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CLINICAL INVESTIGATION

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Autosomal dominant vitreoretinochoroidopathy with normal electrooculogram in a German family

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Abstract ● Background: Autosomal dominant vitreoretinochoroidopathy (ADVIRC) is a rare disorder previously described in four families residing in the USA and one family residing in Germany. We report the clinical and unexpected electrophysiological findings in a sixth family, residing in Germany. ● Methods: An affected 23-year-old man, his 52-year-old affected mother and his 55-year-old unaffected father were examined by testing visual acuity, fluorescein angiography, visual fields, dark adaptation, electrooculography (EOG) and electroretinography (ERG). ● Results: The 23-year-old man showed a circumferential retinochoroidal dystrophy extending from the mid-periphery to the ora serrata. There was a sharp demarcation between affected and nonaffected retina. Peripheral to the damarcation, bone spicules and yellow-white deposits were present, and the retinal vessels were severely attenuated. In addition, vitreous opacities were present. The EOG light rise was normal. The ERG amplitudes were reduced to 35% of the normal in all recording conditions. The 52-year-old mother showed marked peripheral pigmentation, but no bone spicules, deposits or vitreous opacities. Her EOG and ERG recordings were normal. ● Conclusions: Expression of ADVIRC can be very variable within the same family. A reduced EOG light rise, previously suggested as a characteristic sign for ADVIRC, is not a typical sign for all affected patients.

Introduction

Autosomal dominant vitreoretinochoroidopathy (ADVIRC) is a rare disease, which to date has been described in detail in four families residing in the USA [3, 4, 6, 7, 9, 17]. A summary of the findings in a fifth family residing in Northern Germany was presented recently [16]. ADVIRC is characterized by autosomal dominant inheritance, peripheral circumferential retinochoroidal dystrophy with a sharp demarcation towards the central normal retina and vitreal disorganization. In most cases the dystrophic area is peripheral to the equator. In some cases, however, it reaches more centrally. Early cataract formation, retinal vascular abnormalities and cystoid macular edema may be present. A progression of the disease has not been demonstrated in individuals, but slow progression has been concluded from findings in two families [9, 17].

The characteristic ophthalmoscopic findings distinguish ADVIRC from other hereditary retinal dystrophies. Functional loss depends on the area involved. Visual acuity is good in most cases, and visual fields are normal or slightly constricted. Normal and reduced ERGs have been described [3, 4, 6, 7, 9, 17]. In one family EOGs were recorded, and all affected family members had a reduced light rise [6].

We report the clinical and functional findings in a small German family in which the two affected members had normal EOGs.

Patients and methods

We performed a basic ophthalmologic examination in the 23-year-old male propositus, his 55-year-old father and his 52-year-old mother. In addition, the propositus and his mother underwent detailed functional evalution. There were no known eye problems in other family members. They were not available for examination. The father is of Austrian origin, the mother from the southeastern part of Germany, and the parents are not consanguineous. None of the ancestors of this family is known to have emigrated to the USA. There is no known relation to the family in northern Germany [16].

Electrooculography (EDG) and electroretinography (ERG) were performed as described in detail previously [10]. The recording techniques were in accordance with the standards for clinical EOG [14] and ERG [13]. EOG was performed with maximal dilated pupils (2.5% phenylephrine and 0.5% tropicamide) using a method described by Behrens et al. [1]. The response was described as the ratio of the maximum amplitude to the amplitude before the luminance was increased (light peak versus baseline). Normal ranges for baseline and light rise were defined by calculation of the median values and the 95% confidence intervals in one eye of 40 probands.

For ERG recording a Nicolet Spirit [Nicolet, Madison, USA] in combination with a Nicolet Ganzfeld was used. Recordings were performed with a contact lens electrode and with maximal dilated pupils (2.5% phenylephrine and 0.5% tropicamide). No averaging was done.

ON and OFF responses were recorded using red and green LEDs (3 cd·s/m^2) and flashes of long duration (200 ms) [Roland Consult, Brandenburg, Germany]. Recordings were done after 10 min of light adaptation (10 cd/m^2). 128 responses were averaged.

