

Electroretinograms and Visual Evoked Potentials Elicited by Spectral Stimuli in a Patient With Enhanced S-Cone Syndrome

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Purpose: To evaluate the properties of the retina of a Japanese patient with enhanced S-cone syndrome by analyzing electroretinograms (ERGs) and visual evoked potentials (VEPs) elicited by different spectral stimuli.

Methods: Ganzfeld spectral flashes in the presence of strong white adapting background illumination were used to elicit cone ERGs and VEPs.

Results: The cone ERG elicited in the patient by short wavelength stimuli was distinctly different from the normal S-cone ERG. The action spectrum of the cone ERG confirmed its relative hypersensitivity to short wavelengths. The action spectrum of the VEP for the patient showed a similar relative hypersensitivity to short wavelengths. The response of the VEPs to short wavelength stimuli was different in waveform from the VEP response to longer wavelength stimuli observed in a normal subject.

Conclusions: These results indicate that the hypersensitivity to short wavelengths is transmitted to the central nervous system and that there is a short wavelength transducing photopigment in many of the photoreceptors, either abnormal S-cones or photopic rods. **Jpn J Ophthalmol 1999;43:433-437** © Japanese Ophthalmological Society

Key Words: Color flash stimuli, electroretinogram, enhanced S-cone syndrome, visual evoked potential.

Introduction

There have been several reports of a unique retinal dystrophy that can be diagnosed mainly by electroretinography (ERG).¹⁻¹⁰ This disease, called the enhanced S-cone syndrome, is characterized by night blindness, cystoid maculopathy, and an unusual pattern of ERG responses.^{5,6} There is no detectable rod ERG, and the cone ERG is reduced to long and middle wavelength stimuli but enhanced to short wavelength stimuli. Early investigators presumed that this atypical enhanced response to short wavelength stimuli was due to rods that act abnormally under photopic conditions.¹⁻⁴ However, subsequent electrophysiological and psychophysical studies have revealed an S-cone-like hypersensitivity in these pa-

tients.⁵⁻¹⁰ In this paper we describe a Japanese patient with the enhanced S-cone syndrome whose cone ERGs and visual evoked potentials (VEPs) were tested with different spectral flash stimuli and compared with test results in a normal subject.

Patient and Methods

Case Report

A 52-year-old Japanese woman complained of night blindness and visual disturbance of long duration. Her past medical history was unremarkable. Three brothers and two sisters had been diagnosed as having retinitis pigmentosa by other ophthalmologists. Unfortunately, none of their medical records could be obtained because they were very old and/or lived in remote areas. The parents of the patient were not consanguineous.

The patient's visual acuity was 20/40 OU. Slit-lamp examination revealed normal findings in both eyes. Fundusoscopic examination showed a symmetri-

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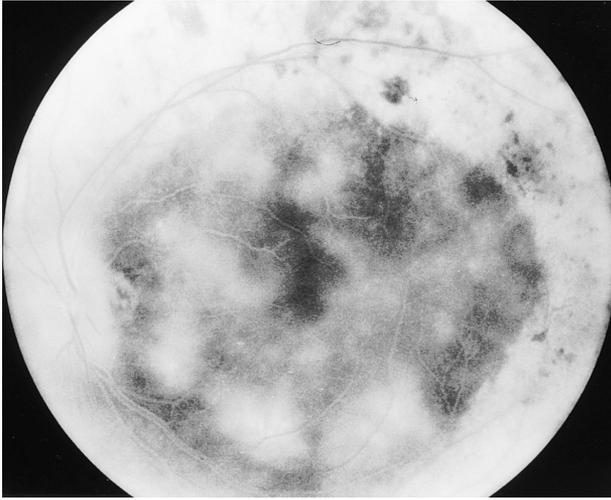


Figure 1. Late-phase fluorescein angiogram of left eye in patient with enhanced S-cone syndrome (left) showing multiple dye leakage in posterior pole.

cal ring of retinal degenerative changes bilaterally in the vascular arcade region. The central macula lacked the foveal reflex bilaterally. Fluorescein angiography demonstrated multiple leakage of dye in the posterior pole of the retina bilaterally (Figure 1). The visual fields tested by Goldmann perimetry showed ring scotomas bilaterally. Color vision was normal as determined by the Farnsworth Panel D-15 test. Rod dark adaptation, tested by Goldmann-Weekers adaptometer, was absent and the cone adaptation showed elevated final threshold.

