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ENHANCED S CONE SENSITIVITY SYNDROME: LONG-TERM FOLLOW-UP, ELECTROPHYSIOLOGICAL AND PSYCHOPHYSICAL FINDINGS

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Summary—1. Six patients with enhanced S (short wavelength sensitive, blue) cone sensitivity syndrome including a follow-up between 1 and 19 y are described. Four patients were male, two were female; two patients were brothers. The enhanced S cone sensitivity syndrome is of autosomal recessive inheritance with variable expression even within a family.

2. Recording the standard electroretinogram (ERG) showed similar responses at dark and light adapted conditions and reduced flicker responses. ERG recordings were unchanged up to 9 y follow-up. The reduction of ERG amplitudes induced by light adaptation is shifted to higher background intensities compared to normals.

3. ERGs elicited by chromatic stimuli revealed only blue cone responses for all stimulus conditions. There was no evidence for L (long wavelength sensitive, red) or M (middle wavelength sensitive, green) cone or rod activity in the ERG.

4. Colour vision was normal. Spectral sensitivity measurements showed no evidence for rod activity but the presence of all cone photopigments. A normal course of transient tritanopia indicated an interaction between L and S cones.

5. The differences between psychophysical and electroretinographical findings indicate the existence of functioning receptors and neuronal pathways in all three cone systems in the presence of altered intraretinal electrical phenomenas

Key words—Electroretinography; spectral sensitivity; transient tritanopia; cone; retinal degeneration; enhanced S cone syndrome.

The enhanced S cone sensitivity syndrome was described by Marmor *et al.* (1990) as a new retinal degeneration. It is characterized by night blindness, small yellowish retinal flecks along the vascular arcades and electroretinographic responses that are similar at dark and light adaptation (Jacobson *et al.*, 1990; Kellner and Foerster, 1991; Marmor *et al.*, 1990). Visual loss, maculopathy and peripheral retinoschisis may occur. The natural course of the disease, the origin of the unusual ERG responses and of the normal or enhanced sensitivity to blue stimuli compared to the marked sensitivity reduction to red stimuli are still unknown.

We have observed six patients with this disorder in Germany. Three patients were included in the initial report (Marmor *et al.*, 1990). The purpose of this study is to present data on long-term follow-up and results of further electrophysiological and psychophysical evaluation.

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ELECTROPHYSIOLOGIC METHODS

Electrooculograms (EOG) were recorded according to the method of Rhode *et al.* (1977). The ERG recording protocol includes all recordings according to the standard for clinical electroretinography (Marmor *et al.*, 1989) and has been described in detail (Kellner *et al.*, 1990). Stimulus duration was 10 ms. Six stimuli (1–6) with an intensity range of 6 log units were used for recordings in the dark. The maximum light intensity was 7.8 cd·s/m^2. Light-adapted recordings were performed in the presence of white light adaptation of 4.5 cd/m^2 and with the light stimuli 4–6. Brighter background illuminations with an intensity of 78 and 780 cd/m^2 were used to test adaptation properties in the ERG.

Duration of light adaptation before recording was 10 min, at brighter backgrounds it was 2 min.

The technique of ERG recordings with chromatic stimuli has been described previously (colour ERG; Kellner and Foerster, 1992). The Kodak Wratten filters used were No. 98 for blue stimuli with a maximum transmission at 450 nm and No. 29 for red stimuli (629 nm). A white background was used for light adaptation. Recordings were done following the same protocol as with white stimuli. No averaging was done either in the standard or colour ERG except for the oscillatory potentials (64 sweeps).

S cone responses were recorded with another setup. A Schott filter (BG 28) was used for blue stimuli. A yellow background was obtained by Schott filter OG 515. The stimuli had a duration of 10 and 250 ms. 64 responses were averaged.

PSYCHOPHYSICAL METHODS

Colour discrimination

Colour vision was tested with Ishihara's pseudoisochromatic plates, Panel D 15 test desaturé, Farnsworth–Munsell 100 Hue test and Nagel anomaloscope. Additionally in patient 3 colour discrimination was determined for all wavelengths between 440 and 640 nm in 10 nm steps with a technique described by Reitner *et al.* (1991).

Visual field

Visual fields were tested using Goldmann perimeter and the Tübingen Automatic perimeter. Colour visual fields were examined with the standard colour filters of the Tübingen Automatic perimeter. This setup includes five different colour stimuli which are blue (combination of Schott filters GG4, BG 12 and BG 39), green (Cinemoid No. 24), yellow (Kodak Wratten No. 9), red I (Kodak Wratten No. 31) and red II (Cinemoid foil No. 6).

Dark adaptation

Dark adaptation was tested with the Goldmann Weekers adaptometer. After a 10 min bleach of 1.400 cd/m^2 in a Ganzfeld sensitivity thresholds were determined during a period of 45 min. The target size was 11 deg in diameter in the upper field 10 deg from the fovea.

Spectral sensitivity

Spectral sensitivity functions were determined for 30 monochromatic test lights (13 deg in diameter, foveal fixation) in presence of a white background (10,000 td, 30 deg in diameter) and after 30 min of dark adaptation. A dark red (686 nm) field with a hair cross served as central fixation mark. The quantal energy necessary for a threshold sensation evoked by different monochromatic test lights was then plotted against wavelength.

