# Pattern of dysfunction in progressive cone dystrophies – an extended classification

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**Abstract.** An extended classification for progressive cone dystrophies is proposed on the basis of the retrospective analysis of the clinical and electrophysiological findings obtained in a series of 91 patients with progressive cone dystrophies and of a review of the literature. This classification depends on the different patterns of electroretinographic responses. Four main categories and ten subgroups are distinguished. Generalized cone dystrophies are most frequent (76/91), affect all types of cones, and may be subdivided according to the degree of rod involvement. In selective cone dystrophies (8/91), the three cone types are affected differently as detected with the color electroretinogram. They are subdivided on the basis of the cone type predominantly involved. Additional inner retinal transmission defects may occur in cone dystrophies (3/91). They are identified by an alteration in the b/a-wave ratio on the electroretinogram and may affect the cone or rod pathway. Localized cone dystrophies (4/91) are limited to certain retinal areas.

**Zusammenfassung.** Basierend auf einer retrospektiven Analyse klinischer und elektrophysiologischer Befunde in einer Serie von 91 Patienten mit progressiven Zapfendystrophien und einer Literaturübersicht wird eine erweiterte Klassifikation der progressiven Zapfendystrophien vorgestellt. Die Differenzierung erfolgt aufgrund typischer Veränderungen im Elektroretinogramm. 4 Hauptgruppen mit 10 Untergruppen werden unterschieden. Generalisierte Zapfendystrophien sind am häufigsten (76/91), betreffen alle Zapfentypen und können abhängig von der Beteiligung der Stäbchen weiter differenziert werden. Bei selektiven Zapfendystrophien (8/91) zeigt das Farbelektroretinogramm, daß die 3 Zapfentypen unterschiedlich stark betroffen sind. Sie werden nach dem vorwiegend betroffenen Zapfensystem unterteilt. Zusätzliche intraretinale Transmissionsdefekte können bei Zapfendystrophien vorkommen (3/91). Sie können durch das veränderte B/A-Amplitudenverhältnis im Elektroretinogramm entdeckt werden und in der Zapfen- oder Stäbchentransmission auftreten. Lokalisierte Zapfendystrophien (4/91) sind auf bestimmte retinale Orte begrenzt.

## Introduction

Progressive cone dystrophies are a heterogeneous group of disorders with a variety of clinical findings. Characteristic symptoms and signs are photophobia, visual loss, color vision defects, and central scotomas. Their expression, however, is variable [13, 26, 27, 41]. Ophthalmoscopic findings include bull's-eye maculopathy, central scars, pigment irregularities, or normal fundi [13, 26, 27, 41]. They are unspecific for cone dystrophies, and a large variability of fundus abnormalities has been described even within a single family [19, 27, 41]. Therefore, ophthalmoscopic findings are not helpful for either the diagnosis or the classification of cone dystrophies. The diagnosis can be established with electroretinography. In nearly all patients, reduced or missing responses at light adaptation and to 30-Hz flicker stimulation are seen. The extent of amplitude reduction, however, is variable and the correlation with clinical signs is poor [26].

In 1963, Goodman et al. [13] introduced a classification of cone dysfunction syndromes. Subsequently, progressive cone dystrophies were subdivided into cone and cone-rod dystrophies, depending on the amount of rod involvement [3, 4, 27]. Several "new" diseases involving cone dysfunction have recently been described; they were named according to either ophthalmoscopic or specific functional findings [5, 9, 16, 18, 30, 32, 38, 45]. A comparison between these patients is difficult due to variations in the descriptions, follow-up periods, and tests used.

