Retinal function in incontinentia pigmenti: a long-term electrophysiological follow-up

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Abstract

Incontinentia pigmenti (IP) is a rare, X-linked, dominantly inherited disease affecting mostly females, which is best characterized as an autoimmune disease. It is a multi-system disorder affecting ectodermal tissues. Ocular abnormalities usually occur early in childhood, with subsequent retinal detachment and vision loss. Vision rarely remains intact until adulthood. We present the 17-year visual electrophysiological follow-up of such a rare patient and her mother. The mother was only a carrier, but the daughter developed various manifestations of IP. The aim of our investigations was to obtain information on the progression of functional deterioration in IP.

Electroretinography (ERG), multifocal electroretinography (mfERG), visual evoked potentials (VEP), ultrasound (US) and optical coherence tomography (OCT) were performed at regular intervals between the patient's ages of 9 and 26 years (2003 to 2020).

From 9 to 22 years of age, a characteristic picture of spared vision with minimal ophthalmoscopic alterations and fluctuating ERG anomalies were observed in the left eye. It was only between the ages of 22 and 23 that subjective symptoms developed, and then complete loss of vision in the affected eye ensued rapidly. The right eye remained clinically asymptomatic throughout the observation period. The mother remained completely asymptomatic, but she showed similar ERG alterations.

Electroretinography is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it readily detects their functional effect even in the absence of clinical symptoms. Thus, it is recommendable not only for the long-term functional follow-up of these patients, but probably also for early disease-specific screening. ERG recordings from the presented case suggest that the characteristic, asymmetric pattern of retinal functional involvement may be traced back to the different degrees to which the two eyes were exposed to the intermittent reactivations of the disease.

Keywords: incontinentia pigmenti, retina, visual electrophysiology, optical coherence tomography, ultrasound examination.

Sammendrag

Incontinentia pigmenti (IP), også kalt Bloch-Sulzbergers syndrom, er en sjelden arvelig tilstand med X-bundet dominant arvegang. Den påvirker stort sett kvinner og kan best beskrives som en autoimmun sykdom. Den er en multisystem tilstand som påvirker ektodermalt vev. Øyeforandringer begynner ofte i tidlig barndom og etterfølges av netthinneavløsning og tap av syn. Normalt syn bevares sjeldent til voksen alder. Her presenteres en elektrofysiologisk oppfølging over 17 år av en jente og hennes mor. Moren var kun bærer av genet, mens datteren utviklet diverse symptomer forbundet med IP. Målet med undersøkelsen var å skaffe informasjon om utviklingen av reduksjon av synsfunksjon ved IP. Elektroretinografi (ERG), multifokal elektroretiografi (mfERG), visuelt fremkalte potensial (VEP), ultralyd og OCT ble utført jevnlig fra pasienten var 9 år gammel til hun hadde fylt 26 år (2003 til 2020). Fra 9 års alder og frem til hun var 22 år var det kun små oftalmoskopiske endringer og varierende grad av unormale ERG funn i det venstre øyet. Det var først i 22–23 års alder at pasienten utviklet subjektive symptomer, og deretter fulgte i løpet av kort tid fullstendig synstap i det venstre øyet. Det høyre øyet forble klinisk asymptomatisk gjennom hele observasjonsperioden. Moren forble også asymptomatisk, men tilsvarende varierende grad av unormale ERG funn ble observert. ERG er en nøyaktig indikator når det gjelder okulær immunrespons eller betennelsesreaksjon ved IP, og registrerer effekten av endringer av synsfunksjonen uten at pasienten rapporterer symptomer. ERG anbefales derfor, ikke bare for langtids oppfølging av disse pasientene, men også for tidlig IP-spesifikk screening. ERG resultatene fra denne casen indikerer at den karakteriske asymmetriske effekten på retinal funksjon kan spores tilbake til hvilken grad hvert øye ble påvirket ved gjentatte reaktiveringer av sykdommen.

Nøkkelord: incontinentia pigmenti, retina, visuell elektrofysiologi, OCT, ultralyd.

Introduction

Incontinentia pigmenti (IP, Bloch-Sulzberger syndrome) is an X-linked, dominantly inherited multi-system disease affecting mostly females. Its estimated prevalence is 0.0025% (Swinney et al., 2015). It is a disorder causing dermatological, dental, ocular and neurological alterations. The diagnosis can be made by either histopathologic examination of skin biopsies or by genetic analysis of X-chromosome mutations. Deletions comprising exons 4-10 of *IKBKG*/NEMO gene in Xq28 locus can be found in 80-90% of IP probands (Berlin et al., 2002; Chen et al., 2015; Smahi et al., 2000). The skin lesions are usually the first to appear, days or weeks after birth (Goldberg & Custis, 1993). IP is best characterized as an autoimmune disease (Bruckner, 2004; Piccoli et al., 2012).

