rod response) was 0.03 cd s/m^2. Multifocal electroretinogram (mfERG) was recorded with a 30° stimulus size (61 hexagons) using the RETI scan system (Roland Consult, Wiesbaden, Germany). The stimulus was at a distance of 260 mm, and refractive errors were corrected due to dilated pupils with +3.50 diopters. Recording session consisted of eight trials of 50 s duration. S-cone ERG was elicited with a Ganzfeld Espion ColorDome stimulator (Diagnosys LLC, Littleton, MA, USA) with 0.16 cd s/m^{2,} blue (449 nm) on a yellow background (594 nm). ON–OFF ERG was elicited with a ColorBurst stimulator (Diagnosys LLC, Littleton, MA, USA) with broadband white stimulus (1.7 log cd s/m^2) on a white background (40 cd/m^2). All responses were differentially amplified and stored on a hard disc of the computer.

Mutation screening of the *NR2E3* gene in the proband consisted of direct sequencing of the coding regions and intronGűexon boundaries (primers available on the request). Mutation nomenclature uses numbering with the A of the initiation codon ATG as +1 (http://www.hgvs.org/mutnomen)(NM_014249). DNA of both parents, one sister and two children was available for segregation analysis. The pathogenic potential of missense variants was analysed using PolyPhen (http://genetics.bwh.harvard.edu/pph) and SIFT (http://sift.jcvi.org) prediction servers, as well as the Grantham matrix [9].

The tenets of the Declaration of Helsinki were followed, and informed consent was obtained from the patients before donation of a blood sample.

Clinical examinations were performed at the University Eye Clinic, University Hospital Sveti Duh, Zagreb, Croatia and at the Eye Hospital Ljubljana, University Medical Centre Ljubljana, Slovenia.

Molecular genetic analysis was performed at the Centre for Medical Genetics Ghent, Ghent University Hospital, Ghent, Belgium.