On the basis of a large series of patients with cone dystrophies and a review of the literature, we propose an extended classification of progressive cone dystrophies. The subdivisions are made according to functional properties and mainly depend on electroretinographic characteristics. This classification is not considered to be defin-

**Table 1.** Classification of progressive cone dystrophies

| Present classification | Goodman et al. [13] | Berson et al. [3] | Krill et al. [27] |
|---|---|---|---|
| *Generalized cone dystrophies:* | | | |
| Cone dystrophies | Progressive cone degenerations | Progressive cone degeneration | Diffuse cone disease |
| Cone-rod dystrophies | Generalized cone-rod deficiencies where symptoms relating to the cone dysfunction predominate | Progressive cone-rod degeneration | Cone-rod disease |
| *Selective cone dystrophies:* | | | |
| Cone-rod dystrophy with blue cone hypersensitivity (=enhanced S cone syndrome) | | | |
| Predominant blue cone dystrophy | | | |
| Predominant red cone dystrophy | | | |
| *Cone dystrophies with retinal transmission defects:* | | | |
| In the cone pathway | | | |
| In the rod pathway | | | |
| With supernormal b-waves | | | |
| With reduced b-waves | | | |
| *Localized cone dystrophies:* | | | |
| Central cone dystrophy | | | Central cone involvement |
| Peripheral cone dystrophy | | | Peripheral cone disease |

itive but may evolve as new information becomes available. The purpose of this classification is to delineate the various functional characteristics of progressive cone dystrophies. Finally, it may serve as a reference for molecular genetic analysis.

## Patients and methods

The clinical records and electrophysiological data of 91 patients examined at the University Eye Clinic in Essen during the last 10 years were analyzed retrospectively. The inclusion criteria for this study were: (1) cone dysfunction as determined either clinically (including photophobia, visual loss, central scotoma, and color vision defects) or electroretinographically (including reduced or missing responses at light adaptation or 30-Hz flicker stimulation), (2) predominant cone dysfunction in the presence of rod involvement, and (3) a progressive course of the disease.

A basic ophthalmological examination and standard electroretinography were performed in all patients; visual fields (65/91), color vision (65/91), and electrooculography (73/91) were examined in most patients. Color electroretinograms were recorded in a subset of 10 patients, preferably in those showing unusual findings on the standard electroretinogram. Color vision was examined with Ishihara's pseudoisochromatic plates, the panel D15 desaturé test, the Farnsworth-Munsell 100-hue test, or Nagel's anomaloscope. Visual fields were tested using Goldmann perimetry or the Tübingen automatic perimeter. Electrooculograms were recorded according to the method of Rhode et al. [39].

Our electroretinographic recording technique has been described in detail previously [24]. Recordings were done according to the standard for clinical electroretinography [29]. The stimulus duration was 10 ms. Six different light intensities (stimuli 1–6) increasing in steps of 1 logarithmic unit from the b-wave threshold of the normal eye were used for the dark-adapted recordings. The maximal light intensity was 7.8 cd sm$^{-2}$. 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. White light from a xenon light source served as the stimulus in all examination using standard electroretinography. For color electroretinography, Kodak Wratten filters were used for blue, blue-green, green, yellow, and red stimuli (filters 98, 44A, 61, 16, and 29 respectively), the method has been described in detail elsewhere [22]. The color stimuli were not matched in photopic luminance. The color electroretinograms were recorded with the same protocol used for the standard electroretinograms.

## Results

On the basis of electroretinographic and clinical findings in 91 patients and descriptions in the literature, we have distinguished 4 categories with 10 subgroups of progressive cone dystrophies, an overview of which is given in Table 1.

### Generalized cone dystrophies

In generalized cone dystrophies, blue-, green-, and red-sensitive cones are similarily affected. According to the presence of rod involvement, they may be subdivided. These two groups correspond to the classic distinction between cone and cone-rod dystrophies [3, 4, 13, 27] (Table 1). The clinical and electrophysiological findings obtained in our patients with generalized cone dystrophies have been described in detail elsewhere [26]. The basic features are summarized as follows. In both subgroups the age of onset varies between 5 and 75 years, with the mean being 20 years; similar ranges have been described in the literature [27, 41]. Both sexes seem to be equally involved [26, 41].