The normal ranges for ERG and ON and OFF responses were defined by calculation of the median values and the 95% confidence intervals in 20 age-matched probands.

Dark adaptation was tested with the Goldmann Weekers adaptometer. Sensitivity thresholds were determined following a 10-min bleach of 1400 cd/m^2 in a Ganzfeld during a period of 45 min. The target size was 11 deg in the diameter in the upper field, 10 deg from the fovea.

All examinations were performed in conformity with the Declaration of Helsinki after informed consent had been obtained from the patients.

Results

A 23-year-old male patient was referred to us after failing the test for a driver's license. He had never noticed visual deterioration or progressive constriction of visual fields. His first glasses were described at the age of 7. At the age of 17 years he was examined by a second ophthalmologist. At that time his visual acuity was 20/30 in both eyes. Peripheral retinal dystrophy and bone spicules were described and regressed retinopathy of prematurity was suspected, but no definite diagnosis was made. His general medical history was unremarkable.

At the examination in our department, visual acuity was 20/40 in both eyes with a refraction of OD −4.25 −2.5 D axis 19° and OS −4.75−2.5 D axis 158°. The anterior segments were normal, as was the intraocular pressure. The vitreous showed fibrillar destruction. There were peripheral preretinal vitreous opacities, especially in the lower periphery. The posterior pole looked normal. In the mid-periphery a circular sharp demarcation line was visible (Fig. 1). Peripheral to that line there was marked pigmentation of the pigment epithelium as well as intraretinal bone spicule formation and yellow-white flecks. In that area the retinal vessels were severely attenuated. Central to the demarcation line, a small area of hypopigmentation was seen. In this hypopigmented area no bone spicules or flecks were present, and the retinal vessels were normal. Fluorescein angiography revealed normal pigment epithelium central of the demarcation line and severe destruction of retinal pigment epithelium peripheral to that line (Fig. 1). No vascular abnormalities were seen.

Goldmann visual fields were constricted for larger targets to about 30 deg, which corresponds with the ophthalmoscopically visible demarcation line (Fig. 2). Central from that line, the isopters for smaller targets were normal. Color vision testing with the desaturated Panel D-15 test showed minor errors without typical axis of confusion. Dark adaptation showed a normal cone-rod break and a normal final rod threshold.

In the EOG, base values and light rise were in the lower normal range. Base values were OD 0.27 mV and OS 0.26 mV (normal median 0.47 mV, lower limit of normal range 0.25 mV), and the light rises were OD 164% and OS 167% (normal median 186%, lower limit of normal range >160%). In the ERG, a- and b-wave amplitudes at dark and light adaptations as well as 30-Hz flicker amplitudes were reduced to about 35% of normal median (Fig. 3). ON and OFF response amplitudes were reduced to a similar extent (Fig. 4). The b-wave implicit times, 30-Hz flicker implicit times and ON and OFF response implicit times were all within the normal range.

The 52-year-old mother had no known eye problems. Her visual acuity was 20/20 in both eyes without correction. The anterior segments were normal. On ophthalmoscopy, a fine demarcation line was visible. Posterior to that line, there was an area of hypopigmentation. Anterior to the line, the pigmentation of the retinal pigment epithelium seemed more pronounced (Fig. 1). There were no bone spicules, no yellow-white flecks and no vitreous opacities. Fluorescein angiography was not performed.

Color vision (desaturated Panel D-15 test) and Goldmann visual fields were normal. EOG recording showed normal base values (OD 0.38 mV, OS 0.34 mV, normal median 0.47 mV, lower limit of normal range 0.25 mV). The light rise was higher than the median (OD 220%, OS 226%; normal median 186%, lower normal range >160%). In the ERG, responses normal in amplitude and implicit time were recorded at all stimulus conditions (Figs. 3, 4).

