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CLINICAL INVESTIGATION

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Dysfunction of transmission in the inner retina: incidence and clinical causes of negative electroretinogram

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Abstract *Background:* Only limited data exist on the incidence of negative electroretinograms (ERG) in clinical practice. The purpose of this study is therefore to determine the incidence and clinical causes of a negative ERG in a tertiary care centre focused on inherited and acquired retinal degenerations. *Methods:* All ERGs recorded (in accordance with ISCEV standards) in our electrophysiological laboratory from 1992 to 2004 were retrospectively reviewed. The negative ERGs (criterion: ERG with b:a wave ratio≤1 in the scotopic standard combined response in at least one eye) were analysed in the context of further clinical results. The photopic ON- and OFF-responses were recorded with long duration (200 ms) stimuli. *Results:* A total of 1999 ERGs from 1644 patients were performed during the study period. 47/1644 patients (2.9%) presented with a negative ERG and were included in the study. Clinical diagnoses included inherited retinal dystrophies [X-linked congenital retinoschisis (XRS) (*n*=17), congenital stationary night blindness (CSNB) (*n*=6), retinitis pigmentosa (RP) (*n*=6), cone (-rod) dystrophy (*n*=5), choroideremia (*n*=1), Müller cell sheen dystrophy (MCSD) (*n*=1)] and acquired retinopathies (melanoma-associated retinopathy (MAR) (*n*=1), vigabatrin retinotoxicity (*n*=1)). In nine patients a definitive diagnosis could not be established. Unilateral negative ERGs were seen in 10/37 patients where ERG was bilaterally recorded. The fellow eye presented with a b:a wave ratio >1 (8 eyes) or ERG responses were not detectable (2 eyes). Photopic ON- and OFF-responses were recorded in 38 eyes of 29 patients and 32/38 eyes presented with a negative ERG. The ON-response was reduced in 25/32 eyes, whereas the OFF-response was reduced in only 11/32 eyes. *Conclusions:* The incidence of a negative ERG can differ between the laboratories depending on the causes for ERG recording and was in our laboratory 2.9% in a consecutive series of patients with inherited or acquired retinal degenerations. A disorder characteristically associated with negative ERG (e.g. XRS, CSNB, MAR) was diagnosed in 53% of these patients, whereas in 47% the negative ERG indicated an unexpected post-receptoral dysfunction, e.g. in cone (-rod) dystrophy or RP. The ON-bipolar pathway was affected in most cases.

Keywords Electroretinography · Full-field ERG · Negative ERG

Introduction

Full-field electroretinography (ERG) facilitates the evaluation of the function of the entire retina. Important components of the response to a single flash are the negative a-wave and the positive b-wave, these are best seen in the scotopic standard combined response. The a-wave is generated by the hyperpolarisation of the photoreceptors, whereas the b-wave reflects the function of the bipolar cells and the inner layers of the retina [7, 8, 23]. Normally, the amplitude of the b-wave is higher than of the a-wave. However, in cases of dysfunction of transmission in the inner retina, either in the photoreceptor synapses or in the post-receptoral pathway, a selective reduction of the b-wave can occur. The constellation, where the b:a wave ratio is equal to or smaller than 1, was termed a negative ERG [9].

There are hereditary as well as acquired retinal disorders that present characteristically with a negative ERG indicating a predominant dysfunction of the inner retina. Typical disorders with a negative ERG are X-linked congenital retinoschisis (XRS) [12, 20], congenital stationary night blindness (CSNB) [19], ischemic retinopathy caused by central retinal artery or vein occlusion [10, 18], melanoma-associated retinopathy (MAR) [2, 11], and toxic retinopathies caused by drugs (e.g. vigabatrin, quinine) [1] or intraocular metallic foreign bodies resulting in ocular siderosis [22]. In addition, negative ERGs were also reported in few cases of retinitis pigmentosa [3] and cone (-rod) dystrophy [5, 13] and in further rare disorders (for a detailed list of disorders with negative ERGs and their references, see Koh et al. 2001) [15]. Koh and colleagues reported an incidence of 4.8% of negative ERG in their study from one large tertiary care center [15]. No further data on this topic is available. As a result of a series of cases with unexpected negative ERGs, we were motivated to analyse our data to determine the incidence and clinical causes of negative ERGs in our 12-year-experience in one tertiary care centre focused on inherited and acquired retinal degenerations.