Transient tritanopia

The quantal energy, necessary to evoke a threshold sensation for a blue (440 nm) test light of 13 deg in diameter, is determined at various times before (values < 0) and after (values > 0) switching off a yellow adaptation light (575 nm) of 30 deg in diameter (Mollen and Polden, 1977; Zrenner and Gouras, 1981). In normals the threshold to detect the blue test light paradoxically raises immediately after the offset (delay = 0) of the yellow adaptation light for approx. 1 log unit and reaches the lower threshold that was obtained during yellow adaptation only 1 or 2 s thereafter.

CLINICAL FINDINGS

The clinical findings of all patients are summarized in Table 1. Patients 1–3 have been

Table 1. Patient data

P	Age (y)	F-up (y)	Sex	Visual acuity		Fundus
				First exam	Last exam	
1	12	7	m	20/33, 20/25	20/30, 20/200	Flecks, maculopathy
2	16	19	m	20/200, 20/25	20/400, 20/100	Flecks, cystoid maculopathy
3	23	7	m	20/200, 20/20	20/400, 20/200	Flecks, cystoid maculopathy, scars
4	8	3	f	20/30, 20/30	20/30, 20/33	Flecks, peripheral retinoschisis
5	35	6	m	20/25, 20/25	20/25, 20/30	Flecks
6	32	1	f	20/40, 20/25	20/40, 20/25	Flecks

P, patient; F-up, follow-up; y, years; exam, examination; m, male; f, female.

included in the initial report (Marmor *et al.*, 1990). The age at first examination varied between 8 and 35 y and the follow-up time between 1 and 19 y. Four patients were male and two female. All patients had difficulties with night vision. Except for patient 5, all patients complained about reduced visual acuity. In eyes with stable visual acuity during the follow-up period none of the patients subjectively felt worsening of the visual function. At the time of the first examination visual acuity was only moderately reduced in four patients and severely reduced in one eye of both remaining patients. Visual acuity remained unchanged in eyes without maculopathy, and progression of maculopathy was the only noticeable cause for visual loss in our patients. All eyes that developed maculopathy suffered from visual loss to about 20/200. Ophthalmoscopically the maculopathy appeared as a dull fovea in patient 1 and was cystoid in patient 2 and 3. Patient 3 developed central and paracentral scars. The young female patient had peripheral bullous retinoschisis in the temporal quadrants of both eyes. In all patients yellowish flecks along the vascular arcades were found. Besides the development of maculopathy the fundus findings were unchanged during follow-up.

It should be noted, that an addition of blue filter glasses (Schott BG 23) to the refractive lenses improved the visual acuity in patient 2 and 3 from 20/100 to 20/60 and 20/200 to 20/60.

Examination of the family of patient 2 revealed an affected brother (patient 5). He had not noticed any visual problems before our examination. Five of seven children could be examined. They were a daughter and a son of patient 2 and a daughter and two sons of patient 5. All children had normal visual acuity, colour vision and fundus appearance and had no problems with night vision. Electrophysiological examinations were not done due to young age. The parents of patient 4 had normal visual acuity, colour vision and fundus appearance and the mother had normal standard and colour ERGs. The family history was unremarkable in respect to visual loss, night vision deficits or consanguinity in all patients.

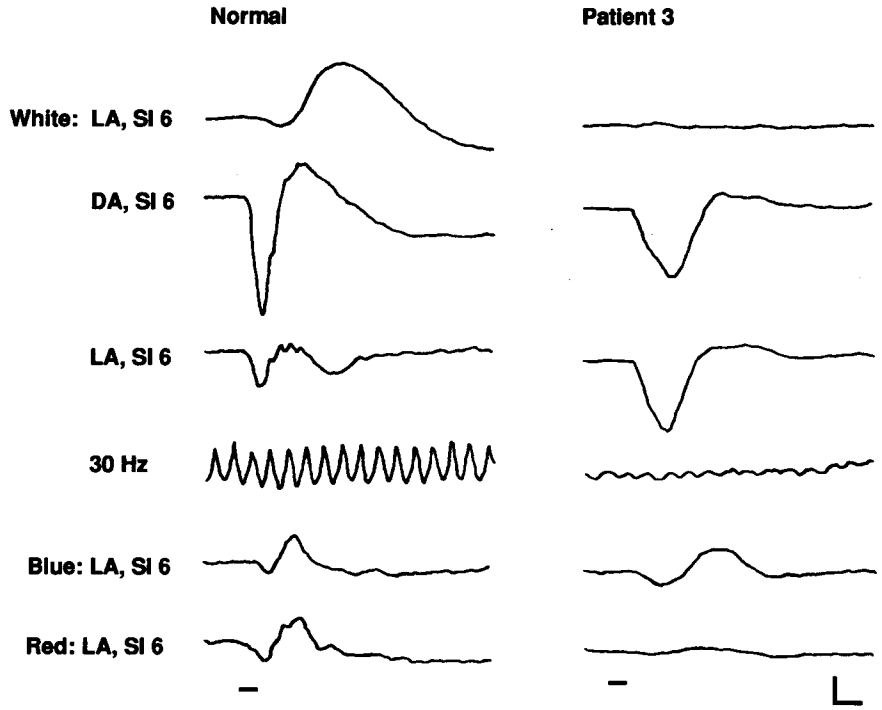

Fig. 1. ERG in response to white and colour stimuli of a normal person and patient 3. DA indicates the responses at dark adaptation, LA at light adaptation and SI the stimulus intensity. Vertical calibration marks indicate 100 μV for all recordings. Horizontal calibration is 20 ms for single flash recordings and 50 ms for flicker responses. The line below the responses indicates stimulus duration for single flashes. In patient 3 responses at dark and light adaptation are similar, the 30 Hz flicker response is reduced, and responses to blue stimuli are larger than to red. *b*-Wave implicit times are markedly prolonged at all stimulus conditions in the patient.

