Cone dystrophies: clinical and electrophysiological findings

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Abstract. We analyzed the clinical and electrophysiological findings of 77 patients suffering from progressive cone or cone-rod dystrophies. The onset of symptoms was at the average age of 19.7 ± 19.4 years. In some patients, the disease started within the 5th decade. The mean visual acuity was 0.19 ± 0.2, while in 38%, the visual acuity was lower than 0.1. Color vision defects and visual field defects were found in most patients. The electrooculogram was recorded in 59 patients and was normal in only 19. On the electroretinogram (ERG), 60 patients had a reduction of the 30-Hz flicker amplitude and of the responses at maximum stimulus intensity when dark and light adapted. The ERG alterations showed a correlation to the visual field defects and to the reduction of the light rise on the electrooculogram. No correlation existed between the ERG amplitudes and visual acuity or color vision. Ophthalmoscopically, the posterior pole was normal in 25 patients. In the remaining patients, fundus changes ranged from mild pigment irregularities to severe pigment clumping. No correlation between fundus changes and functional findings existed.

Introduction

Electroretinography (ERG) allows a separation of retinal degenerations according to the dysfunctioning receptor system. Cone dysfunctions can be separated into stationary cone dysfunctions and progressive cone or cone-rod dystrophies. The electroretinographical and clinical characteristics of progressive cone dystrophies were described by Goodman and coworkers in 1963 [2]. Several reports of cone dystrophies including all types of heredity pattern have been published since then [4, 7]. The clinical and electrophysiological findings show a large variability. Within the past few years, classifications of cone dystrophies according to clinical and electrophysiological findings were proposed by some authors [12, 14]. Patients with cone dystrophies and unusual ERGs indicating selective cone dysfunction or intraretinal transmission defects have been described recently [1, 5, 9, 10, 13, 15]. To evaluate the variability of clinical findings in cone dystrophies and the frequency of additional electroretinographical changes, we analyzed retrospectively data of patients suffering from cone dystrophies who had been examined in the University Eye Clinic Essen.

Patients and methods

The case histories, clinical and electrophysiological findings of 77 patients suffering from cone or cone-rod dystrophies were evaluated. Clinical inclusion criteria were visual loss, photophobia, and color vision defects. Electroretinographical signs of cone dysfunction were reduced b-wave amplitudes in the light-adapted recordings and reduced 30-Hz flicker amplitudes. Patients with signs of additional rod dysfunction were only included when the signs of cone dysfunction were predominant. All patients had undergone clinical and electroretinographical examinations. The mean age at time of the examination was 29.8 ± 19.0 years (range 5–75 years). Forty-three patients were male and 34 female. Seven of our patients were relatives.

Patients were divided into groups A–E depending on the following electroretinographical parameters: b-wave amplitude at maximum stimulus intensity at dark and light adaptation and 30-Hz flicker response (Table 1). Group E was divided in 4 subgroups depending on the reduction of the b-wave amplitude at dark adaptation. Only one eye of each patient was included in the ERG evaluation. In most cases, there was no difference between both eyes. In 7 cases a small difference was found, and the eye with the lower ERG potentials was included. However, in no case did this difference result in a change of more than one group.

Electrooculograms (EOG) were recorded according to Rhode, Täumer and Pernice [11]. The ERG recording method has been described in detail [1, 6]. The recording protocol includes all recordings following the standard of the ERG recording [8]. Stimulus duration was 10 ms. Six different light intensities (1–6) increasing in steps of one logarithmic unit from the b-wave threshold of the normal eye were used for the dark-adapted recordings. The maximum light intensity was 7.8 cd. s/m^2. The light-adapted recordings were performed under white light adaptation to a background of $4.5 \, cd/m^2$ and with light stimuli 4–6. The 30-Hz flicker stimulus had light intensity 5. White light from a xenon light source served as the stimulus in all examinations. This light source was filtered for infrared with Schott filter KG2IR. A normal ERG is shown in Fig. 1.
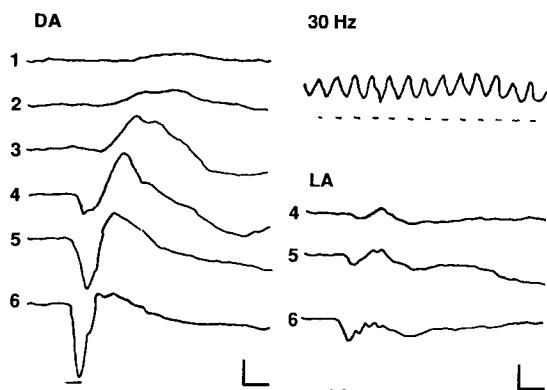
Fig. 1. Normal electroretinogram (ERG). *Left column,* recordings at dark adaptation (*DA*); *lower right column,* recordings at light adaptation (*LA*). The 30-Hz flicker response is shown in the *upper right column. Vertical calibration marks* indicate 100 μV; *horizontal marks* indicate 50 ms for flicker stimulation and 20 ms for all other responses. *Numbers* in front of the recordings indicate the stimulus intensity