The 55-year-old father had no known eye disease. Clinical examination revealed a visual acuity of 20/20 on both eyes with a refraction of OD +0.25 to −0.25 D axis 0° and OS −1.5 to +0.5 D axis 70°. The anterior

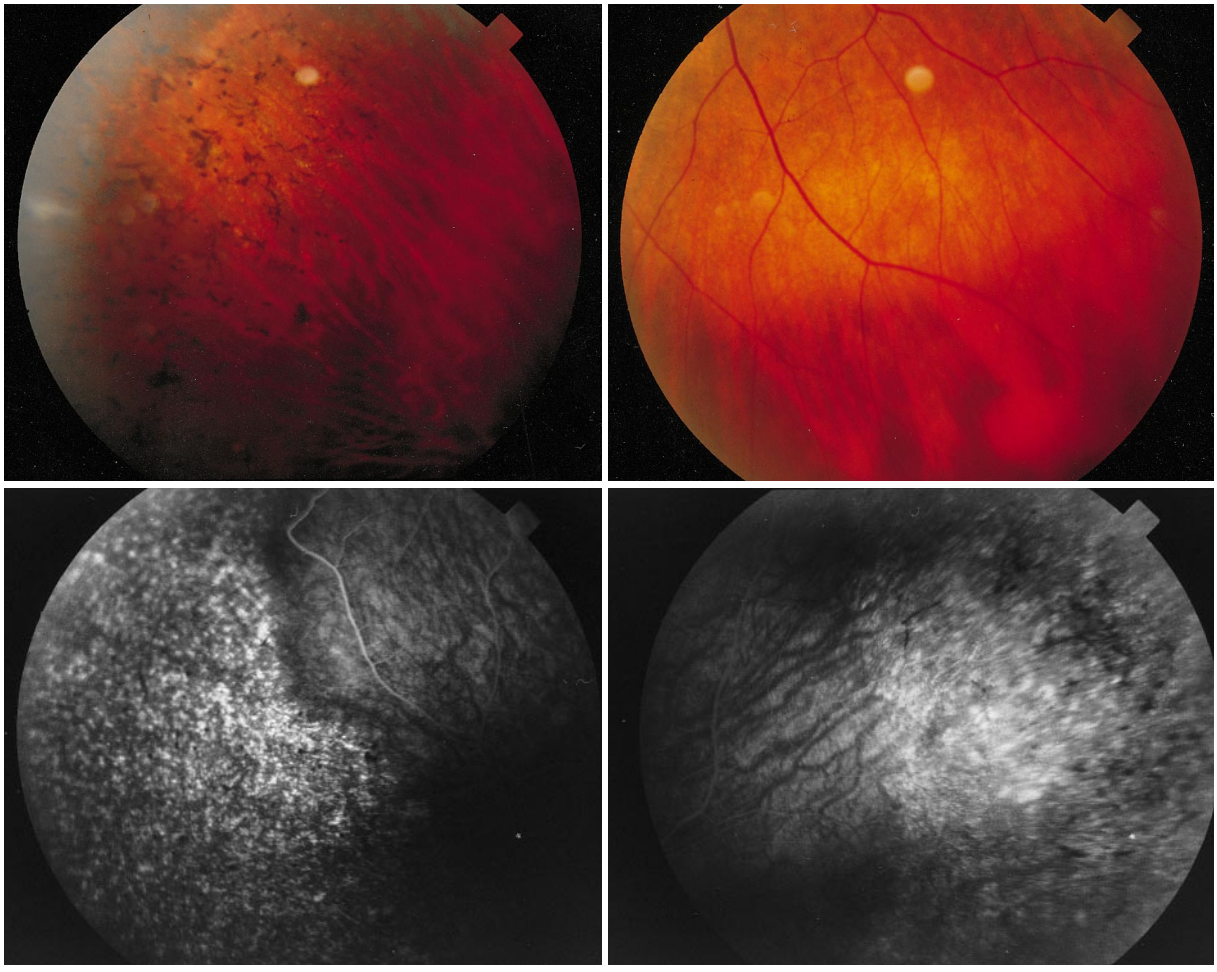

Fig. 1 Ophthalmoscopic findings and fluorescein angiography in ADVIRC. *Top left*: Propositus, OD. Temporal periphery with pigment clumping, depigmentations and pre-retinal vitreous opacities. *Top right:* Mother, OS. Lower periphery with a hypopigmented area central of the more pigmented periphery. *Bottom left:* Propositus, OD, fluorescein angiography. Sharp demarcation between central normal retina and choroid and multiple pigment epithelium defects in the temporal periphery. *Bottom right:* Propositus, OD, fluorescein angiography. Sharp demarcation between central normal retina and choroid and multiple pigment epithelium defects and pigment clumping in the nasal periphery

segments as well as ophthalmoscopic findings were normal.

Discussion

ADVIRC is a rare vitreoretinochoroidal dystrophy. The characteristic demarcation line and the typical findings in the dystrophic area established the diagnosis in our propositus. In his mother the alterations of the peripheral pigment epithelium were very mild. The typical demarcation line and the hypopigmented area central to that line were clearly visible. Retinal vascular abnormalities, neovascularizations and cystoid macular edema, as described in other families [3, 9] were not seen in our patients. Early cataract formation [6, 9, 17] was present neither in the mildly affected mother nor in the young propositus.

Variability of clinical findings have been described before [3, 9]. Most patients with ADVIRC do not have subjective clinical signs and therefore remain undiagnosed. Even in the families described before, patients with more pronounced changes than the mother in our family were diagnosed only during family evaluation. It is not surprising that no eye disease is known in other family members if ophthalmoscopic examination has not been carried out.

The functional loss with constricted visual fields and the reduced ERG in our propositus is explained by the rather central extension of the dystrophic area. Only one 55-year-old male patient with similar mid-peripheral involvement has been described [9]; this patient had the most constricted visual fields and the lowest ERG amplitudes of all his family members. Visual acuity is good in most patients with ADVIRC, when no cystoid macular edema is present. The reduced visual acuity in our patient is more difficult to explain, because the posterior pole ap-