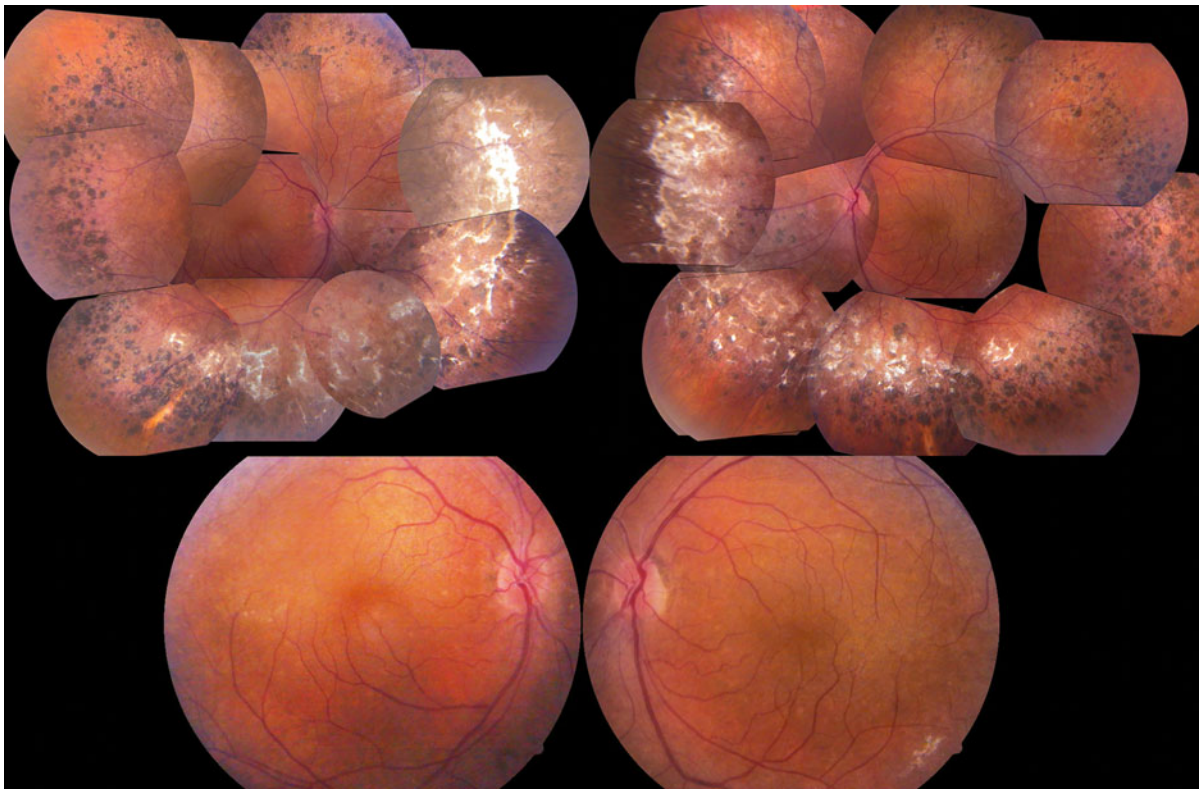

Fig. 1 Fundus photographs of the patient's right and left eye showing nummular pigment depositions outside of the vascular arcades. Areas of chalky white preretinal reticular deposits are present in the nasal and inferior part. In the macula of both eyes, some focal spots of RPE hypopigmentation may be seen (two separate images below)

Results

Case report

A 44-year-old female patient from Croatia, previously diagnosed with retinitis pigmentosa (RP), sought a second opinion. She had had night blindness and wore eyeglasses since she was 8 years old. She also complained of a constricted visual field, although the course of the disease was relatively stable. Both of her parents were healthy as well as her two daughters and sister.

On examination, her BCVA was 0.9 in the right eye (refraction +3.50/+ 0.75 × 170°) and 1.0 in the left eye (refraction +2.50/+ 0.75 × 160°). Anterior segment examination revealed subcapsular posterior cataract of the right eye (grade P1.5 according to Lens Opacities Classification System III). On dilated fundus examination, the posterior pole was clinically normal. In the mid-periphery of the retina, nummular pigment depositions at the level of the retinal pigment epithelium (RPE) were seen as well as areas of chalky white preretinal reticular deposits in nasal and inferior part (Fig. 1). Apart from some focal spots of RPE hypopigmentation, the macula of both eyes otherwise looked normal. No vascular attenuation or typical RP-like bone spicule pigmentation was seen.

Visual fields were symmetrically constricted to 30°–40° on Goldmann perimetry (e I/4), and central static perimetry showed peripheral loss of retinal sensitivity with relatively preserved central sensitivity (Fig. 2). Colour vision examination with Ishihara plates was 14/15 right eye and 13/15 left eye. Fundus autofluorescence imaging showed absence of autofluorescence areals outside the vascular arcades (Fig. 3). Dark adaptometry showed a monophasic curve, indicating a sensitivity loss of the rod system of approximately 2.2 log units. Spectral-domain OCT showed relatively preserved macular structure of both eyes without cystoid changes or macular schisis (Fig. 4).