Table 1. Patient groups

Group	n	ERG parameters
A	2	Normal 30-Hz flicker amplitude
B	3	Only 30-Hz flicker amplitude reduced
C	7	30-Hz flicker + b-wave amplitude at dark adaptation reduced
D	5	30-Hz flicker + b-wave amplitude at light adaptation reduced
E	60	30-Hz flicker + b-wave amplitude at dark and light adaptation reduced
E1	13	b-wave amplitude at dark adaptation between 229 and 305 μV
E2	18	b-wave amplitude at dark adaptation between 153 and 228 μV
E3	15	b-wave amplitude at dark adaptation between 76 and 152 μV
E4	14	b-wave amplitude at dark adaptation ≤75 μV

b-wave amplitude at dark adaptation 305 μV = lower limit of normal range (mean minus 2 standard deviations, 408–103 μV)

Results

Case history

The general medical history of all patients was uneventful. The average age at onset of symptoms was 19.7 ± 19.4 years. Some 42% had symptoms before the age of 10 years, 57% before 20, and 66% before 30. There was no difference between the patient groups. Photophobia was found in 19 cases, color vision defects in 7 cases, and visual field disturbances in 6 cases as primary symptoms at the beginning of the disease. Visual loss was found in all patients. In many cases, it was impossible to determine from the records whether the visual loss was detected subjectively by the patient, by the parents, or during screening examinations. Fifteen patients (20%) had affected family members, and in 8 cases more than one family member was affected.

Clinical findings

The anterior segments were unremarkable in all patients. Ophthalmoscopy revealed normal optic discs, retinal vessels, and retinal periphery in most patients. A pale disc was found in 9 and a waxy pallor in 6 patients. The retinal vessels were narrowed in 22 patients. Irregularities of the retinal pigment epithelium (RPE) were found in 14 and bone spicules in 10 patients. Most of the patients with pathologic findings of the optic disc, retinal vessels, or peripheral retina belonged to group E. Within group E, most of them belonged to group E4, characterized by a severe amplitude reduction of the ERG. In 25 cases, the posterior pole was normal. A bull's-eye pattern or a central scar were seen in 6 cases each (Fig. 2). Some 37 patients showed RPE irregularities which were rather variable in expression and the area affected. In some eyes, these were limited to a small area around the fovea; in other cases, the posterior pole showed marked changes reaching beyond the vascular arcades. Whitish or yellowish flecks with a variable distribution were found in 5 patients. In 3 cases, a missing macular reflex was the only pathological sign of the disease. Fundus findings were almost similar in both eyes of one patient except for those with small central scars. These were unilateral in 4 cases and bilateral in 2. In the unilateral cases, the other eye showed pigment irregularities.

Visual acuity and refraction

The visual acuity was reduced to 0.19 ± 0.2. In 38% of patients, the visual acuity was lower than 0.1 and 75% lower than 0.3. Refractive errors were found in 41 patients, ranging from −18 to +8 dpt. Thirty-two patients had an astigmatism with a maximum of 4.5 dpt. An oblique axis was found in 6 patients. There was no correlation of visual acuity or refractive error with the patient groups.

Color vision

Color vision was examined in 51 patients using Ishihara's pseudoisochromatic plates, the Panel D 15 test, and the Nagel anomaloscope. Three of these 51 patients had normal color vision. Protanomaly and protanopia were found in 3 patients each, and deuteranopia was present in 2 patients. Ten patients had moderate color vision disturbances without a typical axis, and 30 patients showed an achromatopsia. No correlation between color vision findings and patient groups was found.

