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Electrophysiologic alterations in patients with optic nerve hypoplasia

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Abstract. The clinical and electrophysiologic data (electroretinograms and visual evoked potentials) were studied in 45 patients with optic nerve hypoplasia. The patients were divided into three fairly distinct groups on the basis of their electrophysiologic alterations. Group 1 consisted of 13 patients with almost extinguished visual evoked potentials and with mild electroretinographic alterations. These were the cases that are traditionally recognized as optic nerve hypoplasia. The serious visual impairment in these cases was accompanied by various developmental ophthalmologic and nonophthalmologic abnormalities. Group 2 included 26 patients without any significant visual evoked potential or electroretinographic alterations, but with overt funduscopic signs of optic nerve hypoplasia. These patients were consistently suffering from strabismus and/or amblyopia. The visual functions based on visual evoked potential and electroretinographic recordings could be fairly normal apart from a pathologic ophthalmoscopic picture characteristic of optic nerve hypoplasia. Group 3 included six patients with abnormal albeit well-recordable visual evoked potentials and subnormal or negative-type electroretinograms that suggested an accompanying retinal disease. This finding seems to prove that a subset of patients with optic nerve hypoplasia with nystagmus may have a primary retinal abnormality. Our study provides further evidence that optic nerve hypoplasia is not a uniform disease entity.

Introduction

Optic nerve hypoplasia (ONH) is a nonprogressive, congenital, unilateral [1, 2] or bilateral [3–5] abnormality of the optic nerves (ONs). It can be accompanied by other ophthalmologic alterations, such as tilted discs [6, 7] and colobomatous defects of the iris, choroid or ON head [6, 8, 9]. The rather frequent occurrence of neurologic [10–12] and endocrine [12–15] abnormalities is well known.

The estimation of visual function in ONH is often difficult, since most patients are very young (less than 1 year) and frequently mentally retarded. In most of the reported cases, the patients displayed serious visual defects, impaired vision to total blindness. In contrast, some authors report bilateral ONH with a normal or almost normal visual acuity [16–18]. Unilateral cases typically show convergent strabismus with consecutive amblyopia. However, amblyopia can also occur in bilateral cases [9, 18]. Our investigations were prompted by the observation that some patients with ONH had serious visual

defects, whereas others had good or at least satisfactory visual acuity. We report clinical data on 45 patients with ONH. Special emphasis was attached to the electrophysiologic assessment of visual function and to the detection of accompanying retinal diseases without a characteristic fundus picture. We succeeded in classifying our 45 patients into three distinct groups on the basis of their electrophysiologic recordings. This classification proved to be useful in the further clinical analysis.

Subjects and methods

The clinical and electrophysiologic data on 45 patients (20 females and 25 males; age range, 2 months to 24 years) with ONH were studied. The diagnosis of ONH was based on the appearance of a largely decreased size of the optic disc with a "double ring sign.". Mild cases, where only the disc-macula/disc-diameter warranted the diagnosis in the absence of a double-ring sign [19], were excluded from the study. Various electrophysiologic examinations (visual evoked potential [VEP] testing, including pattern-reversal VEP [PVEP], flash VEP and light-emitting diode [LED]–elicited VEP, scotopic electroretinogram [ERG] photopic ERG and LED ERG) were carried out for objective evaluation of the retina and ON function. In the event of ERG abnormalities, we reexamined the patients every year to check on the stability of the alterations. The efficiency of orthoptic treatment was evaluated on repeated VEP recordings.

The ERG examinations were carried out under scotopic and photopic conditions, using monochromatic blue and red filters, respectively. For flash stimulation, a stroboscopic bulb (light intensity, 0.1 W) was employed, which shed its light onto a ganzfeld screen. The background illumination was 1.5 cd/m^2 under photopic conditions. With patients less than 3 of years of age, an NIC-107 LED stimulator (Nicolet, Madison, USA) was used. Fifty responses were, averaged. Every trial was repeated at least twice for reproducibility. Monocular stimulation was used while the contralateral eye was covered. ERG recordings were generally achieved with a skin electrode (Sensor Medic, Anaheim, USA) attached to the middle of the lower eye-lid, with a reference electrode clipped to the linked earlobes. In cases with subnormal ERGs, DTL electrodes were also used, which invariably increased the amplitudes without significantly altering the waveforms [20].

