Cone-Rod Dystrophy With Serpentine-like Retinal Deposits

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Objective: To describe the clinical and electrophysiologic findings in a novel retinal dystrophy.

Methods: Ophthalmologic and electrophysiologic examinations were performed in 3 affected members of 1 family: a 10-year-old girl, her 30-year-old mother, and her 59-year-old maternal grandfather. Electrooculography (EOG) and electroretinography (ERG) were performed according to the standards of the International Society for Clinical Electrophysiology of Vision.

Results: In all 3 family members, gray, serpentine-like deposits were seen at the level of the retinal pigment epithelium (RPE). These were most distinct in the child, less prominent in her mother, and barely visible in the grandfather. Visual acuity was 20/25 OU in the child and 20/200 OU in both adults. Visual field testing showed normal outer limits and small paracentral scotomas in both adults. Electroretinographic recording revealed slightly reduced amplitudes in the 10-year-old girl, cone dysfunction in her mother, and cone-rod dysfunction in the grandfather. Multifocal ERG responses were reduced but recordable in the mother. The EOG light peak amplitude was normal in both females and borderline in the grandfather. The light peak was delayed in all 3 patients.

Conclusions: Similar deposits at the level of the RPE have not been described in other inherited retinal dystrophies. This family appears to have a novel form of cone-rod dystrophy with deposits at the level of the RPE and probable autosomal dominant inheritance.

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A LARGE VARIETY of cone and macular dystrophies have been described.[1-7] The most common clinical sign is the progressive loss of visual acuity. Additional findings may include central or paracentral scotomas and color vision deficiency. Ophthalmoscopic findings range from very subtle retinal pigment epithelium (RPE) alterations to severe atrophic changes of the retina and RPE. Macular and cone dystrophies can be distinguished by Ganzfeld electroretinography (ERG): in macular dystrophies the amplitudes are mostly normal or only slightly reduced, whereas the cone dystrophies are characterized by severely reduced or missing cone responses.[3-7]

Accumulation of material at the level of the RPE has been observed in various hereditary retinal dystrophies, eg, Best disease,[1] Stargardt disease,[2] and dominant radial drusen.[8] To the best of my knowledge, gray, serpentine-like deposits have not been reported previously. The clinical and functional findings of a novel form of cone-rod dystrophy with serpentine-like deposits at the posterior pole are described in the present study.

RESULTS

PATIENT 1

At her first ophthalmologic examination, performed in the Krankenhaus Friedrichshain at 5 years of age, visual acuity was 20/25 OU (OD: + 2.25 D – 2.0 D × 105°; OS: + 2.25 D – 0.5 D × 180°). Gray deposits were observed at the posterior pole and in the midperiphery. Color vision testing with the 28 Hue de Roth test gave normal results for both eyes. An EOG showed a delayed light peak (17 minutes in both eyes) with normal amplitude (OD: 215%, OS: 230%). Electroretinographic responses were recordable; however, detailed analysis was hampered by multiple artifacts.

At the age of 10 years, the patient was referred to me for further evaluation. She complained about slightly reduced visual acuity. No other signs of visual dysfunc-

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PATIENTS AND METHODS

Three affected patients of 1 family were examined: a 10-year-old girl (patient 1), her 30-year-old mother (patient 2), and her 59-year-old maternal grandfather (patient 3). All 3 patients were only children. The grandfather reported that his mother had reduced visual acuity throughout most of her life, although the degree of her visual loss had been less severe than his. She could see sufficiently to live on her own until she died at the age of 79 years. Results of her ophthalmologic examinations were not available.

Earlier ophthalmologic and electrophysiologic examinations of all 3 patients were performed by Ä. Petzschmann, MD (Department of Ophthalmology, Krankenhaus Friedrichshain, Berlin, Germany). In her evaluation, electro-oculography (EOG) was performed according to the method of Rhode et al.[9] The lower limit of the normal range for the light peak amplitude was 152%. The upper limit of the normal range was less than 11 minutes from the onset of the light phase to the light peak maximum. Electroretinograms were recorded using a Toennies DA II system (Toennies, Freiburg, Germany) and a 100-D contact lens.