Ocular abnormalities, such as strabismus, corneal opacification, cataract and/or vascular retinopathy with epiretinal membrane formation may occur (Holmstrom & Thoren, 2000; O'Doherty et al., 2011). Subsequent retinal detachment develops generally in early childhood. The excessive neovascularization of the retina and the vitreous can cause fibrosis manifesting as pseudoglioma (Brown, 1988). The process has a very poor prognosis, it often leads to total blindness (Wald et al., 1993). Severe visual deterioration has been reported in 35–77% percent of the cases (Holmstrom & Thoren, 2000; Swinney et al., 2015). Only a few publications have reported late retinal involvement (Cates et al., 2003; Chen et al., 2015).

No therapy is known to prevent blindness as a sequela of IP. There is some evidence to indicate that cryotherapy or laser therapy may be helpful (Jandeck et al., 2004; Rahi & Hungerford, 1990). Contrary to this, peripheral nonperfusion and neovascularization often remain stable showing spontaneous regression over time without treatment (Cates et al., 2003; Chen et al., 2015). Fluorescein angiography (FLAG) was suggested for early detection of the vascular abnormalities of the peripheral part of the retina associated with IP (Goldberg, 1994). Later, for the detection of structural abnormalities and progression of retinal damage, spectral-domain optical coherence tomography (OCT), in combination with FLAG were applied (Basilius et al.,

2015; Chen et al., 2015; Liu et al., 2018; Mangalesh et al., 2017). Repetitive FLAG examinations in infants or very young children necessitate repetitive general anaesthesia and require a specialized examination team, which is usually not readily available. FLAG is also an invasive method; therefore, its use should be limited. It must be added here that in infants the progression of the retinal damage can be rather fast, with not enough time remaining to prevent blindness.

Changes in retinal and optic nerve function can be detected with electrophysiological tests after 2–3 years of age, without general anaesthesia. These tests are not invasive and are readily available; therefore, they are optimal for follow up of the retinal function in IP, even when the visual disturbance does not develop in infancy. Still, we found only one case report where ERG was utilized, in a 13-month-old girl, only on one occasion and under general anaesthesia (Ferreira et al., 1997). Here, we demonstrate the effectiveness of visual electrophysiological methods in the detection of changes in the functioning of the different retinal cells through the seventeen-year follow-up of an IP patient and her mother, an asymptomatic carrier of the same dysfunctional gene.

Methods

The protocol adhered to the tenets of the Declaration of Helsinki, with informed consent obtained from each participant or their legal guardians. Besides the routine ophthalmological examinations (refractometry, Snellen visual acuity, tonometry), Goldmann kinetic and static perimetry (Octopus 1-2-3 V10.17, greyscale), ultrasound and optical coherence tomography (OCT: Heidelberg Spectral, Heidelberg Engineering, Germany) were also performed. Ocular refraction was measured with a NIDEK 510A refractometer (Nidek, Japan). For the Snellen acuity measurements, the patient sat 5 metres from the chart. Retinal fundus photos, anterior segment images (TRC-50DX, Topcon, Tokyo, Japan), and ultrawide-field images (Optos California, Optos Inc., Marlborough, USA) were also taken.

For the electrophysiological tests, the Roland Instrument (Electrophysiological Diagnostic System, Wiesbaden, Germany) was used, according to the relevant ISCEV standards (Hood et al., 2012; Marmor et al., 2009; Marmor et al., 2003; McCulloch et al., 2015). Visual evoked potentials (VEP), pattern electroretinograms (PERG), standard electroretinograms (ERG), and electrooculograms (EOG) were recorded with the Reti-port system. Multifocal electroretinograms (mfERGs) were recorded with the Reti-scan system. VEPs were evoked with 60′ and 15′ reversing black and white checkerboard pattern stimulation, while for PERG, 40′ check-size was used. The refraction was corrected to the distance from the monitor. For the mfERG recordings, pupil dilation was used, both in the monocular and binocular conditions. Before testing standard ERG, the patient's pupils were also fully dilated (≈7.9 mm). For pupil dilation, 0.5% Tropicamide eye drops (ATC: SO1FA06) were applied three times over 90 minutes (one drop at a time, the last drop at the beginning of dark adaptation). For dark adaptation, the patient was kept in a totally darkened room for 30 minutes. ERGs were recorded with DTL (Dawson-Trick-Litzkow) electrodes (Dawson et al., 1979). During the stimulation, the patient fixated on a red point in the centre of the Ganzfeld stimulator. Electrophysiological testing usually lasted 2 to 3 hours (with breaks between the tests).