The pattern stimulation was delivered by a black-and-white checkerboard pattern, appearing with a checksize of 20′ or 40′ on a television screen. The checks were alternated at a rate of 1.8 Hz to give a reversing display with a constant luminance of 20 cd/m^2. In each trial, 100 stimuli were processed by an amplifier and a signal averager. The bandpass filters were set at 0.3 and 100 Hz. The recording was performed with an electrode in a midline

position 1–2 cm above the inion according to the circumference of the child's head (10–20 international electroencephalography system). Reference electrodes were clipped to both earlobes and linked together. An electrode on the forehead served as ground. The impedance of any electrode was less than 5 kOhm. The patient underwent a battery of ophthalmologic and neurologic examinations (visual acuity, slit lamp, ophthalmoscopy, perimetry, color vision, strabismus, nystagmus and pupillary reactions), depending on his or her age and mental condition. All children were also examined by a pediatric neurologist. Computed tomography was carried out whenever appropriate.

Two control groups were employed in this study. Ten children under 3 years of age with good vision and without ophthalmologic and neurologic alterations were stimulated with an LED while their ERGs and VEPs were detected. These data served a control value for group 1. Another 20 patients between 3 and 15 years of age with good visual acuity and without ophthalmologic or neurologic alterations provided ERG and VEP data for a statistical comparison in groups 2 and 3. We obtained informed consent from the parents of all the children. The study was approved by the Human Research Ethical Committee of our university.

Results

The 45 patients in our study were divided into three classes according to the following features of their clinical and electrophysiologic data (Table 1).

Group 1 consisted of 13 patients, mostly children less than 3 years of age. We additionally included in this group three older patients whose mental condition or visual acuity was so poor that pattern-reversal stimulation could not be performed. We could employ only LED stimulation to evolve the VEP and ERG in these 13 patients. All the patients displayed nystagmus. The original purpose of the ophthalmologic examination was to demonstrate or exclude blindness (Fig.1).

Other ophthalmologic alterations were also found, such as aplasia of the ON in two fellow eyes, hypoplasia accompanied by retinal detachment in one eye, a colobomatous defect around the ON and the periphery of the retina in 10 eyes and microphthalmos in one eye.

Nonophthalmologic complications occurred frequently in group 1. These included microcephaly in one case, septo-optic dysplasia in seven cases, and mental retardation in four cases. One child suffered from an accompanying metabolic disease (maple-leaf syrup disease). Polydactyly was detected in two cases, and one child had been operated on for clubfoot.

The electrophysiologic findings were in line with the serious clinical conditions. No reproducible VEPs were detected in 20 eyes. However, abnormal but reproducible VEPs were obtained in six eyes, which verified the residual

Table 1. Clinical and electrophysiologic data of the 45 patients with ONH

Group	Age (y)	Sex	Vision	Refraction	Ophthalmologic complications	Other complications	VEP	ERG
1 (13 patients, 26 eyes)	1.5; range, 0.5–24	6 males, 7 females	4 light perception, 9 no light perception	8 myopic, 1 emetropic, 4 hypermetropic, 13 astigmatism (-8.0 to +2.0 diopters)	1 ONH + microphthalmos, 2 aplasia ON, 1 ONH + retinal detachment, 10 ONH + coloboma (12 eyes only ONH)	1 microcephaly, 7 septo-optic dysplasia, 4 mental retardation, 2 polydactyly, 1 clubfoot	6 reproducible, 20 not reproducible	4 extinguished, 8 subnormal, 14 normal
2 (26 patients, 52 eyes)	6.1; range, 3–9	13 males, 13 females	0.61; range, 0.25–1.0	21 myopic, 5 hypermetropic (-6.0 to +2.0 diopters)	18 amblyopia, 26 astigmatism	- -	20 normal, 6 mild alteration	26 normal
3 (6 patients, 12 eyes)	9; range, 5–12	6 males	0.51; range, (0.25–0.6); binocular, 0.8	6 myopic+astigmatism (-16.0 to - 1.5 diopters)	5 hemeralopia, 1 coloboma, 6 astigmatism, 2 deuteranomaly	- - - -	6 increased latency, decreased amplitude*	5 negative type, 1 submormal+

* See Table 3.

+ See Table 2.