ELECTROPHYSIOLOGICAL FINDINGS

Electrooculogram

The light rise in the EOG was reduced in all eyes with a mean of $116 \pm 19\%$ (normal range: $186 \pm 35\%$). The EOG remained unchanged during follow-up.

Standard ERG

The standard ERG findings have been described in detail (Marmor *et al.*, 1990; Kellner and Foerster, 1991). Characteristic features were the similarity of responses in the dark and light adapted state, the prolonged *b*-wave implicit times unchanged with increasing stimulus intensity and the reduced 30 Hz flicker amplitudes (Fig. 1). The *b*-wave threshold was elevated and the amplitude–intensity function steeper than normal. During follow-up, the variation of amplitudes was $<20\%$ with no tendency to lower values over time. Therefore the standard ERG findings were considered unchanged in amplitudes and implicit times of *a*- and *b*-waves in patients 1, 2, 3 and 4 for 7, 9, 7 and 3 y respectively.

ERGs in presence of brighter than usual background illuminations were recorded in a normal person and patient 3 (Fig. 2). In normals, the *a*- and *b*-wave amplitudes in presence of our usual background illumination (4.5 cd/m^2) are about 30% of the value at dark adaptation. In patient 3 there was only a small difference of about 10% as in the other patients. At brighter backgrounds the amplitudes of normals showed an additional reduction. In patient 3 brighter backgrounds led to a marked amplitude reduction reaching the values of normals at 780 cd/m^2 intensity.

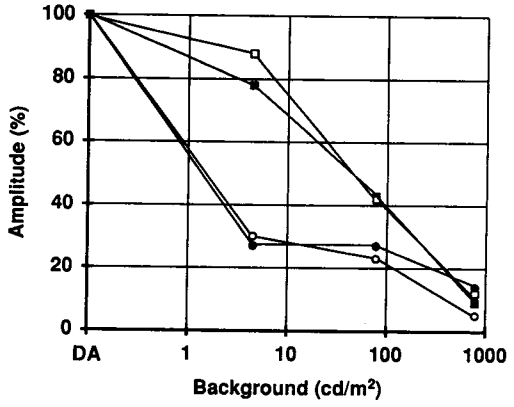

Fig. 2. ERG to white stimuli with maximum intensity. A decrease of the *a*- (open symbols) and *b*-wave (solid symbols) amplitudes (in % of the value at dark adaptation) with increasing background intensity is observed in a normal person (circles) and patient 3 (squares). The decrease is shifted to brighter backgrounds and is less steep in the patient compared to normals.

Table 2. 30 Hz flicker amplitude (μV)

	Blue stimuli	Red stimuli
Normal (mean + SD)	80 ± 14	117 ± 6
Patient 1	30	0
Patient 2	80	40
Patient 3	30	0
Patient 4	Not recordable	Not recordable
Patient 5	30	0
Patient 6	40	0

Colour ERG

Colour ERG recordings in some of our patients have been described previously (Kellner and Foerster, 1991, 1992). The responses were similar at dark and light adaptation. The *b*-wave implicit time was prolonged at all stimulus intensities and for all different colour stimuli. The main diagnostic feature in the colour ERG is that at light adaptation and flicker stimulation responses to blue stimuli are always larger than to red stimuli contrary to the normal findings (Fig. 1). A 30 Hz flicker response was present to blue stimuli in all patients, but only in one patient a small response to red was found (Table 2). The oscillatory potentials were not measureable to red but a small amplitude was found for blue stimuli.

A comparison of the colour ERG responses of all patients showed no correlation between ERG amplitudes and morphological findings or visual acuity. For example in the brothers, ERG responses were considerably smaller in patient 5 compared to patient 2, although patient 2 suffered from severe maculopathy.

S cone ERG

Normal persons show two *b*-wave peaks with a short stimulus (10 ms). The first peak with a short implicit time originates from M and L cones and the second peak with a long implicit time most probably from S cones [Fig. 3(a); Gouras and MacKay, 1990]. The second peak is missing when red stimuli are used. In patient 2 and 3 ERGs could be recorded with this stimulus condition. Their responses showed only a single *b*-wave peak with a large amplitude and a long implicit time similar to the implicit time of the second peak in normals.