Case presentation

Initial presentation

A 9-year-old girl was referred to our laboratory for electrophysiological examinations in 2003 with the preliminary diagnosis of inveterate chorioretinitis. As she had no previous complaints of visual disturbance, ophthalmological examination was performed only because of mild strabismus of her left eye. In this eye, a central retinal vascular abnormality was found. In the temporal periphery of the retina, pigment clumps were detected without abnormal vessels (see Figure 1).

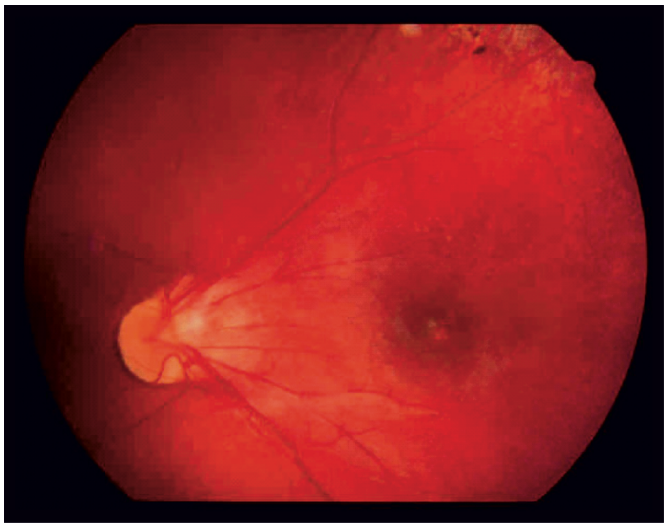

Figure 1: *Fundus photograph of the left eye at the age of 9. Note the dragged optic disc and some mild pigment clumps in the upper temporal, peripheral part of the retina.*

The patient's history revealed erythematous, vesicular skin lesions some days after birth, which were resistant to antibiotic treatment. This was the first occasion when the possibility of IP emerged. Later she exhibited several characteristic systemic symptoms, including delayed tooth eruption, patchy hair loss, and hearing loss. Subsequent genetic testing confirmed the diagnosis: *IKBKG* / NEMO: Xq28, NM_001099856, nonsense mutation of the pathogenic c.388C>T, p.Arg130Ter (rs137853323) in heterozygous formation was identified in the patient and in her mother, too.

The ophthalmological status at this time was as follows: the left eye had mild exo-deviation (8Δ). The axial length of both eyes the eyes was 24 mm. There was only mild astigmatism (RE +0.5DC at 180°, LE +0.75DC at 10°). The Snellen acuity was 1.0 on the right eye and 0.8 on the left eye (without correction).

Ophthalmoscopy of the left eye revealed a dragged optic disc, from which abnormal vessels ran towards the macular area. The picture resembled retinopathy of prematurity, but the patient was not born prematurely. Some smaller pigment clumps were found in the upper temporal peripheral part of the retina without visible abnormal vessels. The retina of the right eye was free of abnormalities. The visual acuity of the left eye improved to 0.9–1.0 after one year of orthoptic treatment. Kinetic perimetry showed normal isoptres on the right eye, while the isoptres were mildly narrowed on the left side, corresponding to the mild peripheral pigment defect.

As the patient cooperated well, it was possible to test the retinal and optic nerve function with standard electrophysiological methods. The results were compared to our laboratory controls (see Figure 2) and the responses from the two eyes were also compared. The patient's dark-adapted 0.01 ERG (rod response) and the dark-adapted 3.0 ERG (combined rod-cone response) showed extreme side differences. The amplitudes of the responses from the right eye were subnormal, while the waveform was normal. On the left eye, where the central retinal vascular abnormality was found, the responses were supernormal, and the 'b' wave of the left eye's response continued in an abnormal elevation, instead of slowly returning to the baseline, as seen in healthy recordings. We examined the possibility of an artefact, but we ruled it out, as the resistance of the electrode was below 5 kOhm, the patient cooperated well (no muscle arte-

fact), and the phenomenon was detected in the left eye only (see Figure 3A).