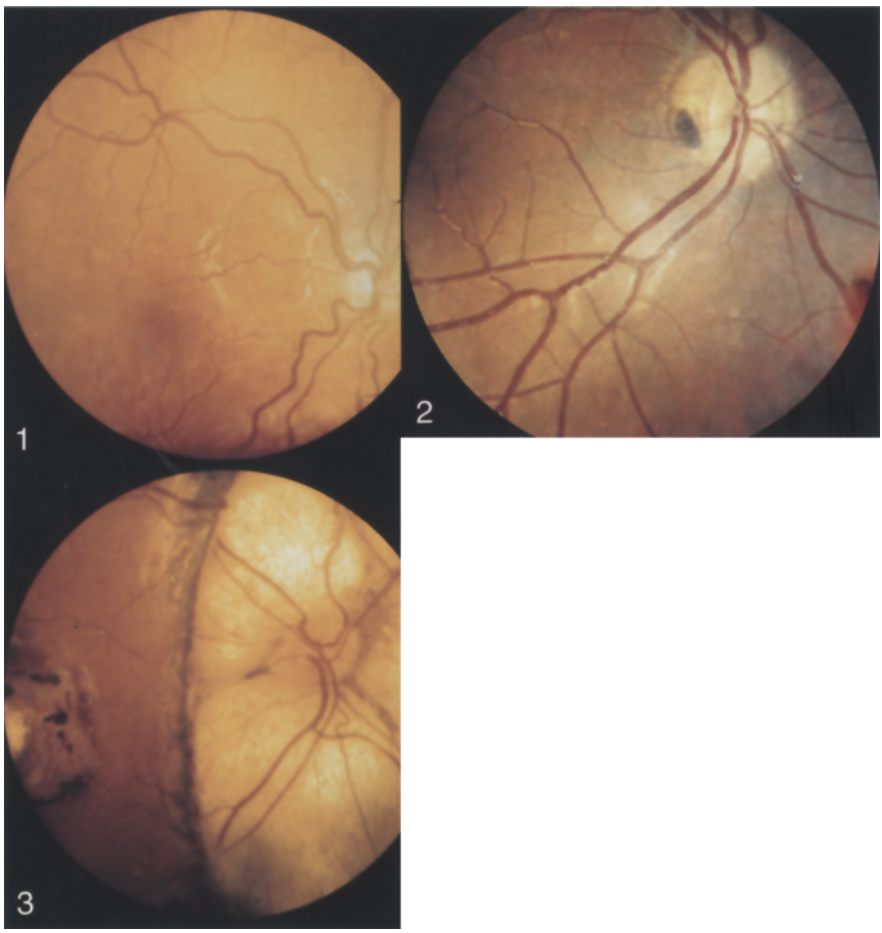

Fig. 1–3. Fundus picture of the right eye of a patient in group 1. Fundus picture from a patient in group 2. Fundus picture from the sixth patient in group 3.

light perception. The ERGs were extinguished in four eyes. These were the cases with microphthalmia and retinal detachment; no ERG could be detected in either eye of one patient without any characteristic visible retinal alteration. Subnormal ERGs were found in eight eyes, and normal ERGs in 14 eyes (normal values: PVEP, 40′: latency, 114.0 ± 6.1 ms; amplitude, 22.75 ± 5.45 μV; scotopic ERG, a-wave: latency, 27.2 ± 2.2 ms; amplitude, 10.1 ± 3.2 μV; b-wave: latency, 52.6 ± 4.0 ms; amplitude, 41.4 ± 4.1 μV; n = 20).

In group 2, the ophthalmologic and electrophysiologic data on 26 children with ONH (23 bilateral and three unilateral manifestations) were analyzed. The optic disc abnormalities due to strabismus or deteriorated visual acuity were revealed on ophthalmoscopic examination. None of these children

Table 2. Latency and amplitude values of scotopic ERGs in group 3

	Latency (ms)				Amplitude (μV)			
	a-wave		b-wave		a-wave		b-wave	
Patient	R	L	R	L	R	L	R	L
1	27	27	52	54	9	7	8	5
2	28	27	57	57	10	9	8	8
3	28	30	57	59	15	15	10	10
4	26	27	52	52	11	10	10	10
5	26	26	54	50	12	10	9	9
6	27	27	50	50	10	12	16	18
Normal	27.2±2.2		52.6±4. 0		10.1±3.2		41.4±4.1	

R = right eye, L = left eye.