*Cone dystrophy.* The dystrophy was limited to the cones in 10/91 patients, 2 of whom were blood relatives (father
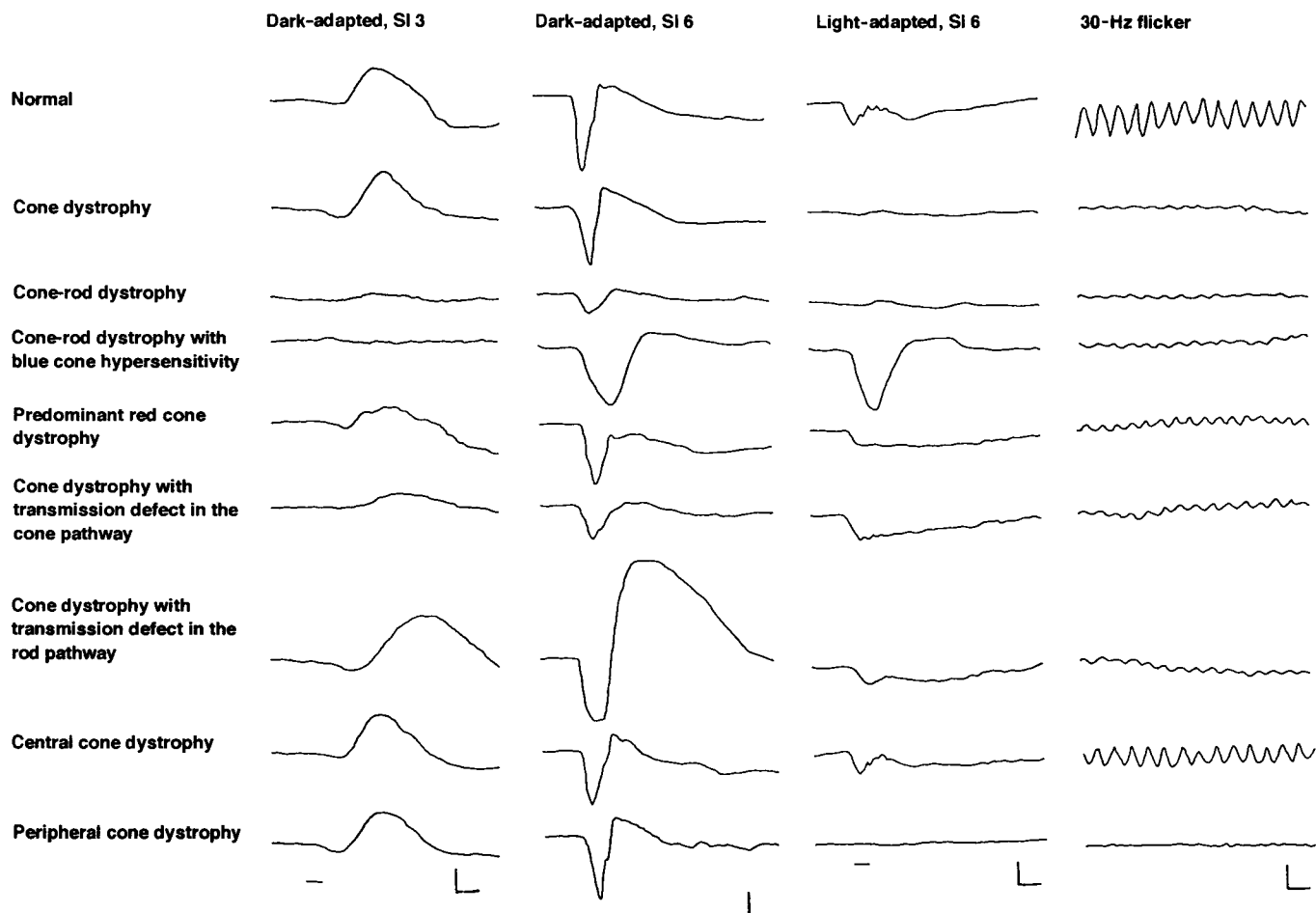
Fig. 1. Typical standard electroretinography responses for a normal subject and patients with different types of progressive cone dystrophies. Each type is identified to the *left* of the row of recordings. The *outer left column* shows the recordings obtained under dark-adapted conditions at stimulus intensity (*SI*) 3, and the *middle left column* shows those obtained at SI 6. The *middle right column* shows the recordings obtained under light adaptation at SI 6, and the *outer right column* shows those obtained at 30-Hz flicker stimulation. The *vertical calibration marks* indicate 100 μV, and the *horizontal marks* indicate 50 ms for flicker stimulation and 20 ms for all other responses