Visual field

Visual fields were examined using Goldmann perimetry in 51 patients. Visual fields were normal in 8, but showed absolute central scotomas in 18, central and peripheral scotomas in 6, and peripheral scotomas in 19 patients. Of the 25 patients with peripheral scotomas, 11 patients had
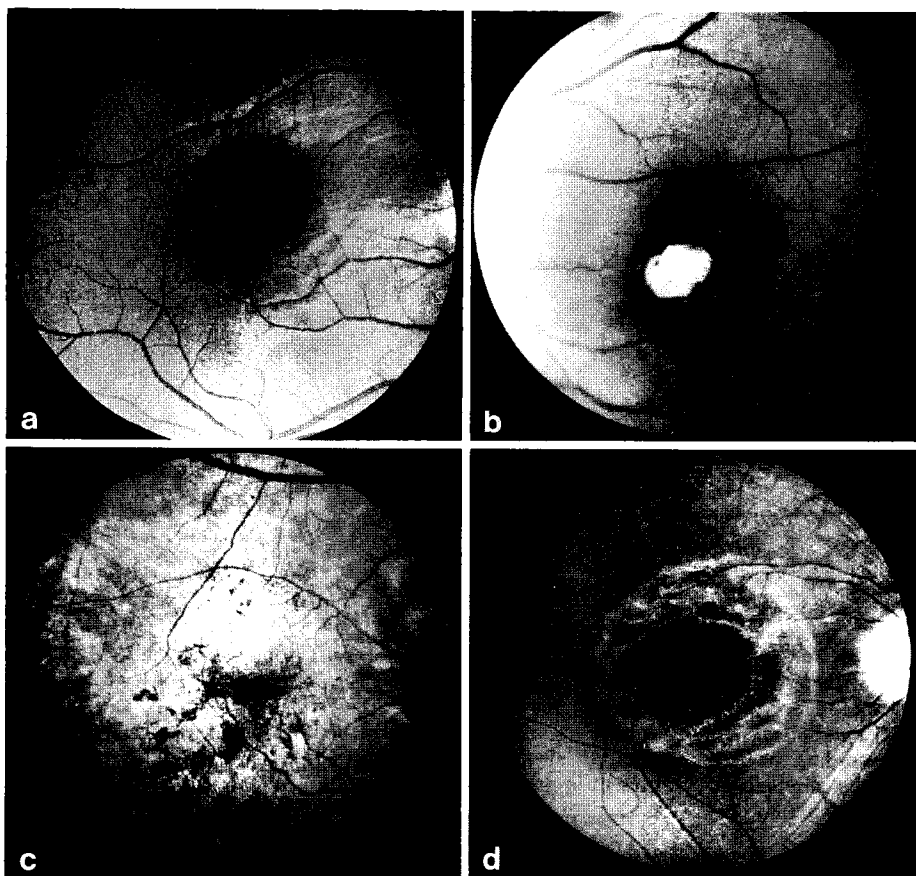
Fig. 2a–d. Fundus photographs of the posterior pole in patients with cone dystrophies. a A 22-year-old male patient (group B). A thin line within the fovea is the only fundus abnormality. b 50-year-old male patient (group E1) has a central scar on his left eye and pigment irregularities in the right eye. c A 32-year-old male patient (group E1). Although the ERG was not different from the patient shown in b, the fundus in this patient showed central pigment clumping; pigment epithelial irregularities reached far beyond the vascular arcades, and a tapetoid reflex was seen on the posterior pole. d A 12-year-old male patient (group E3). The fundus changes were limited to the macula, but the ERG showed a severe amplitude reduction compared with the patients shown in a–c

a mild narrowing of the visual field to 45°, 2 patients had a constriction to about 30° and 7 patients, to about 20°. Five patients had scotomas at 20°–40°. Central scotomas were found in patients of all groups; peripheral scotomas were limited to patients of group E and were most often found in groups E3 and E4 with a marked reduction of all ERG amplitudes.

Electrooculography

EOGs were recorded in 59 patients and were normal in 19. The mean light peak was reduced to 133% ± 31.3% (lower normal range 151%). In groups A and B, all EOGs were normal, and in group E4, all EOGs were pathological. The reduction of the light rise correlated with the reduction of ERG amplitudes.