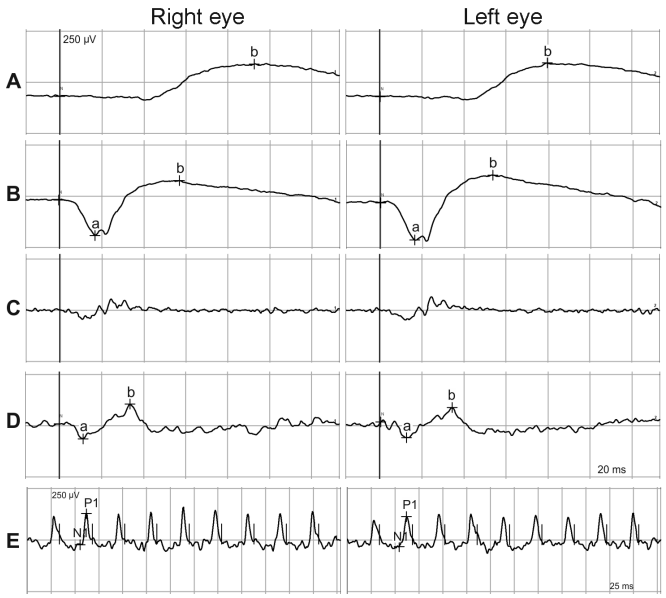

Figure 2: *Standard ERGs from an 18-year-old control patient from the reference pool of our laboratory, recorded according to ISCEV standards. Note the similarity between the two eyes. 'a' and 'b' indicate the two main wave components. A: dark-adapted 0.01 ERG; B: dark-adapted 3.0 ERG; C: dark-adapted oscillatory potentials; D: light-adapted 3.0 ERG; E: light-adapted 30 Hz flicker ERG. For relevant laboratory normal values see Table 1.*

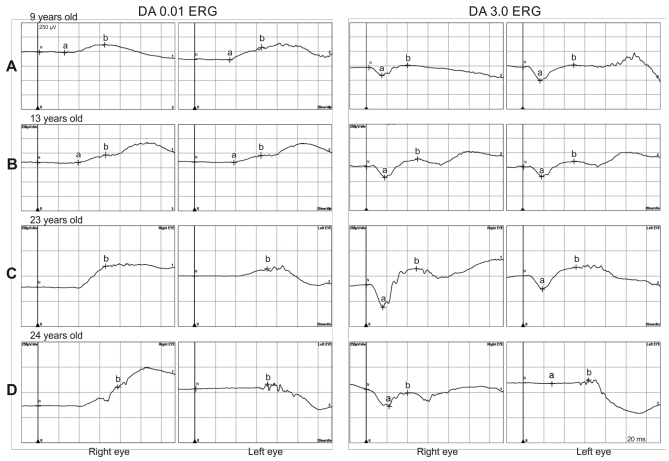

Figure 3: *Electroretinography at different time points during the follow-up: dark-adapted 0.01 and dark-adapted 3.0 ERGs recorded at (A) 9 years of age (2003), (B) 13 years of age (2007), (C) 23 years of age (2017) and (D) 24 years age (2018). 'a' and 'b' indicate the two main wave components. Note the marked difference between the eyes, the changing amplitudes and the late, high-amplitude positive deflection that gradually turns into a deep negative deflection.*

The oscillatory potentials (OP), the photopic ERG and the flicker responses were normal in both eyes without waveform alterations or differences between the eyes. PERG was normal in both eyes. As for VEP, the P100 peak times of the VEPs were normal in the right eye. The waveform of the left eye's response was bifid and only mildly subnormal.

The 4-year follow-up

The next electrophysiological follow-up took place four years later (2007), at the patient's age of 13. The reason for this long interval was that the patient had no visual complaints. Visual acuity was 1.0 for the right eye and 0.8 for the left eye, without correction. The extreme side difference of the dark-adapted 0.01 and 3.0 ERGs described 4 years previous had disappeared by this time. However, the elevation anomaly of the 'b' wave remained (see Figure 3B), what is more, it was now observable in both eyes, which was a further piece of evidence against this anomaly being an artefact. The oscillatory potentials (OP), the light-adapted 3.0 ERG (cone response) and the flicker responses were mildly, but not significantly, subnormal on both sides. Because of the central retinal alterations and mild strabismus of the left eye, we recorded mfERG with both monocular and binocular stimulation. The mfERG was normal in both eyes, without side differences (see Figure 4A). This result proved that there was no hypoplasia or other structural damage in the macula, despite the characteristic ophthalmoscopic picture of the left retina.