Electrophysiology

The techniques for recording the ERG and VEP have been described previously.¹¹⁻¹⁴ The pupils were

fully dilated with tropicamide eye drops, and the ERG was recorded simultaneously bilaterally with bipolar Burian-Allen contact lens electrodes. The VEP was recorded with a silver cup electrode placed at Oz, with a reference electrode on the earlobe. A Ganzfeld stimulator provided flash stimuli and white background illumination. The maximum white flash intensity was $5.0 \text{ cd}\cdot\text{s}/\text{m}^2$. A bright flash ERG elicited by the maximum white stimuli and averaged 10 times at 0.1 Hz was recorded after 30 minutes of dark adaptation. Cone ERGs were recorded to the maximum white stimulus presented at 5 Hz under white background illumination ($50 \text{ cd}/\text{m}^2$). Rod ERG responses to dim blue flashes presented at 1 Hz were recorded after 30 minutes of dark adaptation. Spectral stimuli were isolated by Kodak Wratten color filters #98 (450 nm), #48 (471 nm), #61 (534 nm), #21 (593 nm), and #29 (633 nm) (Eastman Kodak, Rochester, NY, USA), on the same white background illumination as used for the cone ERGs and VEPs. The stimulus frequency was 5 Hz, and 500 responses were averaged using a Neuropack 2 averager (Nihon Kohden, Tokyo).

Results

The bright flash ERG was markedly reduced and the implicit times of the a- and b-waves were delayed (Figure 2, top). The waveform of the cone ERG was somewhat similar to that of the single flash ERGs, and both a- and b-waves were reduced in amplitude with prolonged implicit times (Figure 2, middle). The rod ERG was almost nonrecordable (Figure 2, bottom).

Figure 3A illustrates the cone ERGs elicited by different spectral stimuli. In the normal subject, the

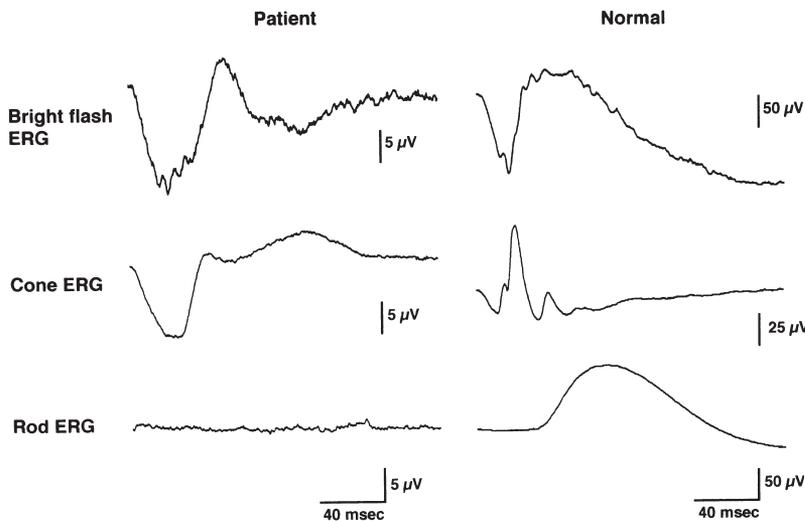
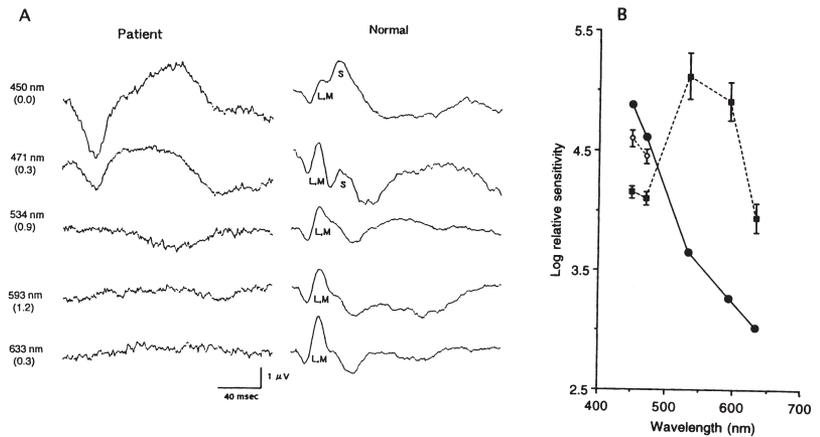


Figure 2. Bright flash ERG in same patient after 30 minutes of dark adaptation (top left), cone ERG to white flashes in presence of white adapting light (middle left), and rod ERG to dim blue flashes after 30 minutes of dark adaptation (bottom left). Comparable ERGs from normal subject are shown in right column.