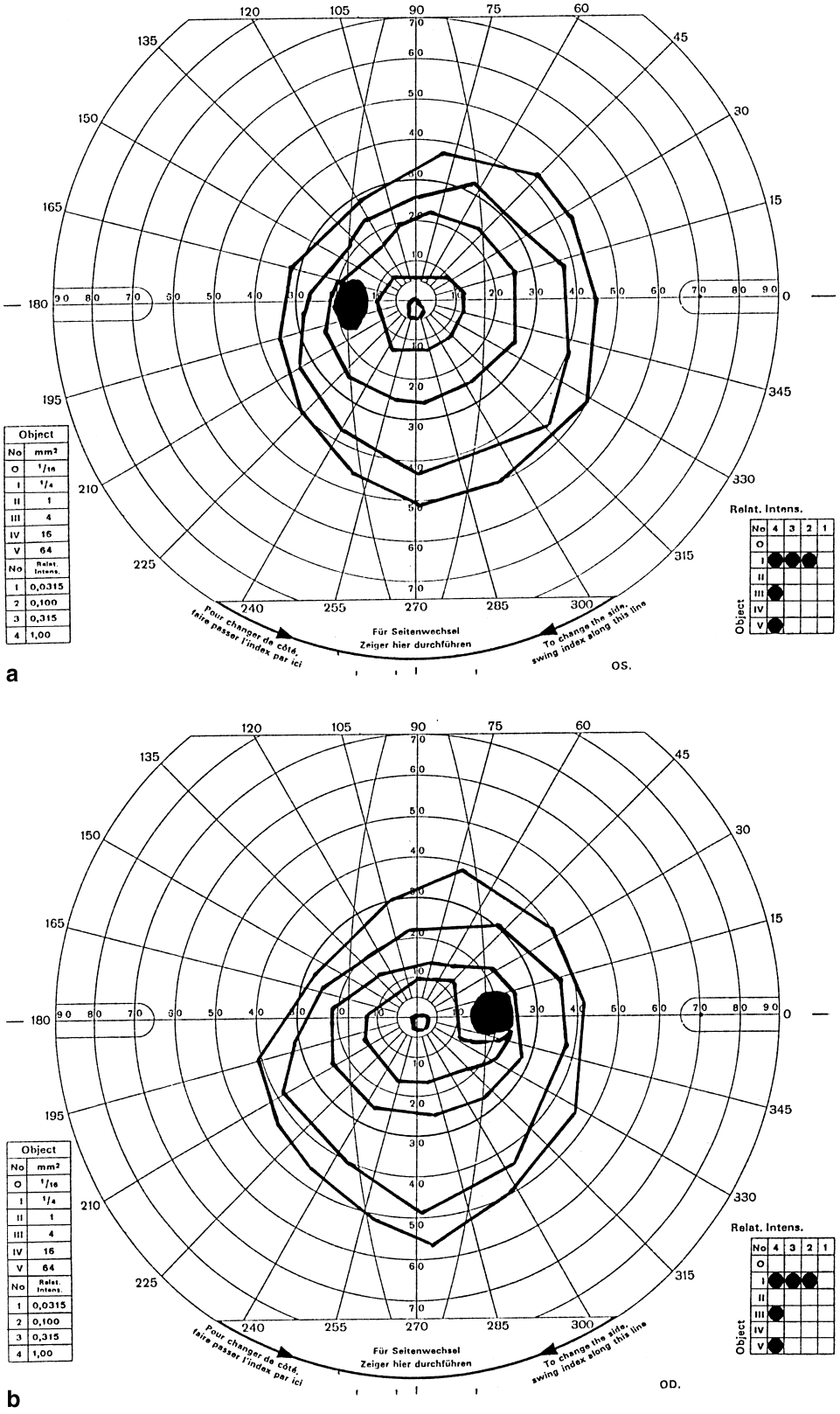

Fig. 2a, b Goldmann visual fields of the propositus show concentric narrowing for larger targets. **a** Left eye; **b** right eye

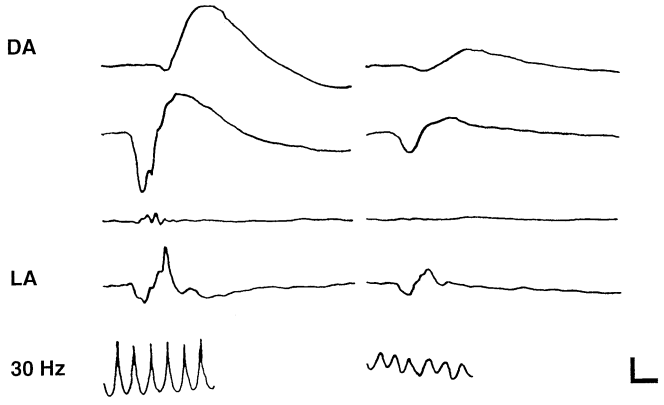

Fig. 3 ERG in response to white stimuli of one eye of the propositus (*right*) and his mother (*left*). The responses of the mother are normal. *DA* Dark adaptation, *LA* light adaptation. From top to bottom, the traces show rod responses, mixed rod-cone responses, oscillatory potentials, cone responses and cone flicker responses. Stimulus intensity was 0.008 cd·s/m^2 for the rod response and 10 cd·s/m^2 for all other recordings. *Vertical calibration mark* 200 μV for DA recordings and 100 μV for LA and flicker recordings, *horizontal calibration* 20 ms for single-flash recording and 50 ms for flicker recordings

Fig. 4 ON and OFF responses to green LED stimuli of the propositus (*lower trace*) and his mother (*upper trace*). The ON and OFF responses of the mother are normal. *Vertical calibration mark* 25 μV, *horizontal calibration* 50 ms

pears to be normal ophthalmoscopically and during angiography. Visual acuity loss due to ADVIRC can not be excluded. However, one has to keep in mind that his myopia and astigmatism were not corrected until he was 7 years of age. Therefore a moderate amblyopia may be present in both eyes.