and son). Visual acuity was reduced to $0.2 \pm 0.17$. Achromatopsia and central scotomas were found in all but 2 patients. Pigment irregularities within the macular area were seen in 7 patients. The standard electroretinogram showed reduced responses under light-adapted conditions and 30-Hz flicker stimulation, and normal responses under dark-adapted conditions (Fig. 1). Color electroretinograms were not recorded in these patients. Electrooculography gave normal results. Goodman et al. [13] and Berson et al. [4] call this pattern progressive cone degeneration, and Krill et al. [17] refer to it as diffuse cone disease.

*Cone-rod dystrophy.* Most patients (66/91) with cone dystrophies had additional rod involvement. In all 5 patients (2 families) were related, 2 sisters in one family and 1 sister and 2 brothers in the other family. Visual acuity was reduced to $0.16 \pm 0.17$. Color vision defects were seen in nearly all patients tested and varied from red-green deficiencies to achromatopsia. Visual fields showed central, paracentral, or midperipheral scotomas. Fundus-

copic findings varied from normal in one-third of the patients to severe central and midperipheral pigment clumping. The standard electroretinogram showed reduced or missing responses under conditions of light adaptation and 30-Hz flicker (Fig. 1). The amplitudes at dark adaptation were reduced. Depending on the amplitude reduction of dark-adapted responses, subtypes could be defined that correlated with peripheral visual field defects and reductions in the light rise of the electrooculogram [26]. The color electroretinogram recorded in one patient showed equally reduced responses to all color stimuli under light-adapted conditions (Fig. 2).

Goodman et al. [13] call this pattern generalized cone-rod deficiencies where symptoms relating to the cone dysfunction predominante, Berson et al. [3] refer to it as progressive cone-rod degeneration, and Krill et al. [27] call it cone-rod disease. Inverse retinitis pigmentosa is another term that has been used by several authors for cone-rod dystrophies with marked central fundus abnormalities. Depending on the retinal area primarily involved, further subtypes of cone-rod dystrophies have been determined psychophysically [50].
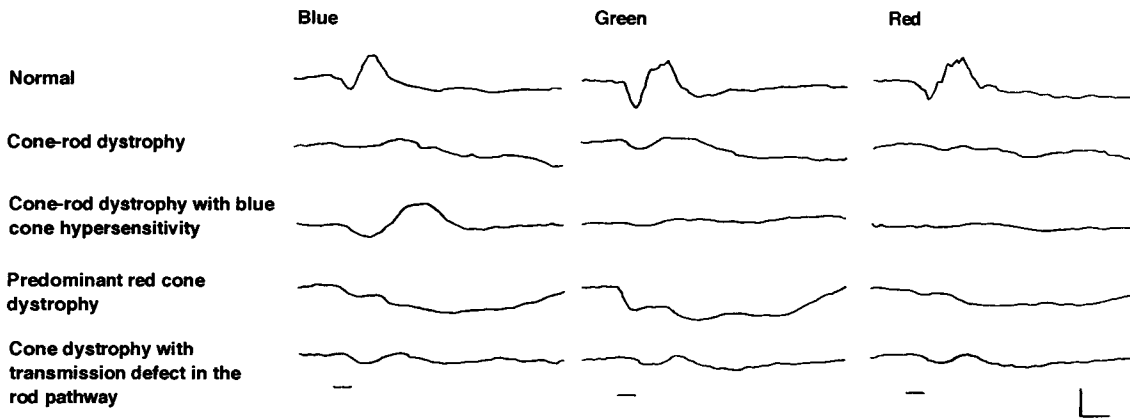
Fig. 2. Color electroretinography responses obtained at maximal stimulus intensity under light adaptation for a normal subject and patients with different types of progressive cone dystrophies. Each type is identified to the *left* of the row of recordings. The *left column* shows the recordings obtained with blue stimuli, the *middle column* shows those obtained with green stimuli, and the *right column* shows those obtained with red stimuli. The *calibration marks* correspond to those described for Fig. 1