Materials and methods

All ERGs recorded between 1992 and 2004 in the electrophysiological laboratory of the Department of Ophthalmology of the Charité Campus Benjamin Franklin, a tertiary health care centre, were retrospectively reviewed. The definition of a negative ERG that served as inclusion criterion was a b:a wave ratio ≤1 in the standard combined response in at least one eye. All negative ERGs included in the study were re-analysed in the context of further clinical results. In addition, ON- and OFF-ERGs, when recorded, were re-analysed as well.

Recording of the full-field ERG was done according to the regularly updated International Society for Clinical Electrophysiology of Vision standards [17]. The recording equipment remained the same during all evaluations. The recording protocols have already been described in detail elsewhere [11]. ERG recordings were carried out with maximum pupil dilation using a Nicolet Spirit and a Ganzfeld bowl (Nicolet, Madison, Wisc., USA). Jet-corneal contact lens electrodes were used (Microcomponents SA, Division Universo Plastique, Le Crêt-du-Locle, Switzerland). Stimulus duration was 0.1 ms. Following 30 min of dark adaptation, four stimuli with increasing intensity (maximum light intensity: 10 cd s/m^2) were used for recordings in the dark. Light-adapted recordings were performed after 10 min of light adaptation in the presence of white background light of 30 cd/m^2 with white stimuli of maximum light intensity. No averaging was carried out. For comparison, age-related normal ranges for amplitudes and implicit times were determined by calculation of the median values and the 95% confidence intervals from single eyes of 70 subjects.

ON- and OFF-ERGs were recorded with long duration stimuli with green LEDs as described previously [21]. Following brief flash ERG recording, ON- and OFF-responses were obtained with an LED-stimulator (Roland Consult, Brandenburg, Germany) using green LEDs (3 cd /sm^2) and flashes of long duration (200 ms) presented on background illumination. Recordings were carried out after 10 min of light adaptation (10 cd/m^2), usually following light adapted recordings in the full-field ERG. A total of 128 responses were averaged. The normal values for ON- and OFF-responses were defined by the evaluation of one eye in 68 subjects. Evaluation in subjects revealed good recordability and reproducibility of ON- and OFF-responses.

Results

A total of 1999 ERGs from 1644 patients were recorded in our ERG laboratory during the study period. In all, 47/1644 patients (2.9%) presented with a negative ERG in at least one eye and were included in the study. The mean age was 35.3 years (3.0–74.7) and median visual acuity was 0.4 (count fingers–1.0). ERGs were performed in 84/94 eyes of the 47 patients. In the remaining ten eyes of ten patients, ERG was not performed due to amaurosis in XRS (n=3), giant tear retinal detachment in XRS (n=1), and reduced compliance in children (n=6).

Seventy-four eyes presented with a negative ERG, eight eyes did not show negative waveforms in the standard combined response, and an ERG was not detectable in two eyes (one with retinal folds and vitreous haemorrhage in XRS and one with an unclarified diagnosis). The clinical diagnoses included mainly inherited and less frequent acquired retinopathies (Table 1). A definitive diagnosis could not be established in nine patients.

The b:a wave ratio of the standard combined response ranged between 0.18 and 0.99 (mean 0.75, median 0.77) in

Table 1 Incidence and causes of negative ERG

Diagnosis	Number of patients with negative ERG
X-linked congenital retinoschisis	17
Congenital stationary night blindness	6
Retinitis pigmentosa	6
Cone (-rod)-dystrophy	5
Choroideremia	1
Müller cell sheen dystrophy	1
Melanoma-associated retinopathy	1
Vigabatrin retinotoxicity	1
Unclarified diagnosis	9

the 74 eyes with a negative ERG. Almost all eyes presented with a b:a wave ratio greater than 0.5. A ratio smaller than 0.5 was only seen in both eyes (0.18 and 0.40) of a 47-year-old patient with retinitis pigmentosa with a ring scotoma.

The amplitude of the a-wave of the standard combined response was normal in 20/74 eyes with a negative ERG, however, reduced in 54/74 eyes. The mean reduction of the a-wave amplitude was to 51.4% (median 52.1%, range 6.8–80.9%) in these 54 eyes. There was no association with certain disorders. All diseases noted in Table 1 presented with a normal as well as a reduced a-wave in different patients. Exceptions were choroideremia with a reduced a-wave, Müller cell sheen dystrophy (MCSD) and vigabatrin retinotoxicity with a normal a-wave in the standard combined response. The rare cases of negative ERG in MCSD and choroideremia have been reported in detail elsewhere ([14] and Renner et al., unpublished data).