Electroretinography

ERGs were recorded in all patients. We evaluated the amplitudes and latencies of a- and b-waves at dark and light adaptation for all stimulus intensities and the amplitude of the 30-Hz flicker response. Typical ERG recordings for each group are shown in Fig. 3.

Amplitudes. The b-wave amplitude at dark adaptation at maximum stimulus intensity, a mixed cone-rod response,

was reduced in 67 patients. In 64 of them, the b-wave amplitude was also reduced at stimulus intensity 3, a predominantly rod response, indicating an additional rod involvement. In groups A and B, only some amplitudes were borderline. In group C, with reduced b-wave amplitudes at dark adaptation and maximum stimulus intensity, a- and b-wave amplitudes were reduced for all stimulus conditions when dark adapted and normal when light adapted. In group D, the a- and b-wave amplitudes at light adaptation were reduced for all stimulus intensities. Responses when dark adapted were normal or borderline. The largest group E, showed reduced a- and b-wave amplitudes under all stimulus conditions; the light-adapted responses were more reduced than the dark-adapted responses.

Latencies and implicit times. The a- and b-wave latencies showed inconsistent findings. In some groups, the latencies were significantly prolonged under some stimulus conditions, but normal at others. This is due to the small normal range with a standard deviation of about 2 ms and a larger variation within the patient groups compared with normal subjects. In our patients, the a- and b-wave latencies were therefore of no value for the diagnosis of cone dystrophy. Moreover, there was no clear difference between the patient groups.

The b-wave implicit times were normal in groups A–D under dark- and light-adapted conditions. In group E and in all subgroups, the b-wave implicit times at dark

DA, SI 3   DA, SI 6   LA, SI 6   30 Hz

Normal

A

B

C

D

E1

E2

E3

E4
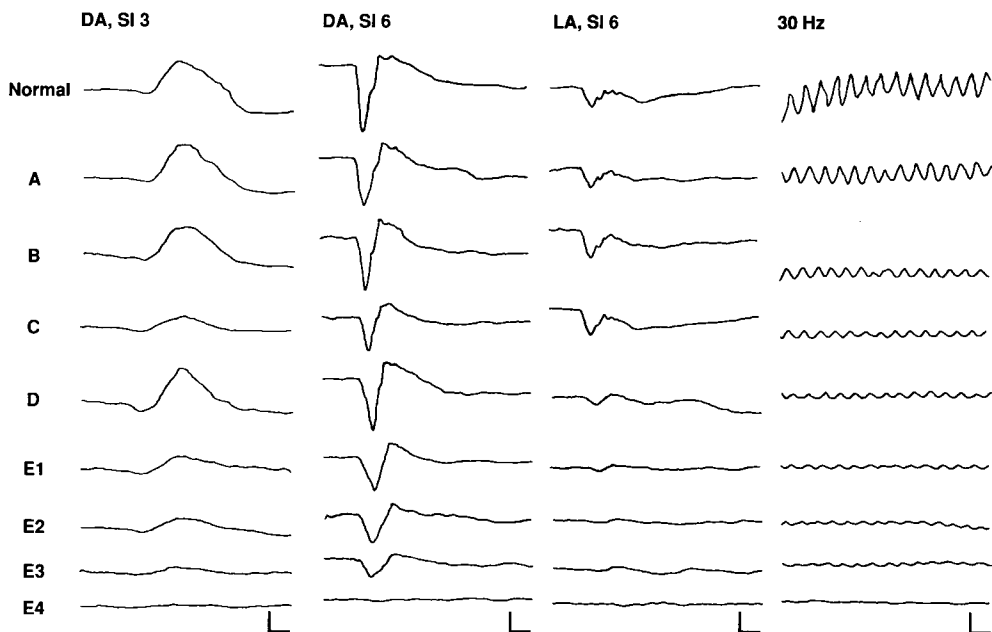
Fig. 3. Typical ERG recordings for a normal subject and the patient groups A–E4. Each group is marked with initials in front of the row of the recordings. *Outer left column* shows the recordings when dark adapted (*DA*) at stimulus intensity (*SI*) 3 and *middle left column*, at SI 6. *Middle right* column shows the recordings at light adaptation (*LA*) and *outer right column* at 30-Hz flicker stimulation. For calibration, see Fig. 1. In group A, the amplitudes are border- line under all stimulus conditions. In group B, only the 30-Hz flicker response is reduced. Group C shows reduced responses when dark adapted and to flicker stimulation. In group D, the flicker response and the response at light adaptation is reduced. In all subgroups of group E, all responses are reduced; no measurable responses are present in group E4

adaptation were prolonged but normal at light adaptation.