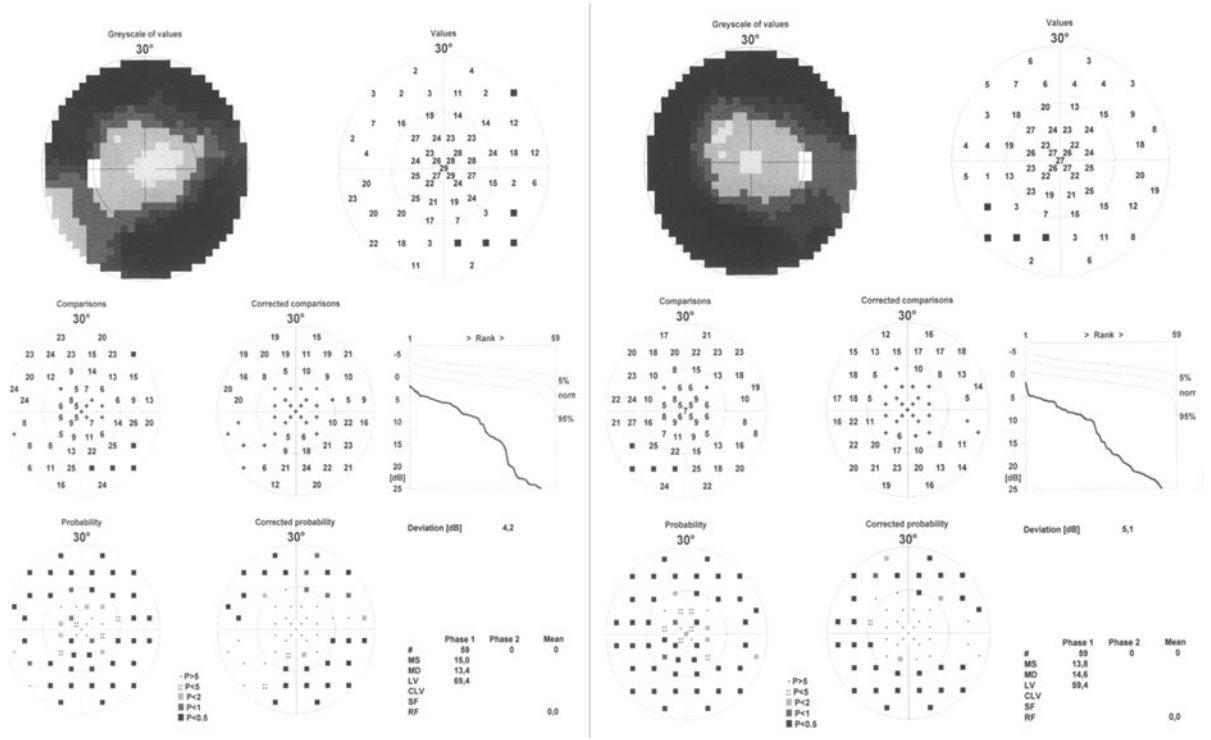

Fig. 2 Central static perimetry showing visual field constriction with relatively preserved central sensitivity of both eyes

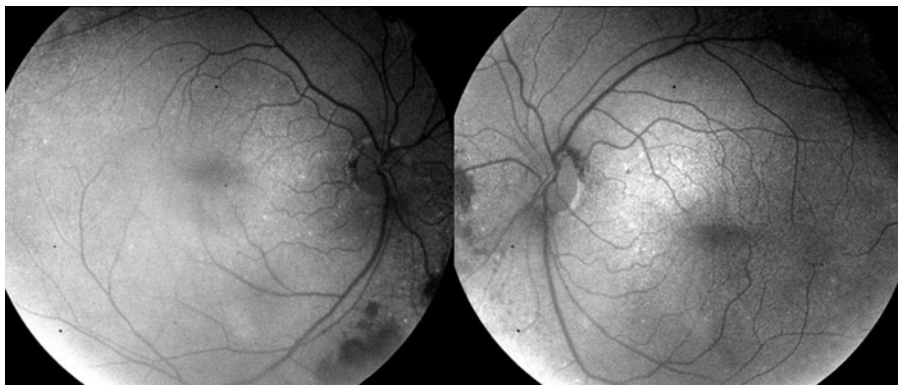

Fig. 3 Fundus autofluorescence imaging showing characteristically reduced autofluorescence areals outside the vascular arcades

The standard full-field ERG showed characteristic features (Fig. 5). The rod-specific ERG was undetectable, and the dark-adapted maximal response and the light-adapted cone response had an essentially similar waveform and were severely reduced and delayed. The 30-Hz flicker was delayed and its amplitude was lower than the cone response a-wave. The additional short-wavelength-specific stimulation was used to observe the activity of the short-wavelength sensitive (S-cone) mechanism (Fig. 5). The S-cone response of the ESCS patient exhibited a waveform, which was different from the control in a manner that an LM-component was absent. This finding was even more distinctive, when response was elicited with higher strength of blue flash (0.25 cd s/m^2, not shown in results). The waveform of the S-cone response in ESCS was essentially similar to the one of the dark-adapted maximal response and light-adapted cone response. Furthermore, also its amplitude was similar, despite the fact that it was elicited with considerably

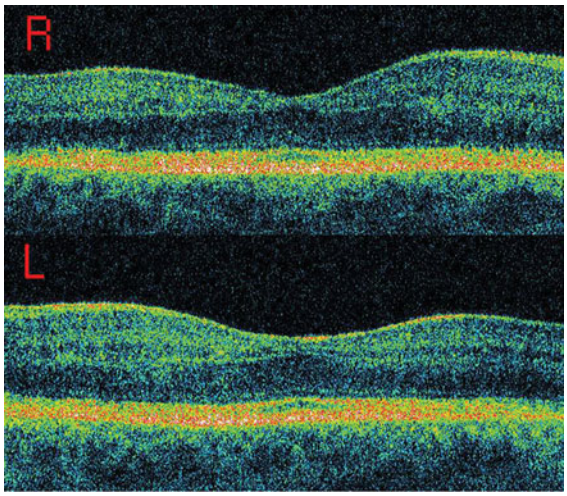

Fig. 4 Spectral-domain OCT scan of the right (R) and left (L) eye showing preserved macular structure without cystoid changes or macular schisis

lower flash strength (0.016 vs. 3 cd s/m^2), indicating that the majority of the ERG response was dominated by the S-cone mechanisms. The responses to long duration stimuli were also recorded to test the possible presence of the OFF-related ERG activity (Fig. 5). Compared to healthy controls, ON-response was barely measurable, while the OFF response was relatively more prominent, but severely delayed and attenuated. Multifocal ERG was subnormal but showed relative preservation of central function and absence of responses with increased eccentricity (Fig. 6).