Photopic ON- and OFF-responses with long duration flashes were recorded in 38 eyes of 29 patients. A negative ERG was found in 32/38 eyes. Twenty-five eyes of these 32 eyes had a reduced ON-response, whereas only 11/32 presented with an additionally reduced OFF-response (Table 2). In none of the 32 eyes was the OFF-response reduced when the ON-response was normal.

Unilateral negative ERG waveforms were seen in 10/37 patients where ERG was bilaterally recorded (Table 3). In 8/10 fellow eyes, b:a wave ratio ranged between 1.02 and 1.31, and ERG was not detectable in two fellow eyes. A hereditary retinal dystrophy was present in six of these ten patients, and the diagnosis remained unclarified in four patients.

In 12 patients with negative ERG, the ERG was recorded more than once within a range of 0.2–9.4 years. In some patients with progressive retinal dystrophy an amplitude reduction was noted, however, in all of the eyes the negative ERG configuration persisted during follow-up.

The following three case reports illustrate a typical negative ERG in congenital stationary night blindness, an unexpected negative ERG with a-wave reduction in cone dystrophy, and an unilateral negative ERG in a patient with an undefined diagnosis.

Table 2 Photopic ON- and OFF-responses in 32 eyes with negative ERG

Photopic ON- and OFF-responses	Number of eyes	Diagnosis
ON- and OFF-responses normal (n=7)	3	XRS
	2	Unclarified diagnosis
	1	Cone-rod dystrophy
	1	Müller cell sheen dystrophy
ON- and OFF-responses reduced (n=11)	1	XRS
	1	CSNB
	2	Unclarified diagnosis
	3	Retinitis pigmentosa
	4	Cone dystrophy
Only ON-response reduced (n=14)	4	XRS
	5	CSNB
	1	Unclarified diagnosis
	2	Choroideremia
	2	MAR

XRS X-linked congenital retinoschisis, *CSNB* congenital stationary night blindness, *MAR* melanoma-associated retinopathy

Case 1: Negative ERG with normal a-wave in congenital stationary night blindness

A 14-year-old boy (patient no. 1627) presented with reduced visual acuity and myopia. He reported night blindness since childhood and mentioned night blindness in his maternal great-grandfather. The patient did not notice any progression in visual disturbances. Visual acuity at the time of examination was OD 0.4 (−3.0–1.5×96°D) and OS

Table 3 Cases of unilateral negative ERG

Diagnosis	Number of patients	Reason for unilateral negative ERG
Unclarified diagnosis	4	b:a wave ratio in fellow-eye: 1.08; 1.11; 1.30 ERG non recordable in fellow-eye
X-linked congenital retinoschisis	2	b:a wave ratio in fellow-eye: 1.02; ERG non recordable in fellow-eye
Retinitis pigmentosa	2	b:a wave ratio in fellow-eye: 1.12; 1.05
Cone dystrophy	1	b:a wave ratio in fellow-eye: 1.03
Müller cell sheen dystrophy	1	b:a wave ratio in fellow-eye: 1.31

ERG was bilaterally recorded in 37 patients. Negative ERG, when b:a wave ratio ≤1

0.5 (−2.25 –1.75×74°D). Complete ophthalmologic examination was normal, except for a conus inferior in both eyes including the optic disc and part of the macula. Colour vision was normal and Goldmann perimetry revealed normal outer limits. Full-field ERG showed a normal a-wave amplitude in the standard combined response with a markedly reduced b-wave showing a negative waveform (b:a wave ratio OD 0.67 and OS 0.65) (Fig. 1). The amplitude of the photopic a-wave was normal but broadened, and b-wave amplitude was reduced to about 60% of the normal value. The implicit time of 30 Hz flicker was 2 ms longer than normal; the amplitudes were reduced to about 65% of the normal value. The photopic ON-response showed a negative waveform and the OFF-response was normal (Fig. 2). All findings were in accordance with a X-linked CSNB.