The most recent evaluation of EOG and ERG was performed as described in detail previously.[10,11] The recording techniques were in accordance with clinical standards.[12-14]

Electro-oculography was performed with maximally dilated pupils (2.5% phenylephrine hydrochloride and 0.5% tropicamide) using a method described by Behrens et al.[15] A Ganzfeld with red light-emitting diodes for fixation was used for stimulus presentation and induction of eye movements. The duration of measurement was 56 minutes. Within the first 40 minutes, the luminance was decreased monotonically by 4 decades (from 2000 to 0.2 apostilb) in a logarithmic manner to become independent of the previous state of adaptation. After this adaptation procedure, a luminance step of 4 decades induced the light peak. The potentials were recorded with a direct current amplifier. The response was characterized by the ratio between the maximum amplitude and the amplitude before the luminance was increased (light peak vs baseline). The normal ranges for baseline and light peak were defined by calculation of the median values and the 95% confidence intervals in one eye of 40 probands. For the baseline, the normal median was 0.47 mV and the lower normal range was 0.25 mV. For the light peak, the normal median was 186% and the lower normal range was 161%. The light peak maximum was reached within 8.4 minutes (normal median; upper normal range, 11 minutes).

A Nicolet Spirit (Nicolet Instrument Technologies Inc, Madison, Wis) in combination with a Nicolet Ganzfeld was used for the ERG recordings. These were performed with Jet contact lens electrodes (Universo SA, La Chaux-de-Fonds, Switzerland) and with maximally dilated pupils. Duration of dark adaptation was 30 minutes. Stimulus duration was 0.1 ms. The maximum light intensity was 10 $(cd \cdot s)/m^2$. After the dark-adapted responses were recorded, eyes were light-adapted for 10 minutes with white light ($30 cd/m^2$). Single-flash and 30-Hz flicker recordings were performed in the same adaptation light with white stimuli of maximum light intensity. Averaging was not performed. The normal ranges for ERG response amplitudes and implicit times were defined by calculation of the median values and 95% confidence intervals in one eye of 20 age-similar probands. The lower normal range of the amplitudes varied from 79% to 86% of the normal median for different stimulus conditions and ages. To avoid presentation of extensive normative data, values reported as reduced are given as percentages of the age-similar normal median. Values within the normal range are reported as normal without numeric specification.

Multifocal ERGs were recorded and analyzed with the VERIS Clinic II System (Tomey, Erlangen, Germany). A black-and-white pattern of 61 fields presented on a monitor was used for stimulation. Complete recording time was 4 minutes, divided in 8 sections of 30 seconds. Recordings were performed with a Jet contact lens electrode and with maximally dilated pupils. The mode of data analysis with the VERIS System has been described in detail by Sutter and Tran.[16] The VERIS Clinic II System allows measurement of the amplitudes and implicit times of the central response and of the ring sums of paracentral and peripheral responses. The normal ranges for these amplitudes and implicit times were defined by calculation of the median values and the 95% confidence intervals in one eye of 15 age-similar probands.

All examinations were performed in conformity with the Declaration of Helsinki after informed consent was obtained.

tion (in particular, photophobia) were noted. Visual acuity was 20/40 OD ($+2.25$ D -1.5 D $\times 162°$) and 20/25 OS ($+1.25$ D -0.5 D $\times 1°$). Findings in the anterior segments were unremarkable. Ophthalmoscopy revealed loss of foveal reflex. On biomicroscopic examination, gray material appeared to be located at the level of the RPE (**Figure 1**). The gray material was accumulated in serpentine-like lines, and the RPE appeared normal between these lines. The retina was elevated in places where more material was present. Material deposition was most prominent at the posterior pole and was less extensive toward the midperiphery. Gray material was not seen in the outer periphery. Mild choriocapillaris atrophy was visible below the optic disc and in the nasal midperiphery. The optic discs showed temporal pallor. The caliber of the retinal blood vessels was normal.