Figure 3. Cone ERGs to spectral stimuli (A) from same patient (left traces) and normal subject (right traces) in the presence of white adapting light. Numbers on left signify wavelengths of stimuli. Numbers in parenthesis indicate neutral density filter used to adjust energies to produce approximately equal early (L- and M-cone) b-waves in normal subjects. Action spectrum of the cone ERG b-wave (B) based on constant amplitude criteria from patient (closed circles), and that of normal S-cone ERG (open circles) and normal L- and M-cone ERG (closed squares). Vertical lines show standard deviation of means in normal patients.



S-cone ERG elicited by short wavelength stimuli (450 nm and 471 nm) consisted of a separate b-wave riding on an earlier b-wave of the mixed L- and M-cone ERG. The mean S-cone b-wave amplitude was $1.6 \pm 0.6 \mu\text{V}$ (mean \pm SD) in our laboratory. Stimulation by middle and long wavelengths elicited only the L- and M-cone b-waves. In our patient there were large and broad ERGs to 450 and 471 nm stimuli, and reduced responses with normal implicit times to longer wavelength stimuli at the strongest stimulus intensity. We determined the action spectrum of the cone ERG b-wave to spectral stimuli based on equal amplitude criteria. Our patient's cone ERGs showed higher sensitivity to short wavelength and lower sensitivity to middle and longer wavelength when compared with test results in a normal subject (Figure 3B).

Figure 4A illustrates the flash VEPs elicited by the same spectral stimuli, adjusted to be approximately equivalent for eliciting L- and M-cone ERGs. In a normal subject, middle and longer wavelength stimuli produced responses with implicit times of about

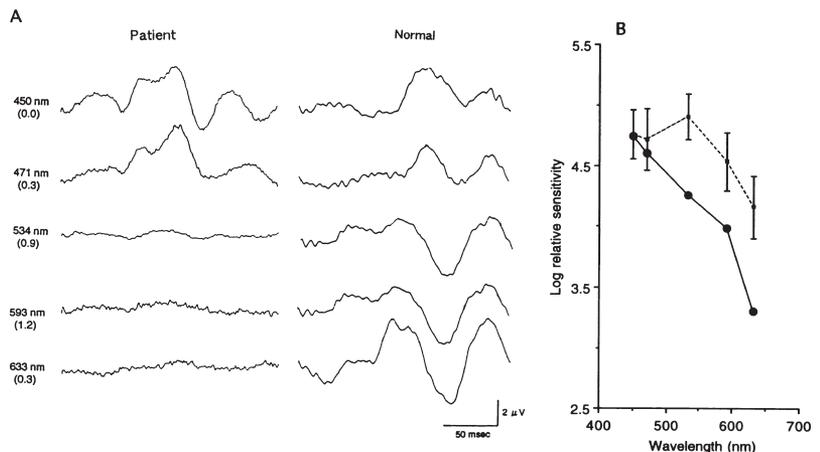
100 ms that resemble the P100 waves. The VEP responses to short wavelength stimuli had longer implicit times than the responses to longer wavelength stimuli. Our patient's VEP responses were elicited only by the 450 nm and 471 nm stimuli and not by middle and long wavelength stimuli.

Figure 5 shows the patient's VEPs to blue and yellow flashes at three different intensities. Stronger yellow stimuli produced VEP responses with implicit times of 96–100 ms. Regardless of the intensity, however, the VEPs produced by blue flashes had two distinct peaks, and were apparently different from those produced by yellow stimuli. An action spectrum of the VEP response based on constant amplitude criteria showed normal sensitivity to short wavelength stimuli and greatly reduced sensitivity to middle and long wavelength stimuli in our patient (Figure 4B).

Discussion

Our patient demonstrated a symmetrical ring of retinal degenerative changes in the vascular arcade

Figure 4. Flash VEPs to spectral stimuli (A) from our patient (left traces) and normal subject (right traces) in presence of white adapting light. Stimulus energies were approximately matched to produce equivalent L- and M-cone ERG b-waves in normal subject. Action spectrum of flash VEP (B) based on constant amplitude criteria from patient (closed circles) and normal subjects (closed squares). Standard deviation of mean in normal subject is shown by vertical lines.