The 250 ms long stimulus in normals elicited an off response, as well as a contribution of M and L cones [Fig. 3(b)]. The patients showed

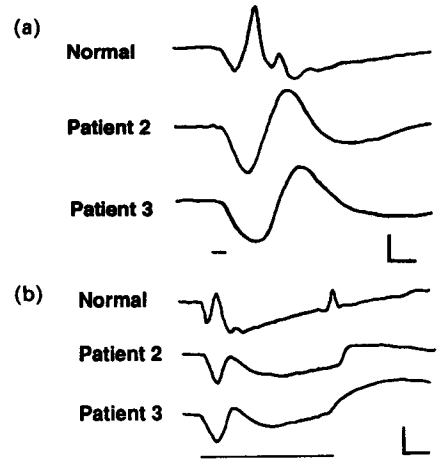

Fig. 3. ERG to blue stimuli in presence of yellow background. Vertical calibration marks indicate 50 μV, horizontal marks 20 ms. (a) Stimulus duration 10 ms: normals show two *b*-wave peaks, in patients there is only one *b*-wave peak with a long implicit time. (b) Stimulus duration 250 ms: in normals an off-response is seen, which returns to baseline. In both patients after stimulus offset a positive deflection without return to baseline is found.

a small positive response at offset and the potential remained more positive than before, whereas it returned to baseline in normals.

PSYCHOPHYSICAL FINDINGS

Colour vision

Colour vision, tested with different tests at several occasions, was normal in all patients. Patient 4 made only one error in the Farnsworth–Munsell 100 Hue test. Color discrimination tested in patient 3 showed a sensitivity shift to short wavelengths with a mild decrease in sensitivity above 510 nm. The discrimination ability was normal, it was below 2 nm between 440 and 590 nm and below 4.5 nm above 600 nm (Fig. 4).

Visual fields

Visual fields to white stimuli revealed relative central scotomas in patients with maculopathy. Patient 4 had scotomas corresponding to her peripheral retinoschisis. The visual fields remained unchanged during follow-up. Colour visual fields were tested in three patients for blue and red stimuli and in patient 3 for all colour stimuli (Table 3). The threshold sensitivity for the blue stimulus was within the normal range ($x \pm 3$ SD) in all patients. For all other colour stimuli the sensitivity was markedly decreased and most severely for red stimuli.

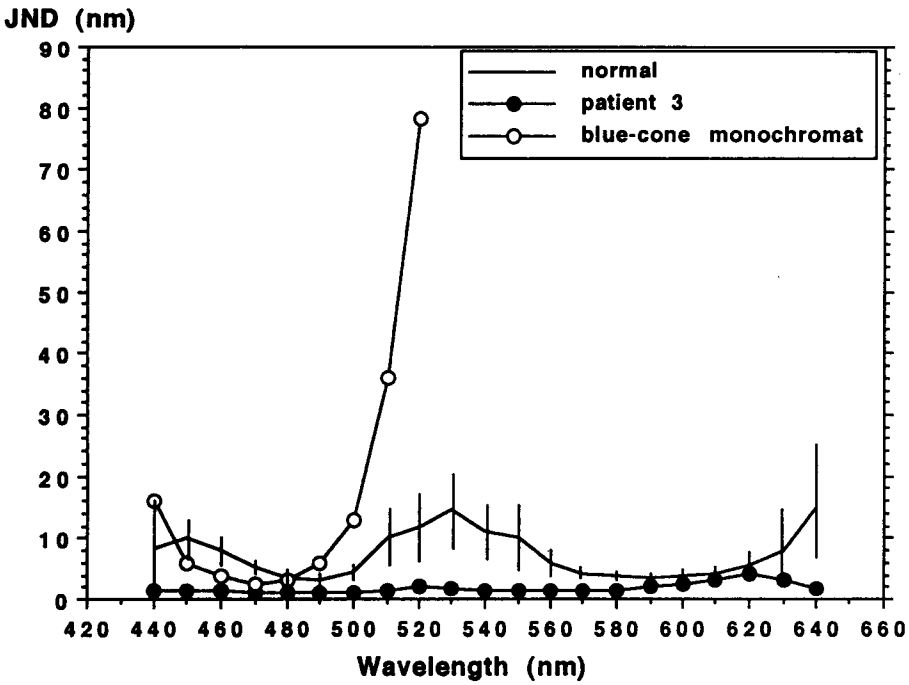

Fig. 4. Colour discrimination: the difference of wavelengths (JND—just noticeable difference) necessary to discriminate two monochromatic stimuli is plotted against wavelength of the reference stimulus. Vertical bars indicate ± 1 SD from the mean normal value. For comparison an average wavelength discrimination curve of blue cone monochromats is shown (Reitner *et al.*, 1991). The patients curve was within the normal range at all wavelengths.

Table 3. Threshold sensitivity (cd/m²)

	Normal		Patients		
	Mean	Mean + 3 SD	2	3	5
Blue	66	210	159	199	63
Green	1.6	5.8		50	
Yellow	0.5	2.6		40	
Red I	5.0	17		631	126
Red II	1.9	7.3	79	200	79

SD, standard deviation.

Dark adaptation

Dark adaptation curves were measured with a Goldmann–Weekers adaptometer. The dark adaptation was monophasic in four patients (1, 3, 4, 6) showing a cone limb but no evidence for rod activity. The dark adaptation was unchanged over 7 y in patient 3.

Spectral sensitivity

Extensive psychophysical testing was done in patient 3. The spectral sensitivity function after 30 min of dark adaptation is shown in Fig. 5. In normals a maximum sensitivity is reached at 500 nm. The overall sensitivity was decreased in our patient according to his thresholds in the dark adaptation function. A maximum sensitivity was reached near 530 nm. There was a second sensitivity peak near 440 nm as well as an indication of an L cone contribution at very long wavelengths.