Results of color vision testing with the desaturated panel D15 test were normal in both eyes. Electroretinographic recording showed normal a-wave amplitudes at dark and light adaptation (**Figure 2**). B-wave amplitudes were slightly reduced to 75% of the normal median at dark and light adaptation. B-wave implicit times were normal. The 30-Hz flicker response was normal in amplitude and implicit time.

PATIENT 2

The mother of patient 1 had had severely reduced visual acuity and horizontal nystagmus since childhood. At her earliest available ophthalmologic examination, performed in the Krankenhaus Friedrichshain at 18 years of age, visual acuity was 20/200 OU. Gray deposits were observed at the posterior pole. Color vision testing with
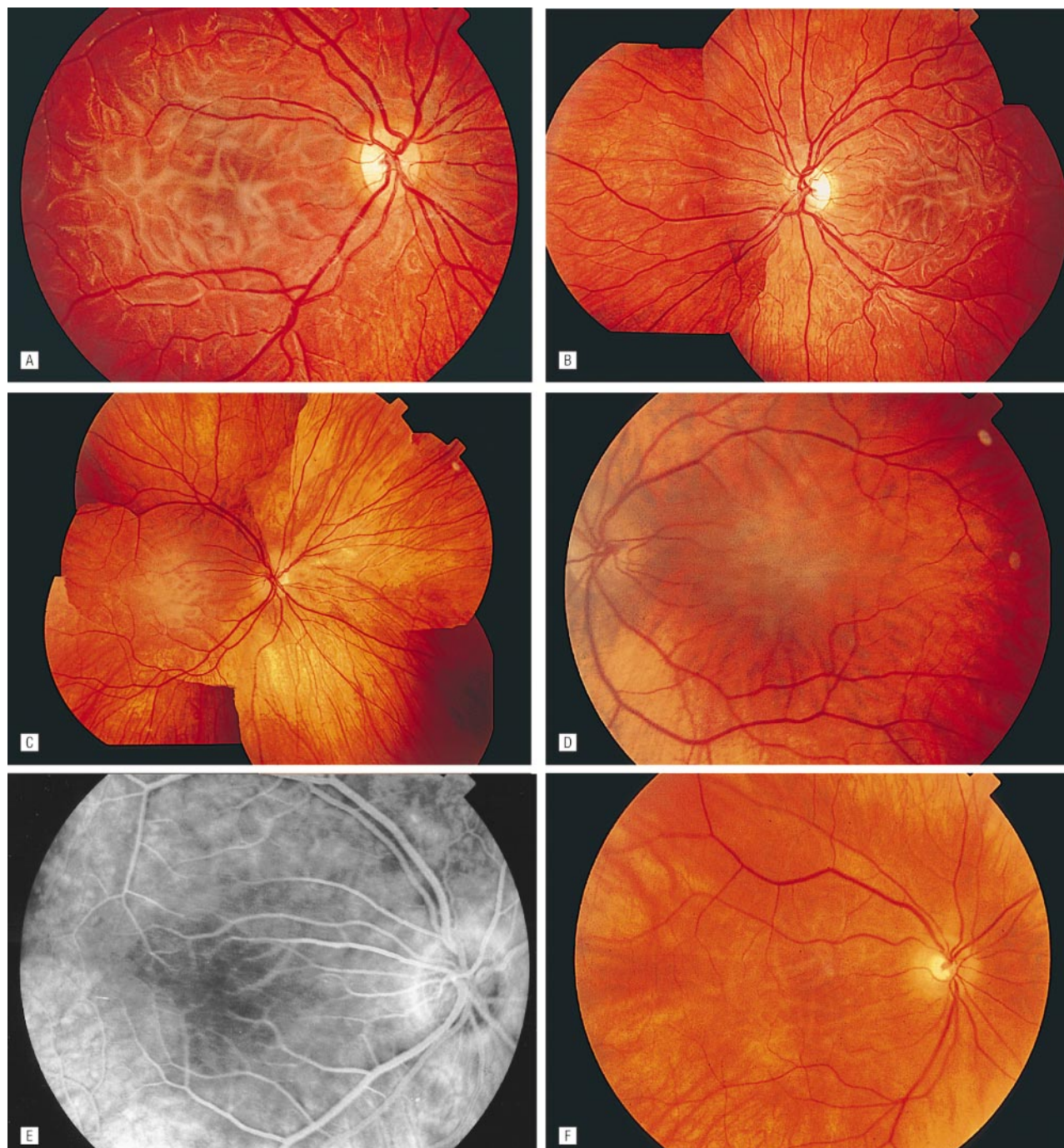
Figure 1. *Fundus photographs. Patient 1: Posterior pole of the right eye (A) and composite of the posterior pole and midperiphery of the left eye (B). Patient 2: Composite of the posterior pole and midperiphery of the right eye (C), posterior pole of the left eye (D), and late phase of the fluorescein angiogram (E). Patient 3: Posterior pole of the right eye (F).*