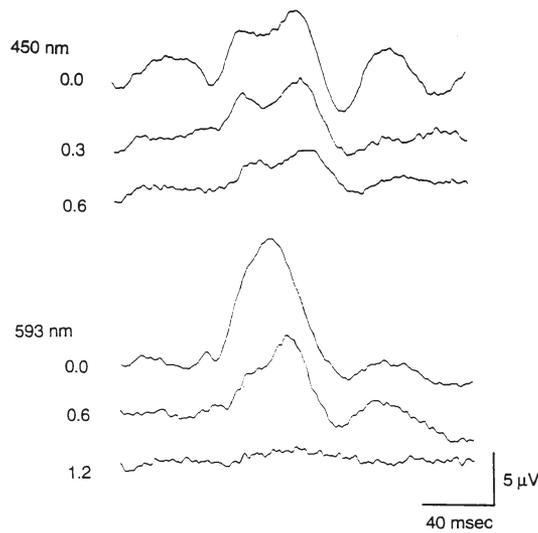


Figure 5. Flash VEPs to blue stimuli (upper three traces) and to yellow stimuli (lower three traces) at three different stimulus intensities in our patient. Numbers on left indicate neutral density filter.

region and multiple fluorescein leakage in the posterior pole of the eye bilaterally. The cone ERGs elicited by short wavelength stimuli were atypical large and broad waveforms, and the rod ERG responses to dim blue flashes were almost nonrecordable. These clinical features are similar to those reported previously in the enhanced S-cone syndrome⁵⁻¹⁰ or the photopic rod syndrome,¹⁻⁴ except for the fluorescein angiographic findings. Previous reports demonstrated cystic changes in the macula without dye leakage. The findings in our patient suggest that there may be some phenotypic variation in this syndrome.

ERG testing in this patient demonstrated reduced and broad waveforms in the single bright flash ERG and cone ERG. The rod ERG to dim blue stimuli was almost nondetectable. The cone ERGs to short wavelength stimuli in our patient showed a striking difference from those in normal subjects. Usually the S-cone a-wave is not detectable because it is overlapped by the L- and M-cone b-wave, and the implicit time of the S-cone b-wave is around 50 ms. In our patient, there was a broad and deep a-wave followed by a slow and large b-wave. To middle and long wavelength stimuli, very small b-waves with normal implicit times were generated at our strongest stimulus intensity. The action spectrum of the cone ERG confirmed hypersensitivity to short wavelength stimuli in our patient. The enhanced short wavelength sensitivity in the ERG could be artifactually produced by the subtraction of the opposing

cone and rod systems. This might be why the early investigators considered this ERG hypersensitivity a rod abnormality.

Several molecular mechanisms have been proposed for this disease.^{8,10} Román and Jacobson⁸ examined the ERGs elicited by long duration stimuli in their patients and observed a positive response to light-offset by short wavelength stimuli. A positive wave at light-offset was not detected in a normal subject. Their study demonstrated that the ERG of patients with this syndrome was S-cone driven, but its properties were distinctly different from those of normal S-cone ERGs. Furthermore, the unusual off-response of the S-cone ERG suggested that there might be molecular abnormalities that shifted the absorption spectra of the L- and M-cone to shorter wavelength, because corneal positive waves to stimulus offset are usually associated with the L- and M-cone mechanism.

The VEP responses, which have never been studied in this syndrome, receive inputs from within 10° of the central retina and, therefore, reflect mainly cone function. The results of our study indicate the relative hypersensitivity to short wavelengths, adding further objective evidence to the fact that the retinal output cells are themselves relatively hypersensitive to short wavelength stimuli. An action spectrum of our patient's VEP showed normal sensitivity in the short wavelength range and very reduced sensitivity in longer wavelength. Another interesting finding in our patient's VEP was that the responses produced by blue flashes were different from those elicited by longer wavelength flashes. At intensities producing almost equal amplitude responses, blue stimuli elicited two positive peaks, whereas middle and long wavelength stimuli elicited a single peak around 100 ms. It has been reported that stimulation of the S-cone mechanism generates a unique VEP that is larger and later than those of the other two cone mechanisms in normal subjects.¹⁴⁻¹⁶ The difference between VEPs to blue and those to longer wavelength stimuli observed in our patient suggested that the postreceptoral mechanism might be normal, and that cone systems might have input to the brain through normal pathways.

In conclusion, the VEP results demonstrated the relative hypersensitivity to short wavelengths and a different waveform to blue flashes as compared with those to longer wavelength stimuli. These results indicate that the hypersensitivity to short wavelengths is transmitted to the central nervous system and that there is a short wave transducing photopigment in many of the photoreceptors, either abnormal S-cones

and/or photopic rods. Furthermore, the fluorescein angiographic findings indicate that there may be some phenotypic variation in the enhanced S-cone syndrome.

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