Han and Lewandowski [6] have described four affected members of one family with markedly reduced EOGs. In none of the other families were EOGs tested. Han and Lewandowski suggested that a reduced EOG is a typical sign for ADVIRC. In our patients, the EOG light rise was normal, indicating that EOG findings vary between families with ADVIRC. To date, the diagnosis of ADVIRC must be based on the characteristic ophthalmoscopic findings.

Electrophysiologic tests are helpful to define the degree of functional loss but not for differential diagnosis. It is important to distinguish ADVIRC from other peripheral retinal disorders such is retinitis pigmentosa [8], retinopathy or prematurity [15], and autosomal dominant [12] or x-linked exudative vitreoretinopathy [11]. In the propositus of our family, regressed retinopathy of prematurity was suspected by one ophthalmologist. Retinopathy of prematurity and exudative vitreoretinopathy may induce peripheral retinal alterations; however, in these disorders the temporal periphery is more frequently affected, in contrast to the circumferential involvement in ADVIRC [11, 12, 15]. Temporal retinal dragging or retinal detachment has not been observed in ADVIRC, but mild cases of autosomal dominant exudative vitreoretinopathy with peripheral retinal vascular abnormalities may be difficult to differentiate [12]. In cases similar to our propositus, retinitis pigmentosa can be excluded when there is a sharp demarcation between peripheral severe pigmented alterations and midperipheral normal retina and no progression. It may be difficult, however, to distinguish mildly affected carriers of x-linked retinitis pigmentosa from females with ADVIRC similar to the mother in our family [8].

The course of ADVIRC has not been clearly established. Our patient had not noted visual acuity loss or progressive constriction of visual fields. His recent ocular examination was performed following failure of a test for a driver's licence. Slow progression has been suspected in two families [9, 17] but was never noted in individual patients. Annular hyperpigmentation has been observed even in a 3-year-old child [7]. Comparison of histologic findings of a 26-year-old and an 88-year-old female with ADVIRC showed no marked differences [4, 7]. Apparently, the dystrophic process starts early in the affected areas, whereas the nonaffected areas retain normal structure and function. The ERG in our patient is reduced due to the large area of affected retina; however, the normal implicit times indicate a normal function of retinal neurons in the nonaffected retina.

The pathophysiologic basis of ADVIRC has not been established. Histologic examination revealed a dystrophic retina with vessel sclerosis, secondary changes in the pigment epithelium and an intact choriocapillaris [4, 7]. Clinical and histologic findings suggest that the alterations of the vitreous and the pigment epithelium are secondary to a primary degeneration of the peripheral retina. Two theories may explain these findings. On one hand, there could be an interruption of fetal retinal development. The peripheral retina which develops following this interruption may show maldevelopment. However, retinal development is centered at the optic disc, as seen in preterm infants [15]. The dystrophic areas in ADVIRC are circumferential and to not show the difference between nasal and temporal periphery that are regularly seen in preterm infants. On the other hand, peripheral retinal dystrophy may be due to differences between central and peripheral retinal physiology. It has been shown, that several genes are expressed in either the central or the peripheral retina [2, 5]. Mutation of a gene with specific peripheral retinal function may explain the peripheral dystrophic process. Variations in gene expression between individuals may

explain the variability of clinical findings. However, one would expect a gradual change in gene expression from center to periphery. Therefore the sharp demarcation line is difficult to explain by variations of gene expression.

New insights into differences between central and peripheral retinal function may emerge when the genetic background of ADVIRC is determined. Most families described to data are of western European origin: Swiss-Welsh [9], Polish-Italian [3], Northern-European–German [6, 16] and, in our study, German. It may be that all these families have a common ancestor and the same gene defect.

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Note added in proof In the meantime the findings reported in [16] have been published in detail: Roider J, Fritsch E, Hoerauf H, Heide W, Laqua (1997) Autosomal dominant vitreochoroidoretinopathy. Retina 17:294–299