the 28 Hue de Roth test gave normal results for both eyes. Results of dark adaptation testing with a Hartinger adaptometer were normal. An EOG showed a delayed light peak (13 minutes in both eyes) with normal amplitudes (181% OD, 180% OS). The ERG recordings showed normal amplitudes at dark adaptation and reduced amplitudes at light adaptation.

At 30 years of age she was referred to me for further evaluation. Her visual acuity remained unchanged at 20/200 OU without improvement with glasses. Findings in the anterior segments were unremarkable. On oph-

thalmoscopy, the foveal reflex was lost, and gray deposits at the level of the RPE were present (Figure 1). In contrast to the findings in her daughter, the deposits were more confluent and did not extend beyond the macular area. The thickness of the gray material was variable. Fluorescein angiography showed blocking of the background fluorescence at the posterior pole, but no leakage of fluorescein (Figure 1). There were no signs of choroidal folds in the angiogram. Partial midperipheral choriocapillaris atrophy was present nasal to the optic disc. The optic discs were normal.
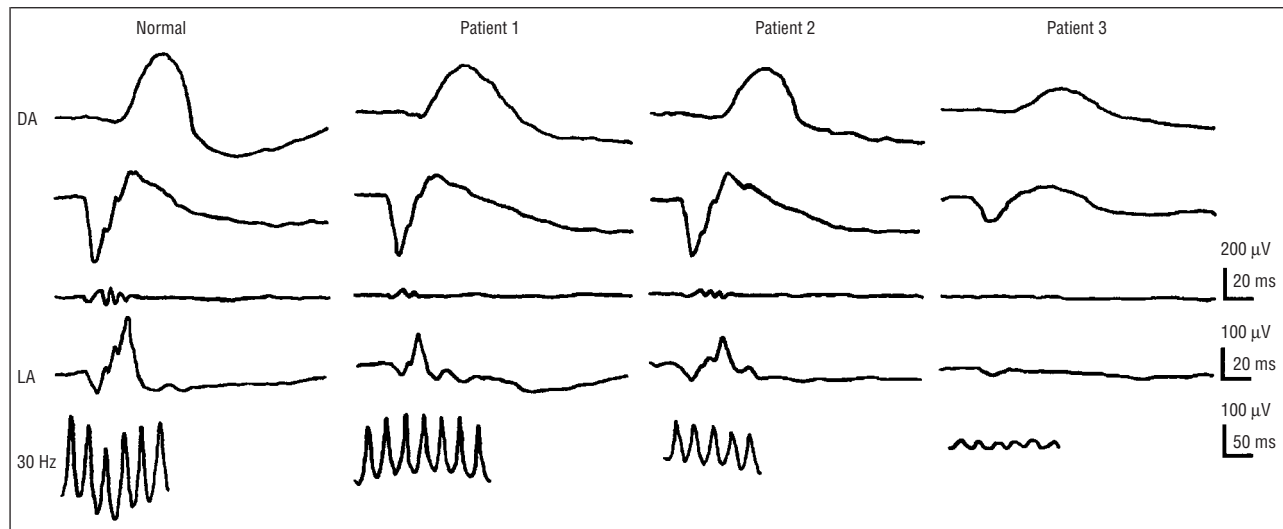
Figure 2. *Electroretinograms showing the responses to white stimuli of a normal proband and patients 1 to 3. DA indicates responses at dark adaptation at low (first row) and maximum (second row) stimulus intensity. The next row shows the dark-adapted oscillatory potentials. LA indicates single-flash responses at light adaptation. The cone flicker response was measured at 30 Hz.*
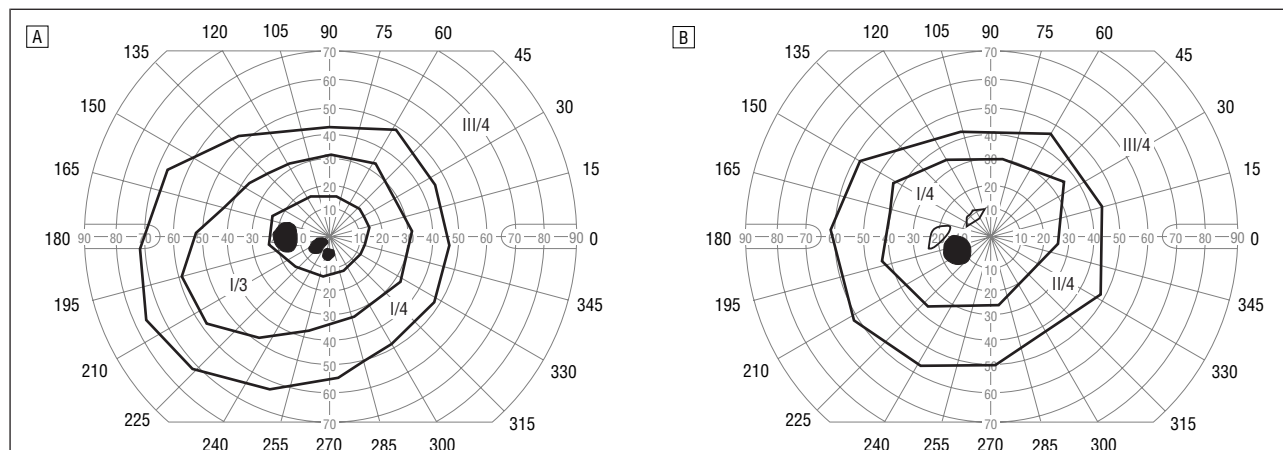