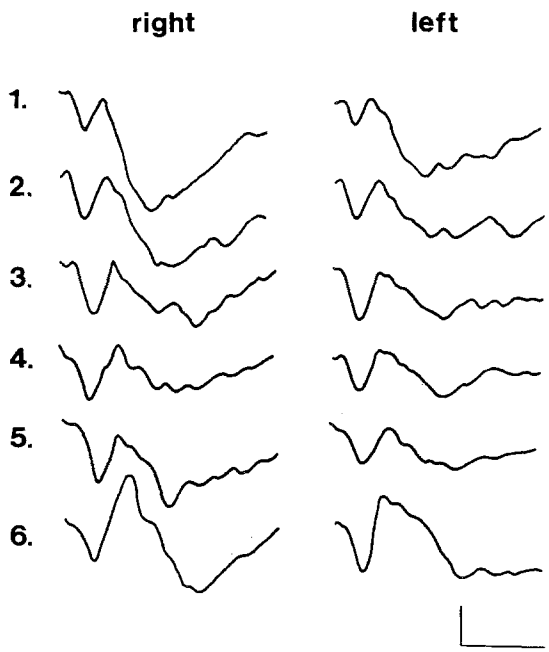

Fig. 4. Scotopic ERGs recorded in the right and left eyes of patients in group 3. Numbers refer to the appropriate case numbers. Calibration: 10μV, 100 ms.

exhibited any neurologic or other health problems. The mean age was 6.1 years (range, 3–9 years). The visual acuity and the electrophysiologic recordings demonstrated fairly good function. The mean visual acuity was 0.6

Table 3. Latency and amplitude values of PVEPs (40′) in group 3

	Latency (ms)			Amplitude (μV)		
Patient	R	L	Binocular	R	L	Binocular
1	142	144	141	15	7.5	26
2	132	136	135	9	11	16
3	127	131	130	6	7	10
4	155	150	150	10	10	14
5	-	130	130	-	17	15
6	124	127	125	15	15	16
Normal			114±6.1			22.75±5.45

R = right eye, L = left eye.

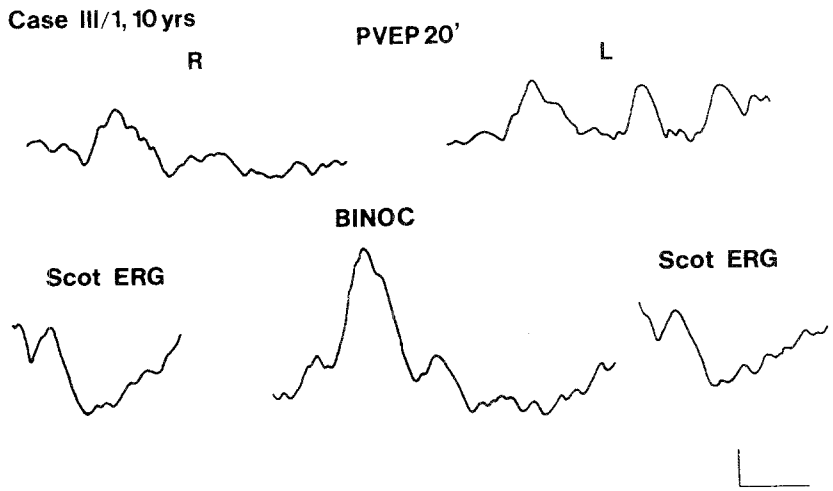

Fig. 5. PVEPs (top) and scotopic (Scot) ERGs (bottom) elicited by stimulating the right eye (R) and the left eye (L) of patient one of group 3. In the middle of the bottom row is a PVEP obtained by stimulating both eyes simultaneously (Binoc). Calibration: 10 μV, 100 ms.

(range, 0.25–1.0). Remarkably poor visual acuity was detected in the three unilateral ONH cases (0.25, 0.3 and 0.25), while much better visual acuities (range, 0.5–1.0) were detected in the bilateral ONH cases. The range of refractory errors was between −6.0 and + 2.0 diopters. Most of the children suffered from astigmatism.

All the scotopic and photopic ERGs were in the normal range for the age-matched controls. The VEPs displayed normal latencies and amplitudes in the binocular cases. In the three monocular cases, the VEP amplitudes

were decreased. The amplitudes of the VEPs, however, were much larger than expected from the visual acuity and ophthalmoscopic findings (Fig. 2). The visual acuity in unilateral cases improved with orthoptic treatment.

Group 3 consisted of six children with abnormal ERGs and VEPs. All were boys, and all of them had had nystagmus from birth. No other neurologic alterations were found. Ophthalmologic examination revealed a hypoplasic ON head in all eyes. Some diffuse pigment alterations were seen on the lower part of the retina in five patients in this group. A large colobomatous defect was found around the small disc and the retinal periphery in both eyes of the sixth child (Fig. 3). All six children suffered from astigmatism and mild myopia. Their visual acuity was between 0.6 and 0.25 with appropriate correction, while the binocular vision was surprisingly good (0.8) in most cases, although one child had a binocular acuity of 0.4.