## Selective cone dystrophies

In selective cone dystrophies the three cone types are variably affected. They may show either reduced function or hypersensitivity. Selective defects of the green-sensitive cones have not yet been described, but we expect that they exist. Possibly predominant dysfunctions of the green-sensitive cones are more easily overlooked than are dysfunctions of cones with sensitivity at either end of the spectrum of visible light.

*Cone-rod dystrophy with blue cone hypersensitivity.* Six patients with this autosomal, recessively inherited condition, also termed "enhanced S cone syndrome", have been observed by us [21, 30]. Two of them were women and four were men, including two brothers. The visual acuity varied between 0.05 and 0.80. Color vision was normal, and visual fields were mostly normal. Funduscopic findings were yellow flecks along the vascular arcades. The macular area may look normal or show a cystoid appearance, and the development of the latter concurs with visual deterioration. The light rise of the electrooculogram was reduced. Electroretinographic responses were recordable only to bright stimuli, but the amplitude-intensity function was much steeper than normal. The standard electroretinogram showed similar responses at dark and light adaptation, and in some patients the amplitudes at light adaptation were much larger than the normal range (Fig. 1). The 30-Hz flicker response was reduced. The electroretinographic responses showed no change for up to 7 years after the primary examination. The most important diagnostic techniques are the color visual field test and color electroretinography [18, 25]. Color visual field testing revealed normal sensitivity for blue targets and severely reduced sensitivity for red and green targets. The color electroretinograms, recorded in all six patients, showed large responses both to blue and blue-green stimuli at dark and light adaptation and to flicker stimulation (Fig. 2). Small or unmeasurable responses to green, yellow, and red were seen under all stimulus conditions. Psychophysical spectral sensitivity measurements revealed the presence of all three cone photopigments and the absence of rod function [25]. Similar cases have been described by Marmor et al. [30] and Jacobson et al. [18, 19]. The discrepancy between normal color vision and reduced sensitivity to red and green stimuli in visual field and electroretinographic testing can be explained by the retinal location tested. Spectral sensitivity measurements revealed a marked loss of red cone sensitivity in the midperiphery [18], which was only mild centrally [25]. Some patients who showed comparable findings on the standard electroretinogram, which had not been definitely proven by either color visual field or color electroretinographic testing, were given various diagnoses [7, 9, 20, 35].

*Predominant blue cone dystrophy.* To date we have not seen a patient with this entity. Two families with a dominantly inherited, slowly progressive cone dystrophy have been reported [5, 45]. Tritan color vision defects were the predominant sign in both families, even in young patients with normal visual acuity and electroretinograms. In the first family, five patients were seen [5]. They had normal visual acuity and pigment irregularities in the macular area. The standard electroretinographic recordings were normal except for the 30-Hz flicker response. Electroretinograms recorded with chromatic stimuli indicated a defect of the blue-sensitive cones. The second family had 13 affected members [45]. Visual loss occurred in the third to fourth decade of life. The size of pigment epithelial defects increased with age. The electroretinograms showed absent or reduced cone responses in older patients. The authors describing the second family claimed that these families represented two different entities because the visual acuity and electroretinographic responses of the second family were more reduced than those of the first family. The patients in the first family, however, were considerably younger than those in the second family and, therefore, only a longer follow-up period, or genetic findings may prove whether the primary defects in these families are different.