Case 2: Negative ERG with reduced a-wave in cone-dystrophy

A 43-year-old male (patient no. 959) presented with visual loss and nystagmus since early childhood and mentioned two strabismus operations on the left eye at the age of 30. He reported good night vision but colour vision defects and photophobia, and an ongoing loss of far vision experienced over several months. Visual acuity at time of examination was in OU 0.1 with hyperopia (+5.0 D). The ophthalmologic examination was normal, except for a missing foveal reflex. Desaturated Panel D 15 test revealed marked colour vision defects in both eyes without any typical axis of confusion. The full-field ERG surprisingly showed a negative ERG with a distinct reduced b-wave amplitude but with a reduced a-wave amplitude as well (b:a wave ratio OD 0.52 and OS 0.50) (Fig. 1). The photopic and 30 Hz flicker responses were almost undetectable. There

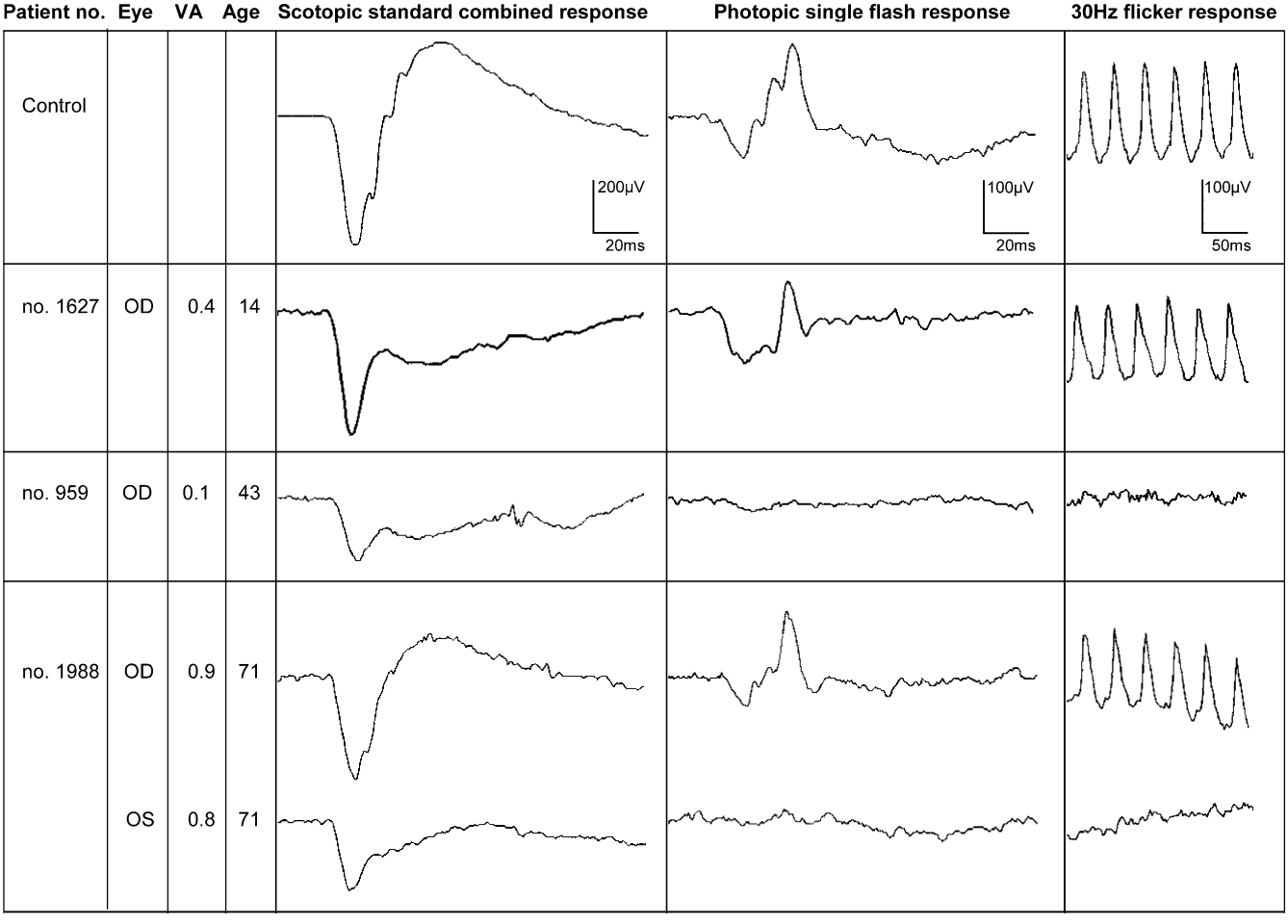

Fig. 1 Full-field electroretinogram (*ERG*) of a normal subject (control) and of three patients. Patient no. 1627: 14-year-old boy with congenital stationary night blindness and a negative ERG in both eyes (OD illustrated). The amplitude of the scotopic a-wave is normal. For details see Results, case 1. Patient no. 959: 43-year-old male with cone dystrophy and a negative ERG with a reduced scotopic a-wave amplitude in both eyes (OD illustrated). For details see Results, case 2. Patient no. 1988: 71-year-old female with a normal ERG in the right eye and a negative ERG in the left eye. The diagnosis is unclarified. For details see Results, case 3. *VA* visual acuity; *Age* age in years