During the 5-year follow-up period, patient's clinical findings remained unchanged. Ophthalmological examination findings of patient's parents, sister and 2 daughters were completely normal.

Mutation screening of the *NR2E3* gene showed that the patient is compound heterozygous for the known mutation c.481delA (p.Thr161HisFsX18)[10] and the novel variant c.1120C > T (p.Leu374Phe). Of note, this variant segregated in the family.

Discussion

This is the first report of a patient with *NR2E3* mutation from Croatia and also a first report of a patient older than 40 years who has ESCS with good central visual acuity, preserved macular structure and severely depressed full-field ERG. Presented patient has relatively mild form of clinically evident retinal degeneration and severely depressed retinal function. Patients with ESCS usually present with night blindness, variable loss of visual acuity and visual field abnormalities. Colour vision is usually normal or only slightly impaired because there are enough medium- and long-wavelength-sensitive cones (M- and L-cones) present centrally. There may be various fundus appearances, the most typical being nummular pigmentary deposition at the level of

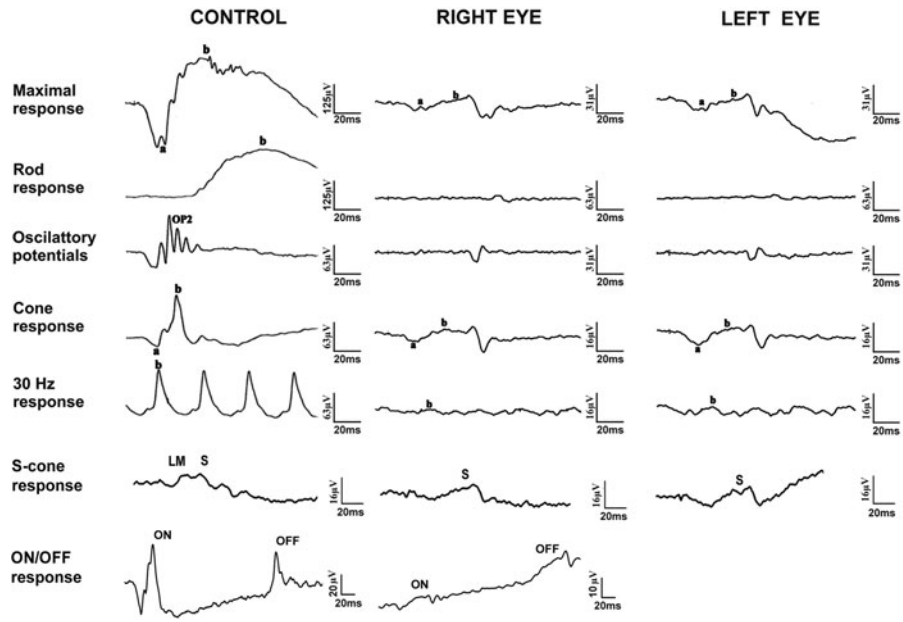

Fig. 5 Standard full-field ERG (maximal response, rod response, Osc. potentials, cone response and 30-Hz flicker response) and extended ERG protocols (S-cone response and ON/OFF response) in the control subject and in patient with ESCS. For S-cone response, LM indicates the component of the L- and M-cone mechanisms, S indicates the component of the S-cone mechanism. For ON/OFF response, ON indicates the component of the ON-retinal pathway, and OFF indicates the component of the OFF-retinal pathway