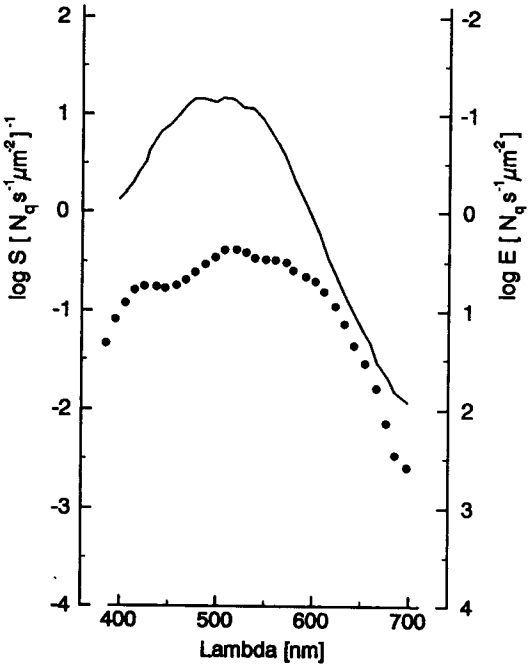

Fig. 5. Spectral sensitivity function after 30 min of dark adaptation. The quantal energy (E, right hand ordinate), necessary for a threshold sensation evoked by monochromatic testlights of 13 deg in diameter is plotted against wavelength. A normal person (line) shows a maximum at 500 nm. In patient 3 (dots) the spectral sensitivity is reduced. The maximum sensitivity is reached near 530 nm. There is a second sensitivity peak near 440 nm as well as an indication of a L cone contribution at very long wavelengths.

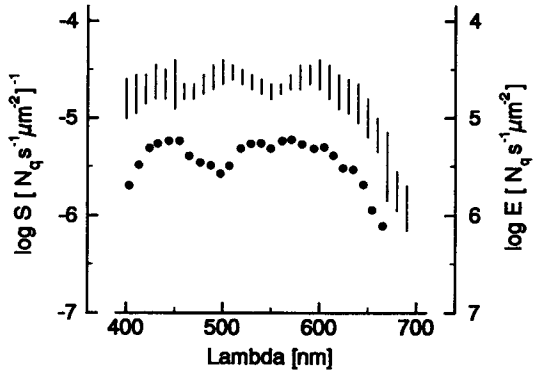

Fig. 6. Spectral sensitivity function during light adaptation in normal observers shows a three peaked function (vertical lines represent ±1 SD). The spectral sensitivity of patient 3 (dots) is decreased in general by approx. 1 log unit. He shows a clear maximum of the S cones near 450 nm but the two peaks of the M cones and L cones are merged.

The spectral sensitivity function during light adaptation in normal observers shows a three peaked function (Fig. 6). The spectral sensitivity of patient 3 was decreased in general by approx. 1 log unit. He showed a clear maximum of the S cones near 450 nm but the two peaks of the M cones and L cones were merged.

The spectral sensitivity measured in presence of a yellow background (Fig. 7) showed a peak at 440 nm and was similar to the normal curve.

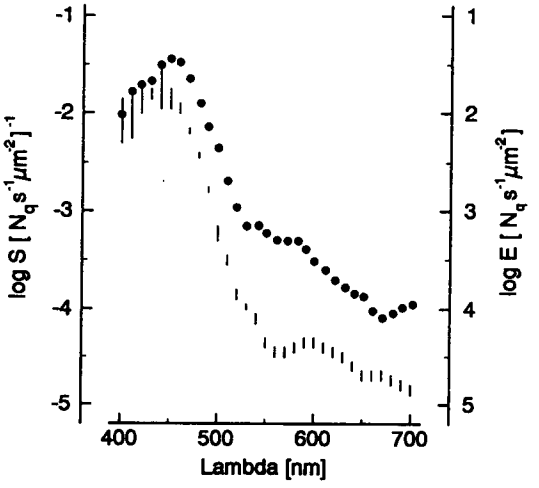

Fig. 7. Spectral sensitivity during yellow background adaptation. The spectral sensitivity in patient 3 (dots) shows a peak at 440 nm and a shape like normals (vertical lines represent ±1 SD).

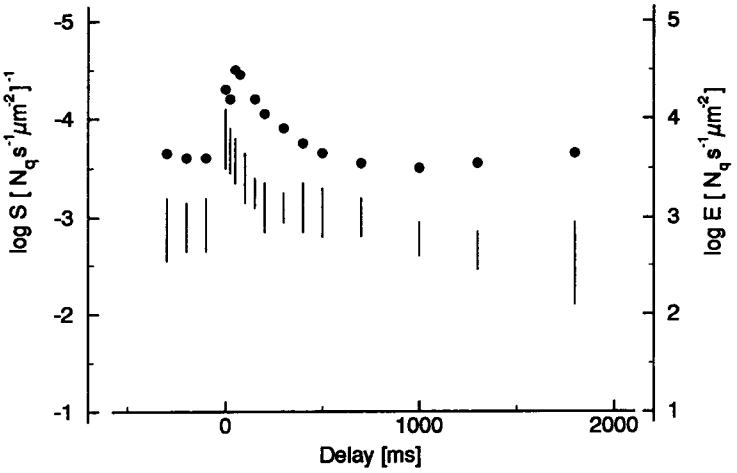

Fig. 8. Transient tritanopia: the threshold for a blue test light is decreasing transiently after the offset of a yellow adaptation light at $t = 0$. In patient 3 (dots) the thresholds are generally increased by approx. 1 log unit as compared with normals (vertical lines ± 1 SD), however, the transient threshold increase is maintained.