Figure 3. *Goldmann visual fields of the left eyes of patients 2 (A) and 3 (B)*

Goldmann visual fields showed normal outer limits and relative paracentral scotomas (**Figure 3**). Results of color vision testing with the desaturated panel D15 test were normal. In the EOG, baseline values were in the lower normal range (0.31 mV OD, 0.27 mV OS), as were the light peak amplitudes (171% OD, 177% OS). The light peak was delayed (15 minutes in both eyes). In the ERG, a- and b-wave amplitudes at dark adaptation were borderline (Figure 2). At light adaptation, a- and b-wave amplitudes were reduced to 60% of the normal median, while 30-Hz flicker amplitudes were reduced to 55% of the normal median. Both b-wave and flicker implicit times were normal. In the multifocal ERG, the amplitudes were reduced, but measurable cone function was still present at the posterior pole (**Figure 4**). In the central field, the amplitude was reduced to 34% of the normal median. Toward the peripheral areas, amplitude increased to 63% of the normal median.

Single-strand conformational polymorphism analysis of the peripherin gene gave normal results (S. Kohl, MD, and B. Wissinger, MD, Department of Ophthalmol-ogy, University Clinic, Tübingen, Germany; written communication; October 1997).

PATIENT 3

In the maternal grandfather of patient 1, severely reduced visual acuity and horizontal nystagmus had been present since childhood. At his earliest available ophthalmologic examination, performed in the Krankenhaus Friedrichshain at 47 years of age, visual acuity was 20/200 OU. Gray flecks were seen at the posterior pole. Visual fields showed central scotomas of 5°. Color vision testing with the 28 Hue de Roth test revealed multiple errors along the deutan axis in both eyes. Results of dark adaptation testing with a Hartinger adaptometer were normal. An EOG showed a delayed light peak (13 minutes in both eyes) with borderline amplitudes (148% OD, 152% OS). The ERG recordings showed reduced amplitudes at dark adaptation and no recordable responses to light adaptation or flicker stimulation.