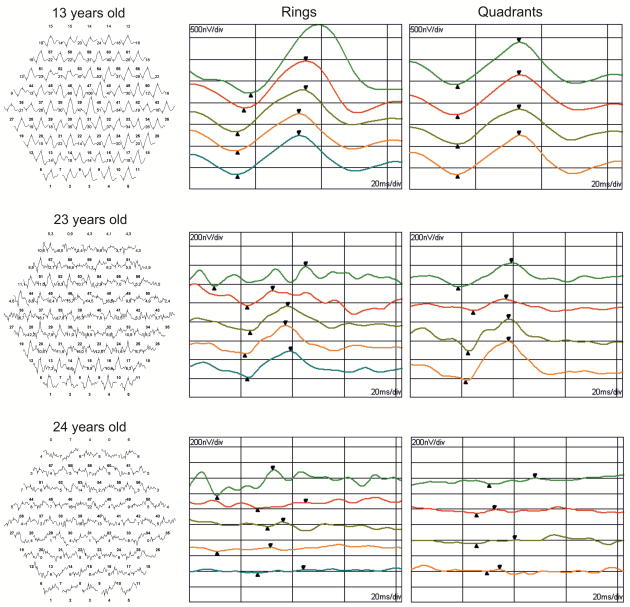

Figure 4: *Changes of mfERGs recorded from the left eye. Left side: the trace arrays, middle: ring analysis, right side: quadrant analysis. Top: 13 years of age, normal status; Middle: 23 years of age, severe functional loss in the 1st and 2nd rings and in the 2nd quadrant. Bottom: 24 years of age, nine months after the successful cataract and epiretinal membrane surgery. The central 30 degrees of the retina are almost completely unresponsive.*

The 6-year follow-up

Two years later, in 2009, another follow-up examination took place. At that time the ophthalmological examination revealed some proliferative membrane spreading towards the periphery from the disc. Surgical therapy was not indicated because the abnormalities were confined to the central part of the retina (thus photocoagulation or cryotherapy were no options either), and the visual acuity was also satisfactory (0.6). The electrophysiological parameters did not show any remarkable change as compared to the status 2 years previous, so they are not discussed in detail.

The 14-year follow-up

The patient's vision in her left eye started to deteriorate rapidly due to cataract formation when she was 22, and by the age of 23, it had dropped to 0.2. We saw her again because of this complaint in October 2017. Both ERG and mfERG indicated the progression of the functional disturbances (see Figures 3C and 4B). Behind the cataract, the ultrasound examination showed sheet-like echo sources that spread from the optic disc towards the nasal and temporal peripheral parts of the retina (see Figure 5A). The anatomical alterations were also observable in the OCT scans (see Figures 6A and 6B). See also Figure 8A for an anterior segment image.

Due to further progression of the cataract, the visual acuity dropped to 0.04 by February 2018 (see Figure 6A). Electrophysiological examinations were performed before surgery to objectively evaluate the possibility of visual improvement after surgery.

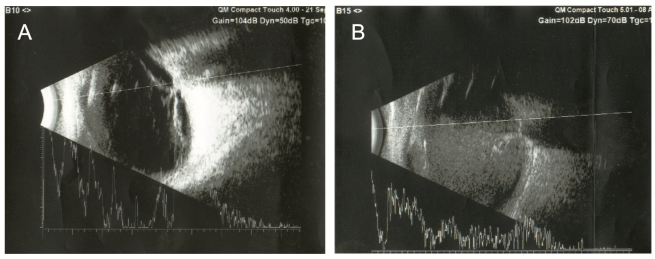

Figure 5: *Ultrasound images of the left eye of the patient. A: Before the cataract surgery (2017). Note the proliferative membranes under the cataract. B: Nine months after the surgery (2018): emulsified silicon oil and the recently formed proliferated membrane was detected.*