*Predominant red cone dystrophy.* Two men with this entity presented with a slow progressive visual loss to 0.2 and

0.4 respectively, in the fourth decade of life. Central scotomas were present in both patients. In one patient, color vision defects progressed from protanomaly to achromatopsia over a period of 20 years [22]. The standard electroretinogram revealed reduced flicker responses, subnormal a-waves, and small or unmeasurable b-waves at light adaptation (Fig. 1). The color electroretinographic responses to red stimuli recorded in both patients were severely reduced. There were, however, well-preserved responses to green stimuli (Fig. 2). Missing red-sensitive cone function and normal blue- and green-sensitive cone function were confirmed with spectral sensitivity measurements [42]. A family with a predominant red cone dysfunction and a red-cone pigment gene defect has been described by Reichel et al. [38]. Standard electroretinograms elicited with single flashes at light adaptation were not reported for these patients. It remains unclear as to whether they had reduced b-waves like our patients or not. The color electroretinographic findings obtained in this family seem to be comparable with those observed in our patients. Heredity could not be determined in our patients, whereas an x-linked inheritance was found by Reichel et al. [38]. Although some features in their patients and our subjects are different, it remains to be determined as to whether these patients suffer from the same entity or two different entities.

## Cone dystrophies with retinal transmission defects

The a-wave of the electroretinogram corresponds to the change in dark current along the photoreceptors. When diminished, it is said to be an indicator of receptor dysfunction. The b-wave originates in the inner retinal layers and is therefore considered to be an indicator of retinal transmission properties. In receptor dysfunctions, the a- and b-waves are usually reduced to the same extent, i.e., the b/a-wave ratio remains normal, indicating that there is a single defect located within the receptors. In some patients, however, the b-wave is either more or less reduced than the a-wave, i.e. the b-/a-wave ratio is altered, pointing to additional defects within the retinal transmission. Although it is simple to suspect a defect in retinal transmission, it is difficult to locate it because of the several steps involved. Changes in signal transmission may be caused by, e.g., inappropriate messengers between receptors and bipolar cells, inappropriate sensitivity of hyperpolarizing or depolarizing bipolar cells, or alterations in the time course of the intercellular ionic exchange due to membrane or Müller cell defects [2, 33, 40, 46–48, 52].

*Transmission defects in the cone pathway.* Two men with a reduced visual acuity of 0.05 and 0.40, respectively, were observed [23]. Color vision testing revealed deuteranomaly in one patient and achromatopsia in the other. Funduscopic findings included pigment irregularities, bull's-eye maculopathy, and pale optic disks. The light rise of the electrooculogram was reduced. Color electroretinograms were not recorded. The standard electroretinogram obtained at light adaptation showed nor-

mal to subnormal a-wave amplitudes and severely reduced b-waves and b/a-wave ratios, a so-called "negative electroretinogram" (Fig. 1). In the dark-adapted responses, the b-wave reduction was less pronounced. The flicker responses were reduced. Similar electroretinographic responses have been seen in animal experiments when the depolarizing bipolar cells are blocked by intravitreal application of APB (2-amino-4-phosphonobutyric acid) [47]. A defect within the depolarizing bipolar cells may explain the electroretinographic findings obtained on our patients. Nine patients with cone dystrophies and similar electroretinographic characteristics have been reported under different terms [15, 49, 53].

Another two patients, mentioned above as having predominant red cone dystrophy, showed a negative electroretinogram under light-adapted conditions. However, the time course of visual loss was much slower in these patients. The deuteranomaly observed in one patient with transmission defects of the cone pathway indicates the retinal defects in these patients to be different. In addition, the inheritance of receptoral defects and defects within the transmission may be independent.

Patients with progressive cone dystrophies and negative electroretinograms have to be distinguished from those with x-linked congenital retinoschisis, incomplete congenital stationary night blindness, and paraneoplastic night blindness. Characteristically these entities show a b-wave reduction. A differential diagnosis, however, is not possible with the electroretinogram [23]. X-linked retinoschisis can be excluded by the specific ophthalmoscopic findings [24]. Visual deterioration does not occur in congenital stationary night blindness [31, 52]. In acquired night blindness with progressive functional loss, a paraneoplastic syndrome should be excluded [2].