Transient tritanopia

In normals (Fig. 8, vertical lines) the threshold for detection of the blue test lights raises immediately after the offset of the yellow adaptation light for approx. 1 log unit. The threshold of patient 3 was elevated generally by approx. 1 log unit. The transient threshold increase after the offset of the yellow light (transient tritanopia) had a normal course. This indicates, that despite decreased sensitivity an interaction between S and L cones exists.

DISCUSSION

The natural course of enhanced S cone sensitivity syndrome shows an early onset, most likely since birth. Night blindness is present as long as patients can remember. In our patients, the only functional loss noted was the development of maculopathy. On eyes without maculopathy visual acuity remained unchanged in this and previous studies (Marmor *et al.*, 1990; Kellner and Foerster, 1991; Perlman *et al.*, 1993). Visual fields, colour vision and electrophysiological findings remained unchanged as well.

The enhanced S cone sensitivity syndrome is an inherited disorder. Two affected brothers with normal male and female children as well as our female patients are consistent with an autosomal recessive inheritance. This is supported by other authors (Jiminez *et al.*, 1990; Jacobson *et al.*, 1991; Perlman *et al.*, 1993). The expression of the disease is rather variable even between two brothers. The primary genetic defect remains unclear. The pigment gene of S cones was examined in one of Jacobsons and one of our patients and was normal in both (J. Nathans, personal communication). Recently, Jacobson *et al.* (1991) suggested a relationship between enhanced S cone sensitivity syndrome and Goldmann–Favre syndrome. ERGs with similar responses at dark and light adaptation have been described previously in Goldmann–Favre syndrome (Fishman *et al.*, 1976; Noble *et al.*, 1978). There was no history of Goldmann–Favre syndrome in the families of our patients.

The standard ERG showed a decreased sensitivity at low stimulus intensities and almost identical responses at dark and light adaptation. The *b*-wave implicit times were prolonged and remained unchanged to different stimulus intensities. In ERGs with chromatic stimuli or backgrounds only responses that best can be attributed to S cones were detectable in our patients. However, the amplitude of these responses is almost 10 times as large as can be expected from a population of S cones in the human retina.

The responses in our patients resemble S cone responses reported by Norren and Padmos (1973) and Sawusch *et al.* (1987). The *b*-wave implicit times of 54–70 ms in our patients are comparable to 60–80 ms measured by Sawusch *et al.* (1987). In his recordings the *b*-wave implicit time did not change with increasing light intensity as was seen in our patients. He found only small or no *a*-wave using the silent substitution technique. However, this difference

may be due to variations of stimulus and background intensities, because Norren and Padmos (1973) found *a*-waves in S cone responses from humans at high background intensities. In the monkey the presence of an *a*-wave was also dependent on stimulus intensity as it was in the cat (Norren and Padmos, 1973; Zrenner and Gouras, 1979).

The similarity of the responses in our patients to S cone responses recorded in normals and the high sensitivity to blue compared to other chromatic stimuli indicates that the ERG is dominated by responses originating from the S cones. The 30 Hz flicker response to blue stimuli is not a contradiction to the S cone origin of all responses, because flicker responses up to 45 Hz were found in blue cone monochromacy (Hess *et al.*, 1989). Roman and Jacobson (1991) presumed a contribution of M and L cones to the flicker responses because the maximum frequency at which responses were recordable to blue stimuli was higher in patients than in normals. Only one of our patients had a small flicker response to green and red and therefore a M or L cone contribution is unlikely in our patients. These flicker responses also exclude a rod origin of the unusual ERG responses, that has been suggested until recently (Marmor, 1989; Fishman and Peachey, 1989; Perlman *et al.*, 1993). The origin of the slow response at offset is unclear. Similar responses were described by Roman and Jacobson (1991). They found no positive off response to blue stimuli in normals, which is in accordance with findings of Evers and Gouras (1986) in the monkey and Zrenner and Gouras (1979) in the cat. Roman and Jacobson (1991) used a yellow background 2 log units brighter than in our setup, which explains the M and L cone contribution in our normal responses. However, the response in these patients is not short and transient as would be expected from M and L cones. Therefore this finding indicates inner retinal defects and cannot be attributed to M or L cone activity.

In accordance with the electrophysiologic findings the dark adaptation and spectral sensitivity measurements showed no rod function. All three cone systems were present in spectral sensitivity measurements. The sensitivity for blue was not enhanced above the normal values as described by Jacobson *et al.* (1990). This may be explained by the different retinal loci examined. In our study sensitivity was measured in the macula with central fixation and Jacobson *et al.* determined sensitivity thresholds at 20 and 36 deg eccentricity. The sensitivity of M and L cones was decreased in our study and in the patients of Jacobson *et al.* (1990). A markedly reduced sensitivity for middle and long wavelength stimuli was also found in colour perimetry. Sensitivity for blue was normal in all patients examined. From these experiments we recommend that patients with suspected enhanced S cone sensitivity syndrome are screened with blue and red targets in colour perimetry and blue and red stimuli in the ERG for verification.