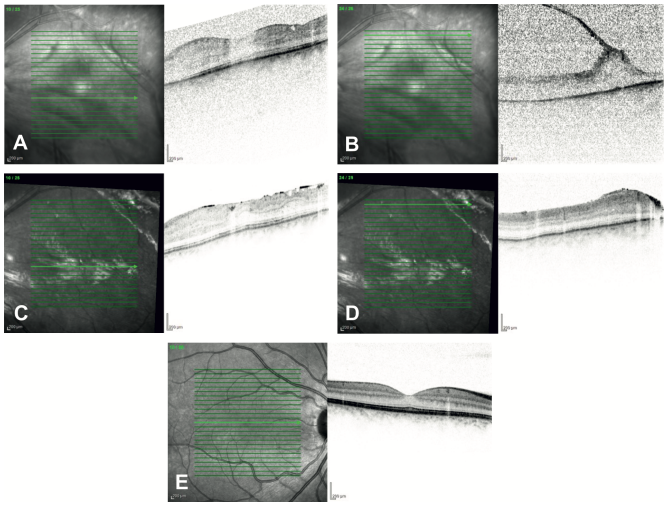

Figure 6: *SD-OCT images of the left eye before and after the cataract surgery. A: foveal section before the surgery. B: section in the zone of traction before the surgery. C: foveal section after the surgery. D: section at the same level as B after the surgery. E: image of the unaffected right eye.*

The amplitudes of both the 'a' and 'b' waves of the dark-adapted 3.0 ERG from the left eye were significantly attenuated (compared to the responses of the opposite eye), and this time the 'b' wave was not followed by a positive deflection but by a negative one (see Figure 3C), while the anomaly still showed as a positive deflection in the right eye. The peak time of the VEPs from the left eye was delayed (130–133 ms) and the amplitude of these responses was subnormal (6.68 μV).

Combined cataract extraction, vitrectomy (membrane peeling and silicon oil implantation), and peripheral laser coagulation were performed without complications. The removed membranes were sent for immunohistochemical analysis, which revealed a complex immunophenotype positivity for GFAP, vimentin, S-100, AE/*AE3*, and SMA to various extents (Janaky et al., 2020).

The visual acuity improved to 0.7 by the third day after the surgery. The macula was free from tractioning membranes previously seen on OCT scans (see Figures 6C and 6D). No visual loss or any retinal sign of IP developed in the right eye (see Figure 6E).

Six months after the surgery, the visual acuity of the left eye started to deteriorate again, and nine months after the surgery emulsification of the silicone oil was detected along with elevation of the retina (see Figure 7A). The patient was then 24 years old. The silicone was removed.

Six months after the repeated vitrectomy, the ultrasound showed a recently formed proliferative membrane and remnants of silicon oil or blood in the vitreous (see Figure 5B). Neovascularization of the iris developed, too. The capsule was thickened and the vitreous was hazy (see Figure 8B).

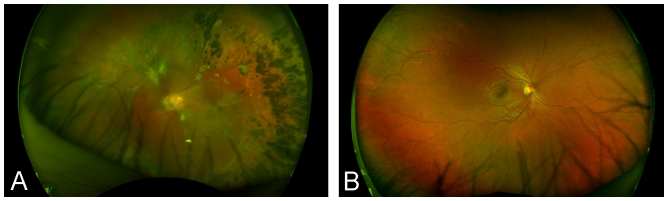

Figure 7: *A: ultrawide-field image of the left eye six months after the removal of the silicon oil. B: ultrawide-field image of the unaffected right eye.*

The electrophysiological examinations revealed severe functional loss of the left retina and optic nerve (see Figure 3D). Light perception was completely lost in this eye. The VEPs were extinguished. The EOG was extinguished, too (LP: DT ratio: 0.8), reflecting the severe functional loss of the retinal pigment epithelium. In the right eye, the dark-adapted 3.0 ERG was subnormal with a bizarre waveform (see Figure 3D). Despite the subnormal ERG, however, the patient had no complaint about vision in this eye and the visual acuity was 1.0. The mfERG and the EOG (LP: DT ratio: 2.5) recorded from the right eye were also normal.

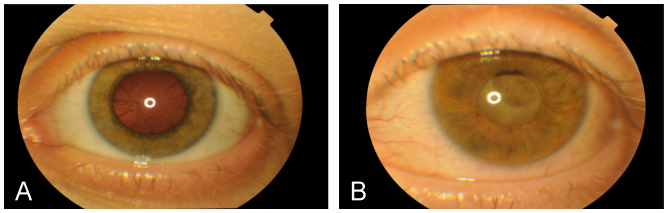

Figure 8: *A: anterior segment image of the left eye before the cataract surgery - the posterior subcapsular cataract prevents clear imaging of the retina. B: anterior segment image of the left eye six months after the removal of the silicon oil; iris neovascularization, capsular thickening and hazy vitreous.*

The 17-year follow-up

The last visit took place in February 2020. The right eye's electrophysiological parameters (VEP, PERG, ERG) were normal for the first time during the follow-up, while the left eye's responses were totally extinguished. Accordingly, the sight of the right eye was spared (acuity: 1.0), but the left eye was completely insensitive to light. Visual acuity and ERG values recorded during the follow-up are given in Table 1.