*Transmission defects in the rod pathway. Supernormal rod b-waves:* One man had a visual acuity of 0.3, achromatopsia, and normal visual field and ophthalmoscopic findings [10]. The standard electroretinogram showed normal a-wave and supernormal b-wave amplitudes at dark adaptation (Fig. 1). The b-/a-wave ratios were elevated. The b-wave implicit times were markedly delayed. Under light-adapted conditions, the a- and b-wave amplitudes were reduced, as was the flicker response. The color electroretinogram obtained in this patient showed reduced responses to all stimuli at light adaptation and to 30-Hz flicker stimulation (Fig. 2). The standard and color electroretinographic responses at light adaptation were similar to those in generalized cone dystrophies. The electroretinogram remained unchanged over a period of 9 years. In all, 9 patients described in the literature [1, 8, 12, 14, 51] were reviewed by Foerster et al. [10], and 3 additional patients were recently described by Sandberg et al. [43].

Supernormal b-wave amplitudes with a delayed time course have been attributed to elevated retinal cyclic guanosine monophosphate levels on the basis of animal experiments [43, 44]. Recent findings indicate an important role for cyclic guanosine monophosphate in the regulation of membrane conductance in retinal bipolar cells [33].

*Reduced rod b-waves*: We have not yet seen a patient fitting into this category. Miyake et al. [32] described four men suffering from progressive visual loss and photophobia. They had variable color vision and visual field defects. All had a bull's-eye maculopathy. Their electroretinograms at dark adaptation showed normal a-waves and severely reduced b-waves and b/a-wave ratios. Under light-adapted conditions, their electroretinograms showed a similar reduction in a- and b-wave amplitudes. These electroretinograms are similar to those seen in congenital stationary night blindness; however, the clinical findings and the progression allow a differentiation.

## Localized cone dystrophies

In most patients with cone dystrophies, all retinal areas seem to be similarily affected, although different patterns of regional dysfunction can be seen [50]. The electroretinogram, which is a panretinal summed response, does not correlate with visual acuity [26]. Some patients, however, show striking differences between electroretinographic responses and visual acuity, indicating localized forms of cone dystrophy. The separation of central and peripheral cone dystrophies was first described by Krill et al. [27]. These regional differences may indicate that a defect is located not within the cones but in closely connected structures such as the pigment epithelial cells or the interphotoreceptor matrix [6, 17, 28].

*Central cone dystrophy.* Two women presented with severe photophobia. Their visual acuity was 0.1 and they had an achromatopsia in the Nagel anomaloscope. Large color plates, however, were named correctly. In both patients, slight central pigment irregularities could be seen. Their electrooculograms and standard electroretinograms were completely normal (Fig. 1). Several macular dystrophies, e.g., Stargardt's disease, may lead to visual loss, color vision defects, and relatively normal electroretinograms. The severe photophobia observed in our patients, however, is not common in these macular dystrophies and indicates a central cone dystrophy. Similar cases have been reported previously [11, 27].

*Peripheral cone dystrophy.* Two patients, one women and one man, had normal visual acuity of 0.9–1.0. In both patients, the fundus showed pigment irregularities in the macular area, whereas the periphery and the vessels were normal. Color vision was normal, but the responses on the standard electroretinogram were severely reduced at light adaptation and flicker stimulation (Fig. 1). The light rise in the electrooculogram was reduced. Their normal visual acuity and color vision separates them from the category of generalized cone dystrophies. Few patients with comparable findings have previously been reported [27, 34, 36, 37].