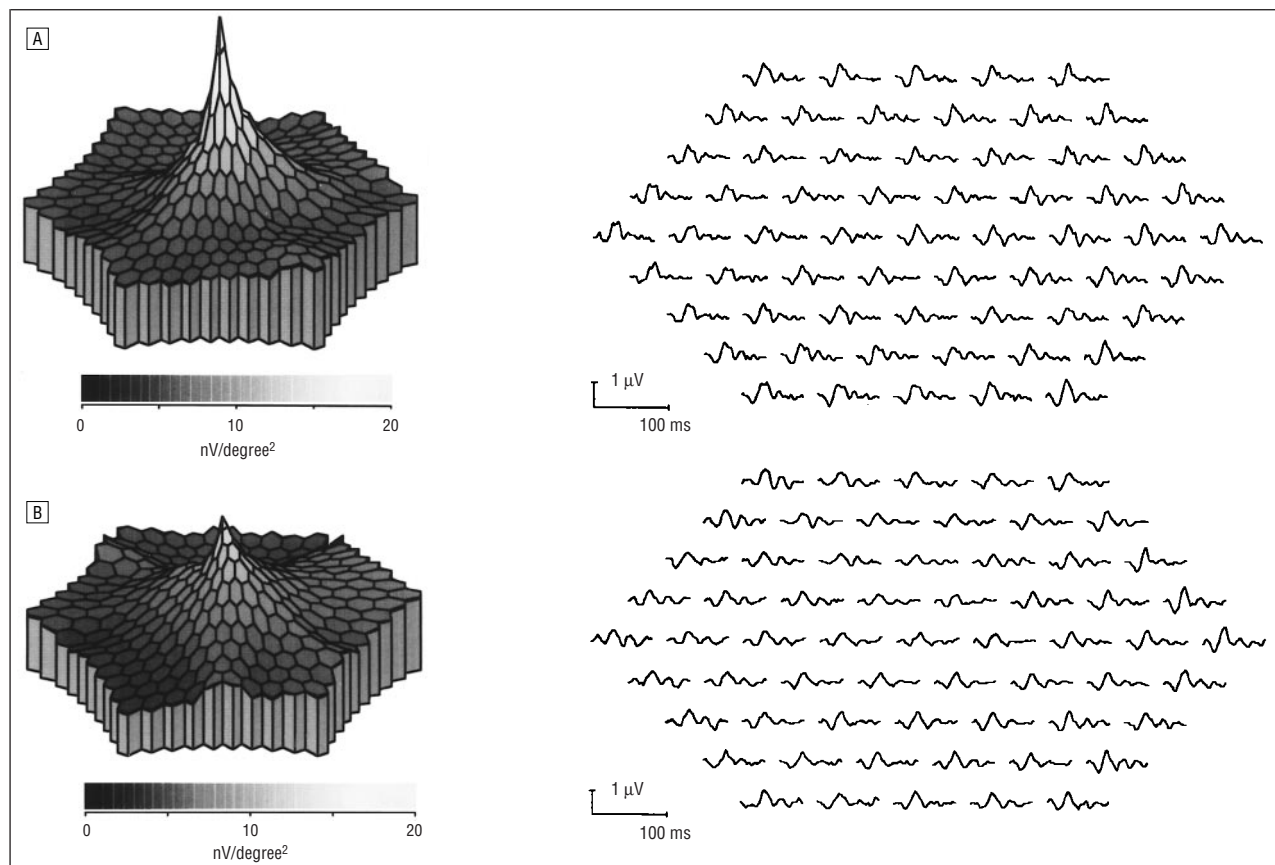At the age of 59 years, the patient was referred to me for further evaluation. Visual acuity was unchanged

Figure 4. *Multifocal electroretinograms (VERIS Clinic II System) of a normal proband (A) and patient 2 (B). Original recordings are shown on the right and the scalar product is shown on the left. The responses of patient 2 are more reduced in the center than toward the periphery.*

at 20/200 OU without improvement with glasses. Findings in the anterior segments were unremarkable. On ophthalmoscopy, the foveal reflex was absent (Figure 1). Subtle lines of gray deposits at the level of the RPE could be seen. Midperipheral choriocapillaris atrophy was present and was most advanced nasally. The optic discs appeared normal.