Although the sensitivity of the M and L cone system is reduced, the inner retinal pathways necessary for cone interaction seem to be unaffected. The normal course of the transient tritanopia indicates an interaction between L/M and S cones, and the colour vision and colour discrimination in our patients were normal.

Apparently the retinal adaptation mechanisms are altered in these patients. There is a lack of the typical adaptation properties in the ERG, which at first was the most intriguing sign of the disease (Marmor, 1989; Fishman and Peachey, 1989). As shown in Figs 1 and 2 the ERG responses to the two strongest light stimuli were identical in the dark adapted and in the light adapted state (4.5 cd/m^2). Very intense background illumination was necessary to reduce the ERG amplitudes to the same extent as in normals. In psychophysical experiments, however, the same patient showed proper adaptation in the spectral sensitivity function, when he changed from the dark adapted into the light adapted state (Figs 8 and 9).

The primary defect of the enhanced S cone sensitivity syndrome is still unclear. Results of psychophysical and electrophysiological examinations are in accordance revealing no measureable rod function. However, they are not in accordance concerning the responses of the S, M and L cones. It remains puzzling (1) why responses of an S cone system can increase up to 300 μV, (2) why patients have normal colour vision but lack of L and M cone responses in the ERG and (3) why patients show unusual adaptation properties in the ERG but not in spectral sensitivity measurements.

Larger responses from the S cone system may be due to: (1) an increased number of S cones; (2) more numerous S cones that feed into rod pathways; and (3) rods containing an altered opsin with features similar to S cone opsin. The regional variance observed in psychophysical

experiments (Jacobson *et al.*, 1990) and the contrast between reduced thresholds in the colour visual field and normal colour vision and good visual acuity could be explained when the number and/or function of L and M cones were normal in the central retina but not in the retinal periphery.

Each of these possibilities would explain larger responses of the S cone system, however, M and L cone mechanisms should at least contribute and thereby show up in the ERG to some extent. Moreover, the altered adaptation properties cannot be explained with these theories.

The normal colour vision requires relatively normal receptors and neuronal pathways in each cone system. The difference between psychophysical and electroretinographical findings is more likely due to inner retinal mechanisms that not directly affect the signal transmission. Therefore one may speculate whether there could be altered membrane properties of the glial cells or changes of the interphotoreceptor matrix (IPM). However, alterations of the Müller cells should affect all three cone systems.

The IPM surrounds photoreceptor outer segments to a variable extent. The thickness and composition of the IPM varies between different photoreceptors and with eccentricity (Fariss *et al.*, 1990; Hollyfield *et al.*, 1990a, b). Differences in light-evoked changes in the IPM between different receptor types have been observed (Uehara *et al.*, 1991a). Changes of the IPM occur during the development of retinal degenerations (Uehara *et al.*, 1991b; Wiggert *et al.*, 1991), although it is unclear, whether these changes were prior or secondary to the degenerative process.

If the electrical properties of the IPM and the ional transport mechanisms through the IPM are altered, a number of effects could be explained: the photoreceptor outer segment and neuronal pathway could still be intact and respond properly in amplitude and time–course (Schnapf *et al.*, 1990). If the IPM surrounding L and M cones is thickened, the effect of light induced potassium release from L cones could be considerably reduced in comparison to that evoked via the S cones, if the latter's IPM membrane is normal. Since the IPM stretches horizontally throughout the retina, the potassium exchange between distal retina and inner retinal layers can be altered and thereby possibly explain the altered Müller cell response that does not have a correlation in psychophysics (Jong *et al.*, 1991).

Finally we want to comment on the terminology. Patients with enhanced S cone sensitivity syndrome have been described with various diagnosis (Noble *et al.*, 1978; Fishman and Peachey, 1989; Jiminez *et al.*, 1990; Perlman *et al.*, 1993). There are strong indications, that this entity is linked with the Goldmann–Favre syndrome (Jacobson *et al.*, 1991). Not in all patients the S cone sensitivity is "enhanced". We cannot prove whether the origin of the enhanced sensitivity is located within the S cones. Therefore we have certain objections for the term "enhanced S cone sensitivity", but we have used it to prevent confusion. We prefer not to use the term "Goldmann–Favre" at the moment for both entities, because until now only a limited number of patients with the enhanced S cone syndrome have findings consistent with the Goldmann–Favre syndrome.

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REFERENCES

Evers H. U. and Gouras P. (1986) Three cone mechanisms in the primate electroretinogramm: two with, one without off-center bipolar responses. *Vision Res.* **26,** 245–254.

Fariss R. N., Anderson D. H. and Fisher S. K. (1990) Comparison of photoreceptor-specific matrix domains in the cat and monkey retinas. *Expl Eye Res.* **51,** 473–485.

Fishman G. A. and Peachey N. S. (1989) Rod–cone dystrophy associated with a rod system electroretinogram obtained under photopic conditions. *Ophthalmology* **96,** 913–918.

Fishman G. A., Jampol L. M. and Goldberg M. F. (1976) Diagnostic features of the Favre–Goldmann syndrome. *Br. J. Ophthal.* **60,** 345–353.

Gouras P. and MacKay C. J. (1990) Electroretinographic responses of the short-wavelength-sensitivity cones. *Invest. Ophthal. visual Sci.* **31,** 1203–1209.

Hess R. F., Mullen K. T. and Zrenner E. (1989) Human photopic vision with only short wavelength cones: post receptoral properties. *J. Physiol.* **417,** 151–172.