The scotopic ERG in this group had a normal implicit time, the a-wave exhibited no significant alterations and the b-waves were severely decreased (Table 2). In five cases the peak of the b-wave only just reached or failed to reach the baseline (negative-type ERG) (Fig. 4). In the last case (case 6), a decreased b-wave amplitude was found, although the slope of the curve was not negative.

Since all these children had undergone regular ophthalmoscopic examinations from 3 years of age, four or five ERG recordings were available to prove the stability of this alteration.

The VEPs obtained by 40′ monocular pattern-reversal stimulation were greatly decreased in amplitude and lengthened in latency (Table 3). No detectable VEP was obtained on stimulation of one eye (the right eye of patient 5. The VEPs showed a great improvement whenever binocular stimulation was used instead of monocular stimulation (Fig. 5).

Discussion

Several reports and reviews have been published on ONH [3–5, 21]. Electrophysiologic examinations for objective evaluation of the function of the retina or the visual pathway have, however, rarely been performed in ONH [22, 23]. We report here electrophysiologic data on a fairly large group of patients with ONH. We succeeded in classifying them into three distinct groups, which supports the notion that ONH is not a uniform disease entity.

In the first group of patients, the ERGs were overwhelmingly normal or subnormal, although the VEPs revealed serious damage of the visual pathway. In the second group, which included the majority of our patients, the ERG was normal. Ewald [2] reported normal ERGs in two cases of complete aplasia of the ON, [2] while the ERGs were severely reduced and even extinguished in two cases described by François and Hruby [24]. Supranormal ERGs such

as those reported by others [22, 25–27] were not recorded in our 45 patients with ONH.

In our third group, five of the six cases displayed negative-type ERGs. All of these patients were boys. These children also had night blindness, but, because of their serious visual problems during daylight, they failed to mention this at the first interview. The alterations in the ERG records proved to be stationary during the follow-up examinations.

The occurrence of congenital stationary night blindness together with tilted disc was reported earlier [28, 29]. The associated manifestation of ONH, colobomatous defects and ON pit has also been described in one patient [6]. We found no reports on congenital stationary night blindness in patients with ONH, and our finding seems to widen the spectrum of developmental anomalies of the ON [6, 7, 17, 30]. The results, thus, seem to prove that a subset of patients with ONH who have nystagmus may have a primary retinal abnormality.

We have established that the VEP is able to detect a residual visual function in serious cases of ONH even in infants, although it permits only a rough assessment of the visual acuity. The contribution of the VEP to the evaluation of the severity of the visual impairment seems important, since the ophthalmoscopic finding does not always correlate with the visual functions in ONH [16, 17, 22].

In our group 2, the presence of normal pattern VEPs is in line with the fairly good vision and proves the existence of an intact papillomacular bundle.

Additionally, the pattern VEP appeared to be useful in verifying amblyopia ex anopsia in patients with ONH. The visual impairment in ONH can be enhanced by amblyopia [9, 16, 31] or astigmatism [32]. The detection of consecutive amblyopia by electrophysiologic examination indicates the importance of orthoptic treatment.

Nystagmus was another symptom that enhanced visual loss in patients with ONH. We found that the detection of ERG and binocular PVEP is important in patients with nystagmus. The ERG alterations seem to be characteristic of the concomitant retinal diseases while being independent of the presence or absence of nystagmus [33]. Monocular stimulation evoked a VEP with decreased amplitude in our third group, although on binocular stimulation the amplitude reduction almost disappeared. PVEP examinations are important not only in the detection of amblyopia ex anopsia in these patients, but also in the follow-up of their orthoptic treatment. Binocular PVEPs were found to correlate better than monocular PVEPs with the visual impairment in the cases with nystagmus. The normal pattern VEP in the case of ONH with good visual acuity and without nystagmus supports the existence of crossed macular axons serving focal vision.

In summary, patients with ONH can be fairly well separated into different groups on the basis of the results of electrophysiologic examinations. The distinctions between these groups run parallel with the developmental stages of the ON [13, 15, 34, 35]. Our first group, which is characterized by accompanying developmental anomalies, seems to involve patients with abnormalities during the early stage of development, while in the second group only the uncrossed fibers of the ON that develop last appear to be damaged. The third group, with concomitant retinal disease, fits into the spectrum of developmental abnormalities of the ON.

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