Goldmann visual field testing showed normal outer limits and relative paracentral scotomas for smaller targets (Figure 3). Color vision testing with the desaturated panel D15 test showed multiple errors without a typical axis of confusion. In the ERG, a- and b-wave amplitudes were reduced to 30% of the normal median at dark adaptation (Figure 2). Light-adapted responses and flicker responses were reduced to 10% to 15% of the normal median. B-wave and flicker implicit times were within the normal range.

COMMENT

A previously unreported retinal dystrophy is described here in 3 members of 3 generations in 1 family. It is characterized by serpentine-like gray deposits at the level of the RPE associated with deficits in both cone and rod function, midperipheral choriocapillaris atrophy, and a delayed light peak in the EOG. The earliest clinical sign was loss of visual acuity beginning in the first decade of life. The degree of visual dysfunction may be variable in this disorder. In both adults nystagmus had been present since

childhood, indicating severe deterioration of central visual function in early infancy. In contrast, the visual loss in the 10-year-old child (patient 1) was mild, and the mother of her grandfather (patient 3) was reported to have had better visual acuity than him throughout her life.

Progression of functional visual loss appears to be slow in this disorder. During follow-up, no further deterioration of visual acuity was observed in either adult. A slight visual loss in the right eye occurred in the child. Visual field defects remained moderate in both adults. Results of ERG and EOG recordings are indicative of slow progression. The ERG amplitudes were borderline in the child; cone dysfunction was present in the 30-year-old woman. Severely reduced but still recordable cone and rod responses were measured in the grandfather. The EOG light peak amplitude was normal in the child, in the lower normal range in the mother, and borderline in the grandfather. This may indicate a progressive dysfunction of the photoreceptor-RPE complex. However, there were no ERG or EOG recordings of 2 family members at a similar age or of a single family member measured over time with comparable methods. Therefore, the decrease of ERG and EOG amplitudes with increasing age may be due either to disease progression or to different severity of disease expression. The pattern of inheritance is most likely autosomal dominant because the disorder developed in 3 or 4 successive generations and looked similar in males and females. However, since males and females of similar ages were not present in this family and since male-

to-male transmission did not occur, X-linked dominant inheritance cannot be excluded.

The ophthalmoscopic findings slightly resemble those of a recently reported disorder termed Müller cell sheen dystrophy,[4] but in that disorder the age of onset is about 5 decades later and the ERG findings are different.[4,17] In Alagille syndrome, a slow, progressive retinal dystrophy can be accompanied by choroidal folds,[18] but no signs of choroidal folds were seen in the angiogram, and other mandatory features of Alagille syndrome were not observed.[18,19]

The functional deficits in these patients—including visual loss, paracentral scotomas, and the ERG findings—are in accordance with a slow, progressive cone-rod dystrophy.[3,7] The gray, serpentine-like deposits and the delayed EOG light peak distinguish this from other cone-rod dystrophies. The gray deposits were most extensive in height and area in the child. They were confined to a smaller area in the mother and were barely visible in the grandfather. Other disorders with deposits at the level of the RPE are Best disease,[1,20] dominant radial drusen,[8] and Stargardt disease.[2] In these disorders, material consisting of lipofuscin or lipofuscin-like material first accumulates within enlarged RPE cells.[21-25] In the later stages, loss of RPE cells as well as photoreceptors occurs, and extracellular subretinal material can be found.[26-28] In the present disorder, biomicroscopic examination suggests that the serpentine-like gray deposits are located either within enlarged RPE cells or within the interphotoreceptor matrix between the photoreceptor layer and the RPE cells. A definite decision, however, is impossible without histologic evaluation.