## Discussion

Classifications usually suffer from certain limitations and we are well aware of some in our proposal. Not all of our patients were examined by all of the tests mentioned; e.g. color electroretinography was recently included after it proved to be helpful in identifying cone-rod dystrophy with blue cone hypersensitivity [18, 25]. Therefore, we may have overlooked further defects or misplaced a patient in a certain subgroup. Moreover, it cannot be determined as to whether certain functional defects are transient or final. In some patients, progression is a matter of months, and in others it takes decades. Therefore, a patient included in one group may have to be repositioned after reexamination years later. Although we increased the number of subtypes of progressive cone dystrophies to ten, there is nonetheless an extensive variability within each group. This may be due to the inclusion of more than one entity in a group or to a variation in the expressivity of a disease between individuals. The mode of inheritance was not used in this classification for two reasons. First of all, most cases in our series and in the literature are single cases. Second, one can find different functional patterns with the same mode of inheritance, indicating that, e.g., there is more than one type of dominantly inherited cone dystrophy [4, 5, 45]. Not included in this series were patients suffering from certain entities with typical morphological findings involving the posterior pole: dominantly inherited drusen, pattern dystrophies, and Best's or Stargardt's disease. The electroretinogram in these diseases is usually normal or slightly abnormal, and the primary defect does not seem to be located in the cones.

This classification summarizes the various functional findings that have been seen in progressive cone dystrophies and is therefore helpful in the diagnosis of patients. Moreover, it reveals that extensive examination is necessary to diagnose a patient correctly. Our recommendation for the examination of patients with cone dystrophies is shown in Table 2. The clinical examination should include visual acuity testing, ophthalmoscopy, and visual field measurements. In color vision testing, different tests should be used: pseudoisochromatic plates, arrangement tests, Nagel anomaloscope, and large color plates to test the peripheral color vision. Standard electroretinography should be performed in accordance with the standard for clinical electroretinography [29], including dark- and light-adapted recordings and 30-Hz flicker stimulation. Color electroretinography with blue, green, and red stimuli at light adaptation and flicker is necessary for the detection of selective cone dystrophies [22]. Electrooculography and fluorescein angiography are often

**Table 2.** Recommendations for the examination of patients with progressive cone dystrophies

Visual acuity
Visual fields
Color vision: pseudoisochromatic plates; arrangement tests: panel D-15, Farnsworth-Munsell 100 hue; Nagel anomaloscope; large color plates
Ophthalmoscopy
Standard electroretinography [29]
Color electroretinography: blue, green, and red stimuli at light adaptation and flicker stimulation

not helpful. Color visual field testing and sophisticated psychophysical tests, e.g. spectral sensitivity measurements and transient tritanopia, give interesting results, but their general use is limited because the equipment is rare and good cooperation of the patients is necessary.

We encourage our patients scheduled for long-term follow-up with repeated extensive clinical, electrophysiological, and psychophysical examinations to understand the course of the disease and to get better data for patient counseling. Only some of our patients are interested as long as no treatment is offered. However, long-term follow-up studies involving numerous patients are lacking, and our knowledge about what will happen to an affected child is limited and based on what we see in relatives and individuals of similar lineage.

Cone dystrophies are considered to represent a primary receptor dysfunction and have been thought to affect all cone types to a more or less similar extent. These generalized cone dystrophies were the most frequent in our series. This classification, however, includes two new pathogenetic concepts for cone dystrophies. Selective cone dystrophies affecting only one or two cone types and cone dystrophies with retinal transmission defects could be clearly separated. The long period of observation of some of these patients indicates that these functional defects are specific entities and not short-term occurrences during progression. We believe that these entities are more frequent but that they may have been overlooked because extensive examinations are necessary to find these defects.

We hope that a more exact classification can be based on molecular genetic findings, indicating which genetic defect induces what kind of functional loss and during which time course. Moreover, the relationship between genetic and functional defects and ophthalmoscopic findings should be defined. At the moment, however, in only one case of cone dystrophy has a genetic defect been identified [38]. Therefore, a classification based on functional findings seems to be most appropriate at this time. This classification may prove to be useful in the selection of patients for molecular genetic examinations.

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