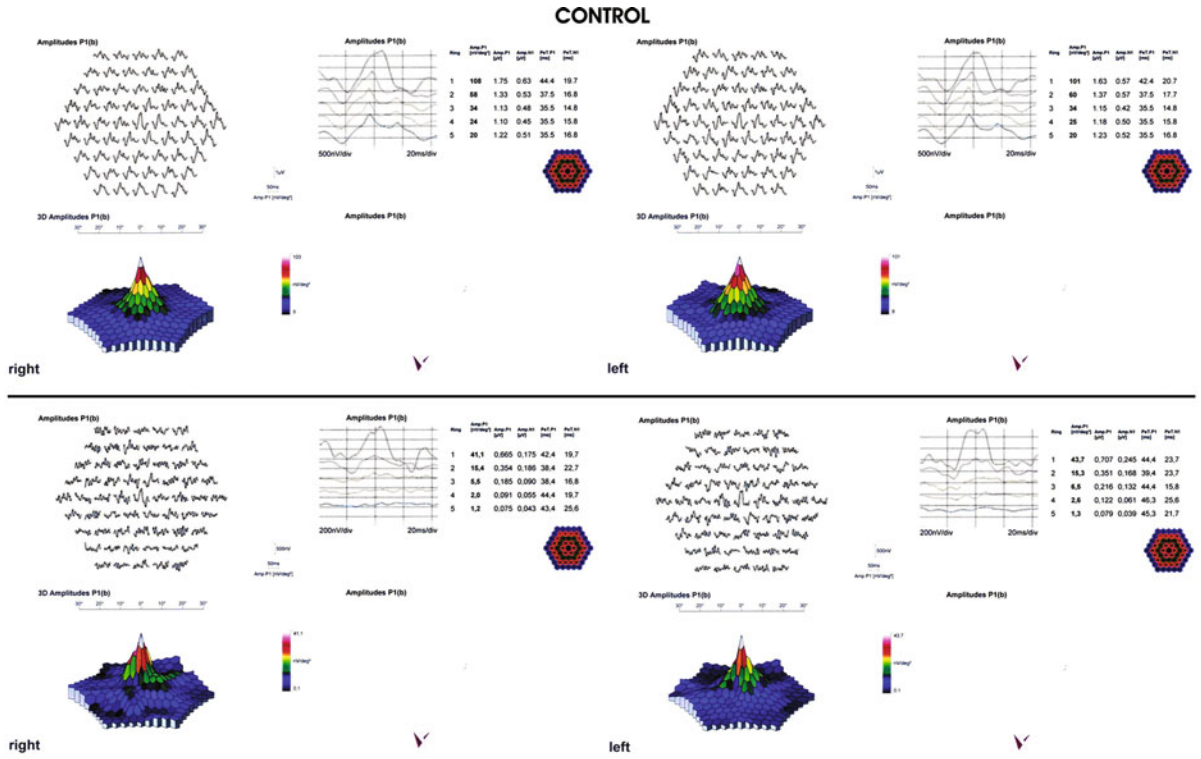

Fig. 6 Multifocal ERG responses of the control subject and the patient with ESCS

the RPE, primarily along the vascular arcades, and macular disturbance, often associated with intraretinal cysts [1, 2, 11]. Patients with ESCS can be recognized by pathognomonic electroretinographic features [1, 2, 11–13].

The nature of the ERG changes allows the diagnosis to be established by standard full-field ERG recording. Electrophysiological description of the ESCS includes reduced to normal or even supernormal amplitudes and grossly delayed implicit times of the dark-adapted mixed rod-cone ERG and photopic cone ERG [14], as well as preserved and sometimes supernormal S-cone-specific response [12]. Characteristic ERG features of ESCS were defined as following: the rod-specific ERG is undetectable, the ERG response to a standard single flash is simplified and delayed, with a similar waveform under photopic and scotopic conditions, the 30-Hz flicker is delayed and of lower amplitude than the single-flash photopic ERG a-wave [11]. The nature of the full-filed ERG findings in our patient was in accordance with these criteria. However, in our patient, the full-field ERG amplitudes were severely reduced, which is in contrast to relatively larger ERG amplitudes reported in the majority of ESCS studies [1, 2, 11–13]. The S-cone-specific ERG was within normal values in this patient, and its amplitude was similar to the one of the full-field light-adapted cone response, confirming predominance of the signal from the S-cone mechanisms as one of the recently defined criteria [11]. This patient also showed possible presence of the OFF-retinal pathway activity. Normally, S-cones make connections only to ON-bipolar cells, whereas in ESCS, it is possible that S-cones may connect to both ON- and OFF-bipolar cells [11, 14]. Thus, the presence of the OFF response in our patient was in accordance with these findings [11, 14].