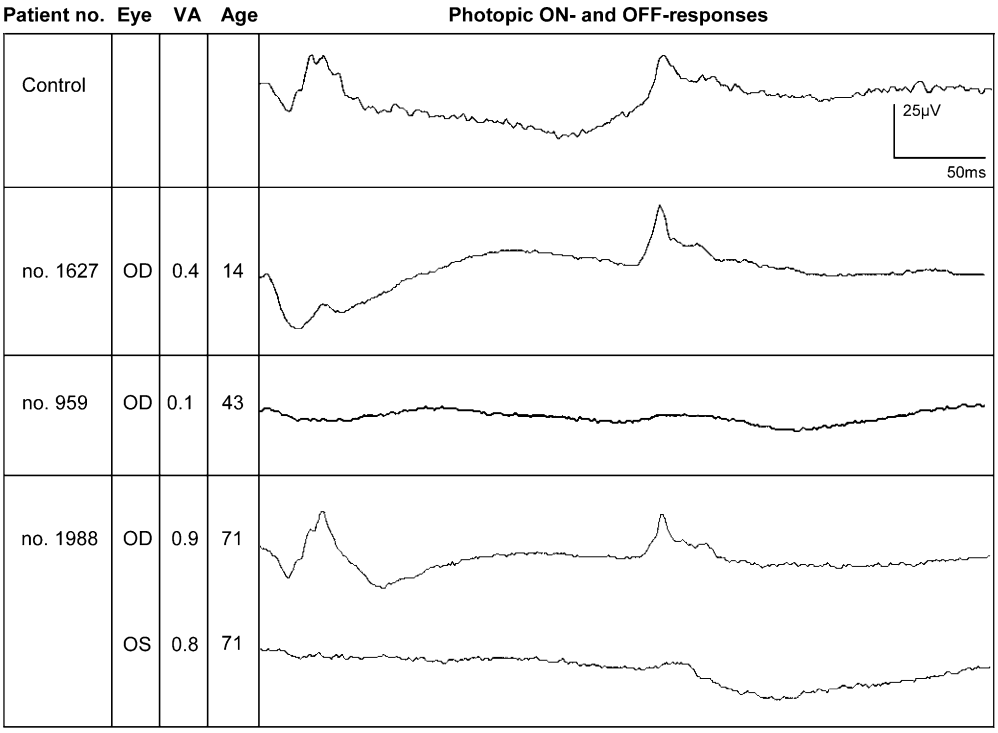

Fig. 2 Photopic ON- and OFF-responses of a normal subject (control) and three patients (same patients as in Fig. 1). Patient no. 1627 showed a negative ON-response and normal OFF-response in both eyes (OD illustrated). Patient no. 959 had a loss of both responses in both eyes (OD illustrated). Patient no. 1988 showed normal ON- and OFF-responses in the right eye but a complete loss of both in the left eye. For details see Results. *VA* visual acuity, *Age* age in years

was a loss of photopic ON- and OFF-responses (Fig. 2). Almost the same results from all tests were obtained during a re-examination 2 years later. The visual field (Goldmann perimetry), performed during follow-up, showed a slightly narrowed visual field in both eyes and a central scotoma in the left eye. CSNB and XRS could be excluded because of good night vision and normal fundus findings. The patient's diagnosis was defined as cone dystrophy with a negative ERG.