The 30-Hz flicker response. The amplitude was only normal in 2 patients. In all other patients it was reduced, the reduction being more pronounced in cases with a reduction of other ERG parameters. In group E4, no measurable responses could be recorded.

Discussion

Characteristic signs of cone and cone-rod dystrophies are visual loss, photophobia, color vision deficits, and central visual field defects. A reduced visual acuity was found in all our patients. Not all, however, had noticed the reduction, due to early onset or slow progression. The other signs were only realized by a few patients. It is difficult to determine the time of onset of the disease. There are no reliable data in the literature. Except for the older individuals reexamined during family examinations, most of the patients were correctly diagnosed in our service for the first time. Some patients had a history of varying ophthalmological diagnoses ranging from optic atrophy to undiagnosed visual loss for up to 30 years. In general, the disease started in the 1st or 2nd decade of life. In some patients, however, normal visual acuity was documented up to the 5th decade, and subjective signs were missing.

Clinical findings showed large variations. One-third of the patients had a normal fundus appearance. Fundus abnormalities ranged from slight pigment epithelial irregularities to severe central and peripheral pigment clumping. Visual acuity was reduced below 0.3 in 75%, and color vision was abnormal in most of our patients. Visual fields showed central scotomas in patients with cone dystrophies and peripheral scotomas in patients with cone-rod dystrophies. The EOGs were normal in patients with normal rod responses on the ERG and could be normal or reduced in patients with cone-rod dystrophy. None of these clinical findings or functional tests were sufficient for the diagnosis of cone dystrophy.

On the ERG, the 30-Hz flicker amplitude was the most reliable parameter for cone dysfunction. Only 2 patients had a normal 30-Hz flicker response. These patients were included in the study despite the normal ERG because all clinical signs (photophobia, color vision deficits, and visual loss) were markedly expressed and the ERG amplitudes were borderline.

In 10 patients, the 30-Hz flicker response was reduced, but the response at light adaptation were normal. Seven of these patients had mildly reduced responses when dark adapted. Only 5 patients had normal responses at dark adaptation and a reduction of amplitudes at flicker stimulation and light adaptation. This would be expected from a disorder selectively affecting the cones. Most patients (78%) had a reduction of ERG amplitudes under all stimulus conditions. Dark-adapted responses at different stimulus intensities were compared to distinguish whether the reduced amplitudes were due to a missing cone component or rod involvement. Nearly all patients who had reduced responses to bright stimuli also had

reduced responses to dim stimuli. This finding indicates that rods are affected in most of these patients, even if only signs of a cone dystrophy are present.

Yagasaki and Szlyk [12, 14] proposed subdivisions of patients with cone-rod dystrophies. According to clinical, psychophysical, and electroretinographical findings, they separated patients who showed a severe loss of cone function and no or minimal loss of rod function from patients who had equally affected cone and rod functions. In our patients, a similar subdivision would separate patient groups A, B, and D on the one hand from groups C and E on the other hand. Even within the small groups, there is a considerable variation of clinical findings and the extent of ERG amplitude reduction. We therefore do not feel that this subdivision is very helpful for the important task of counselling our patients. Only patients of different ages in one family have been used to determine progression [14]. Longitudinal studies are necessary to show the type of progression and the variability in a larger series of patients. In our series only a few patients were reexamined within a short time period of 1 or 2 years. Therefore, insufficient data were present to determine progression.

In recent years, cone dystrophies with unusual findings have been more frequently reported. Selective cone dystrophies affect only one or two cone types, with the other ones either remaining normal [10] or being hypersensitive [5, 9]. In other cases, the a- and b-waves of the ERG show differing alterations, indicating inner retinal defects in addition to the receptoral dysfunctions. Patients with supernormal [1, 3] and missing b-wave amplitudes [13, 15] have been described. Extensive psychophysical, electrophysiological, and molecular genetic evaluation allows the possibility of separating the different mechanisms of retinal dysfunction in these patients [5, 10]. We believe that an evaluation of more patients with cone dystrophies using such techniques is necessary to determine the underlying functional defects and to correlate them with genetical aberrations.

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