Lack of transcriptional repressive effect of NR2E3 on cone-specific genes in rod photoreceptors results in the increased number of S-cones seen in ESCS at the expense of rod photoreceptors [15, 16]. Postmortem histopathological analysis of the retina showed no rods and an increased number of S-cones, with S-cones representing 92 % of cones [17]. Previously reported multifocal ERG findings confirm this postmortem analysis, showing well-formed responses to the central hexagons, but considerable reduction or absence of

responses with increasing eccentricity. It is conceivable that in the central macula, the S-cones use predominantly normal S-cone pathways through the retina, whereas in the periphery where the massive numbers of S-cones occupy space normally occupied by rods, the S-cones communicate abnormally through rod pathways and generate an unusually large and slow b-wave response [18]. In our patient, only the central multifocal ERG responses were recognizable, while not the peripheral. Furthermore, our patient also did not show the typical large and delayed waveform of the full-field ERG as was the case in described multifocal ERG study [18], which leads us to consider that peripheral S-cones in this patient probably do not feed into neural pathways of the rods.

To date, 29 mutations in the *NR2E3* gene have been found in patients with ESCS [4, 10, 17, 19–22]. The most frequent mutations are c.119-2A > C (p.V41AfsX23) and c.932G > A (p.R311Q). All disease-causing mutations are located in the evolutionarily conserved DNA-binding domain (DBD; consisting of about 70 amino acids) and ligand-binding domain (LBD; consisting of about 190 amino acids) of NR2E3 protein. Mutation screening of the *NR2E3* showed that our patient is compound heterozygous for the known mutation c.481delA [10] and the novel variant c.1120C > T. The c.481delA variant is located in the ligand-binding domain of NR2E3 and affects a highly conserved residue. However, the pathogenic potential of this variant remains unclear. The variant is predicted to be possibly damaging by PolyPhen, whereas SIFT prediction and Grantham score calculation do not suggest an effect on protein function.

In patients with ESCS, retinal degeneration can vary from minimal to severe, but little is known about the correlation between genotype and the severity of phenotypic outcomes. Vast diversity of retinal abnormalities could be related to different disease mechanisms. These mechanism, as reviewed by Schorderet and Escher, could include: absence of protein because of frameshift mutation or aberrant splicing, absence of DNA-binding in presence of mutations located in the DBD, altered interactions with transcriptional coregulators and/or corepressors, differential activity of modifier genes and impaired post-translational modifications [21]. Wide variation in phenotype can exist even among a relatively genetically homogenous group of patients (patients who are homozygous for the same mutation and share the same ethnic origin can manifest variable fundoscopic and ERG phenotypes) [23]. Furthermore, Pachydaki and colleagues recently described two patients who had different compound heterozygous *NR2E3* mutations (R311Q/Q350R, R311Q/delF71) and similar phenotype [24]. Interestingly, authors describe that the clinical picture of these patients is different from other patients that are homozygous for the R311Q mutation.

We found only one case in the literature with ESCS who was older than 40 years with preserved macular structure and undetectable scotopic and photopic responses on ERG [24]. The patient had only mild retinal pigment epithelium depigmentation in the macula in both eyes, but unlike our patient, this 60-year-old male had BCVA 20/40 on the both eyes at age 39 years, which makes our patient the only one in the literature with good central visual acuity, preserved macular structure and severely depressed full-field ERG. Hayashi et al. described the 33-year-old female Japanese patient with similar clinical findings as in our patient, but she had detectable rod response of the full-field ERG [20]. Our patient had undetectable rod response, as well as notably lower amplitudes of the other full-field ERG responses.

Recent prospective study with detailed assessment of the pattern of retinal degeneration in patients with ESCS showed that the development of macular retinoschisis may be a significant cause of visual morbidity independently of photoreceptor degeneration [25]. By comparing microperimetry, OCT and autofluorescence findings in 9 patients with ESCS, Sohn et al. showed that macular retinoschisis contributes to attenuated retinal sensitivity that persists after resolution of retinoschisis [25]. This is in accordance with findings in our patient who has preserved both macular structure and central retinal sensitivity.

So far, there is no explanation for development of macular schisis, although it has been hypothesized that macular schisis may be caused by degeneration of inner portion of Müller cells [26]. Chen et al. [15] found that a splice variant of NR2E3 may be expressed in Müller cells and the retinal pigment epithelium, which may explain development of macular schisis in some patients.

Due to slowly progressive nature of the disease as well as potential development of choroidal neovascularisation [27], long-term follow-up of patients with ESCS is necessary. During the 5-year follow-up of our patient, clinical and electrophysiological findings remained unchanged.

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