Hollyfield J. G., Varner H. H. and Rayborn M. E. (1990a) Regional variation within the interphotoreceptor matrix from fovea to the retinal periphery. *Eye* **4,** 333–339.

Hollyfield J. G., Rayborn M. E., Landers R. A. and Myers K. M. (1990b) Interphotoreceptor matrix domains surround rod photoreceptors in the human retina. *Expl Eye Res.* **51,** 107–110.

Jacobson S. G., Marmor M. F., Kemp C. M. and Knighton R. W. (1990) SWS (blue) cone hypersensitivity in a newly identified retinal degeneration. *Invest. Ophthal. visual Sci.* **31,** 827–838.

Jacobson S. G., Roman A. J., Roman M. I., Gass J. D. M. and Parker J. A. (1991) Relatively enhanced S cone function in the Goldmann–Favre syndrome. *Am. J. Ophthal.* **111,** 446–453.

Jiminez J. M., Ponce E. and Quiroz-Mercado H. (1990) Congenital night blindness with rod-like photopic ERG. *Invest. Ophthal. visual Sci.* **31,** 424.

Jong de P. T. V., Zrenner E., van Meel G. J., Keunen J. E. E. and van Norren D. (1991) Mizuo phenomenon in x-linked retinoschisis. Pathogenesis of Mizuo phenomenon. *Archs Ophthal.* **109,** 1104–1108.

Kellner U. and Foerster M. H. (1991) Netzhautdegeneration mit Blauzapfenhypersensitivität. *Fortschr. Ophthal.* **88,** 637–641.

Kellner U. and Foerster M. H. (1992) Color electroretinography—a method for separation of dysfunction of cones. *Documenta ophthal.* **80,** 13–23.

Kellner U., Brümmer S., Foerster M. H. and Wessing A. (1990) X-Linked congenital retinoschisis. *Graefe's Archs clin. exp. Ophthal.* **228,** 432–437.

Marmor M. F. (1989) Large rod-like photopic signals in a possible new form of congenital night blindness. *Documenta Ophthal.* **71,** 265–269.

Marmor M. F., Arden G. B., Nilsson S. E. G. and Zrenner E. (1989) Standard for clinical electroretinography. *Archs Ophthal.* **107,** 816–819.

Marmor M. F., Jacobson S. G., Foerster M. H., Kellner U. and Weleber R. G. (1990) Diagnostic clinical findings of a new syndrome with night blindness, maculopathy and enhanced blue cone sensitivity. *Am. J. Ophthal.* **110,** 124–134.

Mollen J. D. and Polden P. G. (1977) An anomaly in the response of the eye to light of short wavelengths. *Phil. Trans. R. Soc. Lond. B* **278,** 207–240.

Noble K. G., Carr R. E. and Siegel I. M. (1978) Familial foveal retinoschisis associated with a rod–cone dystrophy. *Am. J. Ophthal.* **85,** 551–557.

Norren D. V. and Padmos P. (1973) Human and macaque blue cones studied with electroretinography. *Vision Res.* **13,** 1241–1254.

Perlman I., Leibu R. and Barth J. (1993) Night blindness: a new type with abnormal properties of the electroretinogram. *Clin. Vision Sci.* **8,** 159–169.

Reitner A., Sharpe L. T. and Zrenner E. (1991) Is colour vision possible with only rods and blue-sensitive cones? *Nature* **352,** 798–800.

Rhode N., Täumer R. and Pernice D. (1977) Vorschlag eines verbesserten klinischen EOG Testes. *Ber. dt ges Ophthal.* **74,** 747–750.

Roman A. J. and Jacobson S. G. (1991) S cone-driven but not S cone-type electroretinograms in the enhanced S cone syndrome. *Expl Eye Res.* **53,** 685–690.

Sawusch M., Pokorny J. and Smith V. C. (1987) Clinical electroretinography for short wavelength sensitivity cones. *Invest. Ophthal. visual Sci.* **28,** 966–974.

Schnapf J. L., Nunn B. J., Meister M. and Baylor D. A. (1990) Visual transduction in cones of the monkey *Macaca fascicularis*. *J. Physiol.* **427,** 681–713.

Uehara F., Yasamura D. and LaVail M. M. (1991a) Rod and cone-associated interphotoreceptor matrix in the rat retina. Differences in light-evoked distributional changes. *Invest. Ophthal. visual Sci.* **32,** 285–292.

Uehara F., Yasamura D. and LaVail M. M. (1991b) Development of light-evoked changes of the interphotoreceptor matrix in normal and RCS rats with inherited retinal dystrophy. *Expl Eye Res.* **53,** 55–60.

Wiggert B., Kutty G., Long K. O., Inouye L., Gery I., Chader G. J. and Aguirre G. D. (1991) Interphotoreceptor retinoid binding protein (IRBP) in progressive rod–cone degeneration (prcd)—biochemical, immunocytochemical and immunologic studies. *Expl Eye Res.* **53,** 389–389.

Zrenner E. and Gouras P. (1979) Blue-sensitive cones of the cat produce a rodlike electroretinogram. *Invest. Ophthal. visual Sci.* **18,** 1076–1081.

Zrenner E. and Gouras P. (1981) Characteristics of the blue sensitive cone mechanism in primate retinal ganglion cells. *Vision Res.* **21,** 1605–1609.