Table 1: *Visual acuity (VA) and ERG parameters during the follow-up.*

			DA 0.01 ERG				DA 3.0 ERG						
	eye	VA	b (ms)	b (μV)	diff (μV)	lc (μV)	a (ms)	a (μV)	diff (μV)	b (ms)	b (μV)	diff (μV)	lc (μV)
2003	R	1	67	142	-	-	16	164	-	40	205	-	-
	L	0.8	83	297	+155	+123	17	250	+86	50	250	+45	240
2007	R	1	68	125	+1	+205	18	205	-	50	369	+82	164
	L	0.9	70	124	-	+220	18	205	-	50	287	-	123
2017	R	1	68	205	+82	-	18	264	+100	50	400	+136	123
	L	0.2	69	123	-	–164	16	164	-	50	264	-	–164
2019	R	1	65	164	-	+164	24	205	-	38	123	-	-
	L	-	-	-	-	–287	-	-	-	-	-	-	–327
LN		1	80.5 (±8.69)	237.3 (±93.65)	N/A	N/A	19.95 (±4.28)	201.02 (±75.97)	N/A	47.95 (±7.14)	341.55 (±88.34)	N/A	N/A

Note: R: right, L: left; 'a' and 'b' denote the corresponding wave components of the ERG. Peak times and amplitudes are shown for each component in milliseconds and microvolts, respectively. Difference between the amplitudes of the two eyes (diff) is given in microvolts (where applicable). The difference between the eyes is shown after the eye with the highest amplitude. Late component ('lc') values are given if a late wave component after the 'b' wave was detected at the given follow-up visit. The magnitude of the late deflection is given in microvolts and is marked as + (upward) or –(downward). LN: laboratory normal values. Laboratory normal values are given as mean ± SD.

A summary of the follow-up of the patient's mother

As the genetic analysis confirmed the presence of the mutant NEMO gene in the mother, we tested her retinal function, too. Two examinations were performed. The first one took place in 2003 (at the age of 32), and the second one in 2017 (at the age of 46). Typical skin problems at birth were not possible to confirm. She had no systemic manifestation of the disease. Her visual acuity was good (1.0 in both eyes without correction), and there were no ophthalmoscopic abnormalities of the retina. No visual field defect was detected either. The ERG recorded from her right eye was normal, but the responses of the left eye — tested both at 32 and 46 years of age — were subnormal. The amplitudes recorded from the left eye were approximately half of those recorded from the right eye on both occasions, indicating subclinical loss of retinal function. The mfERG, PERG, VEP, and EOG were normal in both eyes on both occasions.

Discussion

In the described case, the patient and her mother both had the mutant *IKBKG*/NEMO: Xq28, NM_001099856 gene, but systemic manifestations of IP developed only in the patient. It was one of those cases when clinical ocular involvement occurred only late in the course of the disease. From 9 to 22 years of age, a characteristic picture of spared vision with minimal unilateral ophthalmoscopic alterations and fluctuating ERG anomalies were observed. The right eye remained unaffected throughout the observation period, apart from minor electrophysiological alterations. It was only between the ages 22 and 23 that actual clinical manifestations appeared, but then complete loss of vision in the affected eye developed rapidly.

The initially detected extreme difference between the eyes, the constantly detectable but asymptomatic changes of electrical activity also in the unaffected right eye, the appearance of a late supernormal positive deflection, and progressively deteriorating ERG of the affected eye were probably the most characteristic findings. Besides, we observed a late, high-amplitude wave component that appeared as the continuation of the 'b' wave. It is difficult to explain with certainty what brought these changes about, but an intermittent reactivation of the autoimmune process is a probable explanation (Chen et al., 2015; Conte et al., 2014; Smahi et al., 2000). The phenomenon that IP may affect the two eyes to differing extents is known, but its background is uncertain. IP is a rare disease, and no study has ever focused on this aspect. In this specific case, the only meaningful difference in this context was the vascular anomaly in the left eye, which could have meant a higher autoimmune challenge to this eye, hence the different pattern of involvement. Extreme differences between the eyes and temporarily supernormal ERG due to retinal toxicity would not be an entirely new finding. It has been observed, for instance, in cases of mercury and lead poisoning (Tanabe et al., 1992; Tessier-Lavigne et al., 1985). In this sense, if we compare the electrophysiological responses of the left and right eyes at the different time-points during the follow-up, we can formulate a hypothesis regarding the temporal dynamics of retinal damage in this case.