The delayed light peak (period from the onset of the light phase to the light peak maximum) must be interpreted cautiously. The variability of the light peak maximum between normal controls and patients with retinal disorders is small; however, the timing may be influenced by the recording conditions. In large series, the median time to the light peak maximum was 8 to 9 minutes.[29-31] Times longer than 11 minutes were considered abnormal.[29] During the evaluation of 776 EOGs recorded in normal controls and patients with various retinal disorders using both methods,[9,15] only 2 patients with retinal dystrophies and severely reduced light peak amplitudes presented with delayed light peaks (>12 minutes) (unpublished results, 1982-1998). Thus, the delayed light peak appears to be characteristic of the retinal dystrophy presented in this study.

The primary defect appears to be located in or near the RPE. Gray deposits were present when loss of visual function started. The earliest functional defect was a delayed light peak in the EOG. The progressive development of midperipheral choriocapillaris atrophy is in accordance with a primary defect in the RPE followed by photoreceptor dysfunction. Although severe loss of visual acuity was present in both adults, cone function was only moderately reduced in the 30-year-old woman and was still recordable in her father. Moreover, reduced but recordable cone function was demonstrated in the multifocal ERG.

Two hypotheses may explain the findings in this family. One could suppose a defect or delay of phagocytosis of shed cone discs. Such defects might be due to either abnormal cone disc shedding or impaired degradation capacity of RPE cells. Shed cone discs would tend to accumulate in the subretinal space. In childhood, when the material begins to accumulate, cone function can be nearly normal. The loss of cone function develops after gray material is present. With progressive loss of functioning cones, fewer cone discs are shed, and the deposited material gradually disappears with aging. As a second hypothesis, one could propose a deficient transport mechanism in the photoreceptors, the interphotoreceptor matrix, or the RPE cells. Ineffective transport proteins may lead to the accumulation of visible material at the level of the RPE, as recently shown in Stargardt disease.[32] Progressive loss of cone function might be explained either by the deficient transport mechanism or secondary to accumulation of gray material.

At present, the pathogenesis of progressive cone-rod dystrophy in this family cannot be clarified. The normal ERG in youth and the delayed timing of the EOG could be explained by both hypotheses. Further histologic and molecular genetic evaluation will be necessary for a better understanding of this unusual disorder.

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IN OTHER JOURNALS

NEW ENGLAND JOURNAL OF MEDICINE

Use of Inhaled Corticosteroids and the Risk of Cataracts

Background: The use of systemic corticosteroids is a risk factor for the development of posterior subcapsular cataracts, but the association between inhaled corticosteroids and cataracts is uncertain.

Methods: We conducted a population-based, cross-sectional study of vision and common eye diseases in an urban area of the Blue Mountains, near Sydney, Australia. We recruited 3654 people 49 to 97 years of age; the participation rate was 82 percent. We collected information by questionnaire on potential risk factors for cataracts, including the current or prior use of inhaled corticosteroids (beclomethasone or budesonide). Photographs of the subjects' lenses were graded, without information on the subjects, to determine the presence and severity of cortical, nuclear, and posterior subcapsular cataracts.

Results: Three hundred seventy subjects reported using inhaled corticosteroids, 164 currently and 206 previously. Among these subjects, after adjustment for age and sex, there was a higher prevalence of nuclear cataracts (relative prevalence, 1.5; 95 percent confidence interval, 1.2 to 1.9) and posterior subcapsular cataracts (relative prevalence, 1.9; 95 percent confidence interval, 1.3 to 2.8) than among the subjects with no inhaled-corticosteroid use, but the prevalence of cortical cataracts was not significantly higher (relative prevalence, 1.1; 95 percent confidence interval, 0.9 to 1.3). Higher cumulative lifetime doses of beclomethasone were associated with higher risks of posterior subcapsular cataracts (P for trend <0.001); the highest prevalence (27 percent) was found in subjects whose lifetime dose was over 2000 mg (relative prevalence, 5.5). Adjusting for the use of systemic corticosteroids and other potential confounders had little effect on the magnitude of the associations. The associations with posterior subcapsular cataracts, but not those with nuclear cataracts, were less marked when the analyses were restricted to subjects who had never used systemic corticosteroids.

Conclusions: The use of inhaled corticosteroids is associated with the development of posterior subcapsular and nuclear cataracts. (*1997;337:8-14*)

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