Case 3: Unilateral negative ERG

A 71-year-old female (patient no. 1988) presented with ongoing visual loss, photophobia and colour vision defects in her left eye experienced over several months. Visual acuity at the time of examination was at OD 0.9 and OS 0.8. The left eye was pseudophakic. Funduscopy in both eyes revealed few visible choroidal folds near to the upper vascular arcades. The only difference in retinal findings between the eyes was a slightly brighter appearance of the RPE in the left fovea, however, fundus autofluorescence was normal in both eyes. Desaturated Panel D 15 test showed in OD one error and in OS three errors. The visual field (Goldmann perimetry) was normal in OD, whereas the test marks I/4, I/3 and I/2 were constricted in OS beside normal outer limits with III/4. The multifocal ERG amplitude was slightly reduced in ring 1 in OD, but showed distinct generalised reduction in OS. Full-field ERG in the right eye was normal except for subnormal amplitudes of the 30 Hz flicker response. The full-field ERG in the left eye showed a negative configuration with a reduced a-wave and non-recordable photopic single-flash and 30 Hz flicker responses (Fig. 1). Photopic ON- and OFF-responses were normal in OD and OS showed almost complete loss of both (Fig. 2). Further examination for systemic disorders or vascular problems did not reveal any pathology. The choroidal folds were symmetric in both eyes and did not explain the visual disturbances in the left eye. The diagnosis in this patient remains unclear.

Discussion

The incidence of a negative ERG in our electrophysiological laboratory was 2.9%. One of the disorders characteristically associated with a negative ERG such as XRS, CSNB, MAR and vigabatrin retinotoxicity were confirmed in 53% of the patients. The remaining 47% of the patients unexpectedly showed a reduction in the b-wave indicating a post-receptoral dysfunction, e.g. in cone (-rod) dystrophy or RP. The smaller incidence of negative ERG in our series compared with the reported 4.8% by Koh and colleagues is most likely caused by a variation in the patient profile. In contrast to Koh et al., we did not perform ERGs in patients with central artery occlusion or inflammatory retinopathies, of which Koh et al. had several cases in their series [15]. We did perform ERGs only in three patients with metallic intraocular foreign bodies, and none of them had a negative ERG. The incidence of negative ERG in each electrophysiological laboratory is therefore strongly related to the causes for ERG recording and depends on the specialisa-

tion and research interests of individual centres. However, an incidence rate of higher than 5% may be unlikely. The low incidence rate of negative ERG reflects that a dysfunction of the inner retinal transmisson is infrequent in contrast to a dysfunction of the photoreceptors. In some cases (27%) a selective inner retinal transmission defect with normal photoreceptor function demonstrated with normal a-waves can be detected. In the majority of cases (73%), in eyes with a negative ERG there is only a predominant dysfunction of inner retinal transmission with an additional a-wave amplitude reduction, indicating photoreceptor abnormalities as well. Koh et al. also reported abnormal a-waves but only in 34/128 (27%) patients with a negative ERG where all the 34 patients had a rod-cone/cone-rod dystrophy [15]. In our series, an a-wave reduction appeared in XRS, CSNB, cone (-rod) dystrophy, rod-cone dystrophy, MAR and in cases with an undefined diagnosis. The rare constellation of a unilateral negative ERG was seen by Koh et al. in 7/128 patients with normal appearance of the retina and the clinical diagnoses remain undetermined in these patients [15]. In our laboratory, unilateral negative ERGs were seen in 10/37 patients where ERG was bilaterally recorded, and, surprisingly, 6/10 patients presented with retinal degenerations (e.g. XRS, retinitis pigmentosa).

Recording of ON- and OFF-ERGs allows for further subdivision of the causes of negative ERG. The photopic ON- and OFF-responses were pathologic in 25 of 32 tested eyes with negative ERG, giving additional information about the inner retina function. The ON-response, originating in the depolarizing bipolar cells, was predominantly affected, whereas the OFF-response, originating in the hyperpolarizing bipolar cells, was normal in the majority of cases. An ON-pathway dysfunction of transmission either from photoreceptors to bipolar cells or within the bipolar cells is the most frequent origin of a negative ERG.

ON-pathway dysfunction might be due to the structural abnormalities of the photoreceptor synapses in cone-rod dystrophies [6], mutations in genes encoding for transmitters in photoreceptor synapses [4] or antibodies against a subgroup of bipolar cells in MAR [16]. However, for the majority of cases the pathophysiological abnormalities leading to a negative ERG still have to be clarified. The finding of a negative ERG in clinical practice is a helpful sign indicating a group of disorders, which have an inner retinal transmission deficit in common. The negative ERG can confirm certain clinically suspected diagnoses (e.g. XRS, CSNB, MAR). Nearly as frequently, however, the negative ERG is a surprising finding in a patient with retinal dysfunction. Detailed analysis of each case is necessary to establish a particular diagnosis. At present, a group of patients remain where the origin of the inner retinal transmission deficit cannot be determined.

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