As for the unaffected right, eye, the 'a' and 'b' waves were initially subnormal (with a pronounced attenuation of the 'b' wave) and without the characteristic late, high-amplitude anomalous component recorded from the left eye. This means that the corresponding cell types (predominantly rods and bipolar Müller cells) were affected at an early stage of the process (lower immunological challenge). At the patient's first presentation, this difference between the eyes was the most remarkable electrophysiological finding. The supernormal responses of the left eye probably reflect hyperexcitability due to the higher immunological challenge to this eye because of the vascular anomaly. Later during the follow-up, the 'a' and 'b' waves normalized, but the late anomaly also appeared in this eye. Regarding this late, high-amplitude anomaly of the ERG, we were in doubt for some time if it was an artefact or a unique finding. Finally, based on the characteristic pattern of appearance in time and after we have ruled out all possible sources of artefact, we concluded that this phenomenon was uniquely associated with the disease process. The bulk of this late segment of the ERG in humans, historically also known as the 'c' wave (Granit, 1933) is generated in the retinal pigment epithelium, and is usually of small amplitude or missing. Nilsson and Wrigstad (1997) pointed out that this segment can be a sensitive indicator of damage to the retinal pigment epithelium in hereditary diseases. Thus, we assume that this finding reflects the immunological challenge to the retinal pigment epithelium (RPE). Notably, the phenomenon appeared in the clinically unaffected eye later, so it seems that it took longer until signs of RPE involvement appeared. This might indicate a cumulative effect with gradual involvement of different cell types, which was masked in the left eye by the higher exposure to the immunological process (where the cumulative effect showed as destruction and function loss).

An even more intriguing finding is that by the time the patient completely lost her vision in the left eye (after ongoing deterioration evidenced by the recordings), the electrophysiological findings of her right eye became normal for the first time in her history. Long-term follow-up of IP patients suggests that the progress of the disease may halt spontaneously at any stage (Holmstrom & Thoren, 2000). It is impossible to tell at this point if this is what we are seeing, but the sudden normalization of the parameters (never seen previously during the follow-up) is suggestive of such a scenario. Naturally, this also presupposes that the eye-specific trigger had been localized in the left eye and was consumed up in the destructive process that culminated in the blindness of this eye. This complete recovery after 17 years suggests that in the right eye the process caused functional disturbance only, that is, the ERG findings did not indicate significant cell destruction.

As for the rapid worsening of the patient's vision after surgery, it was an unexpected complication, most probably related to the use of silicone oil. It is known that the emulsification of silicone oil might lead to complications. However, those typically include glaucoma and keratopathy (Miller et al., 2014). The immunogenic properties of silicone have also had much attention in the literature, especially in connection with breast implants (Cohen Tervaert et al., 2017). While the literature does not confirm that silicone causes immunologically mediated disease, it is obvious that the presence of silicone in the body means constant stimulation to the immune system, which has also been demonstrated in retinal detachment surgeries with silicone oil (Pastor et al., 2001). The number of observations is low, though. The most we can say about this finding at this point is that it was probably a case of unexplained visual loss following the removal of silicone oil (Moya et al., 2015; Oliveira-Ferreira et al., 2020) which may have been caused by the reactivation of the immune process. The markedly subnormal responses recorded from the right eye seem to support this point.

Finally, the results show that ERG is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it readily detects their functional effect even in the lack of clinical symptoms. Thus, we propose that children in whom IP is suspected, regardless of whether clinical symptoms are already present, should undergo electrophysiological testing for the early detection of ocular involvement.

Conclusions

Electroretinography is a sensitive indicator of the activity of the ocular immune or inflammatory reactions in IP, and it read-

ily detects their functional effect even in the absence of clinical symptoms. Thus, it is recommendable not only for the long-term functional follow-up of these patients but probably also for early disease-specific screening. The ERG recordings from the presented case suggest that the asymmetric pattern of retinal functional involvement may be traced back to the different degrees to which the two eyes were exposed to the intermittent reactivations of the disease. Given the lack of long-term comprehensive follow-ups in IP, and especially ones that involve electrophysiological methods, it is impossible to tell at this point if these findings are entirely patient specific.

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