Documenta Ophthalmologica **86**: 11–22, 1994.

Optic nerve hypoplasia in association with brain anomalies and an abnormal electroretinogram

GERHARD W. CIBIS[1,2] & KATHLEEN M. FITZGERALD[2]

[1]*Department of Ophthalmology and* [2]*Vision Sciences Laboratory, Children's Mercy Hospital Kansas City, Missouri, USA*

Accepted 23 August 1993

Key words: Brain-retina neuroembryodysgenesis, Electroretinogram, Imaging studies, Optic nerve hypoplasia, Retinal dysgenesis

Abstract. Abnormal electroretinograms (decreased amplitude and prolonged implicit time >2 standard deviations) in several patients with optic nerve hypoplasia (ONH) and developmental brain anomalies led us to study the electroretinogram (ERG) in 34 consecutive cases of ONH presenting to our practice. Ages of the subjects were between 7 months and 13 years (mean, 4 years). ERGs were recorded from each eye by means of a contact lens electrode and ganzfeld stimuli. Rod-dominated dark-adapted responses were recorded as well as cone-dominated light-adapted responses. When clinically indicated, brain imaging by either computed tomography (CT) or magnetic resonance imaging (MRI) was performed. The ERG was abnormal in 12 (35%) of the children, including five (42%) with unilateral ONH. Imaging studies of the brain in 12 children with ONH and an abnormal ERG disclosed brain malformations in nine (75%) of them compared to five (23%) in the group with ONH and a normal ERG. An abnormal ERG associated with ONH and brain malformations may represent retinal or transsynaptic degeneration beyond the ganglion cell layer and implies a shared causative mechanism.

Abbreviations: CNS – central nervous system; ONH – optic nerve hypoplasia

Introduction

In normal ocular embryogenesis, there is an overproduction of retinal ganglion cells and axons [1–4]. Seventy percent of these axons degenerate by 33 weeks of gestation [2], a normal process called apoptosis. Presumably apoptosis allows retinal neurons to connect with the proper cells in the lateral geniculate nucleus, which in turn join appropriate cells in the visual cortex by rejecting those axons not properly connected. Factors that interfere with this process lead to excessive regression of axons, resulting in optic nerve hypoplasia (ONH). Mechanical injuries speculated to cause ONH include anomalies of the third ventricle [2], midline tumors [5] or cysts that prevent axons from reaching their target [6]. Central nervous system (CNS) anomalies associated with ONH are porencephaly [7], colpocephaly [8], cerebral atrophy [9], anencephaly [10–12], supraseller tumors [2],

hydranencephaly [13], schizencephaly, cerebral infarcts and hydrocephalus [10, 14]. These insults may occur as late as the second trimester [1], up to the 22nd week [3].

DeMorsier syndrome is a sporadic, nonfamilial subset of bilateral ONH associated with absence of the septum pellucidum, partial or complete agenesis of the corpus callosum and dysplasia of the anterior third ventricle [10]. Endocrine disturbances are commonly associated with DeMorsier syndrome [15].

Hypoplasia of the optic nerve is characteristically associated with a normal electroretinogram (ERG), according to most investigators [16–18]. For example, Harcourt [19] emphasized that the ERG is normal in both amplitude and wave form, which differentiates ONH from congenital amaurosis of Leber and achromatopsia. However, in 1976, Francois and DeRouck [20] found ERG abnormalities in eight (36%) of 22 cases of ONH (16 bilateral, six unilateral), citing a mild reduction in overall amplitude as the most common abnormality.

We have found an abnormal ERG in some children with ONH. These children also had a higher incidence of brain malformations seen on imaging studies. To investigate the meaning of this finding and the incidence of an abnormal ERG associated with ONH, we studied a consecutive series of 34 children with ONH.

Subjects and methods

The subjects were recruited from the Children's Mercy Hospital (Kansas City, MO, USA) Department of Ophthalmology and our private offices. Informed consent was obtained after approval of the study protocol by the internal review board. Subjects were 34 consecutive children between the ages of 7 months and 13 years (mean, 4 years) who were clinically determined to have bilateral or unilateral ONH. The determination of ONH was made in each case by an experienced pediatric ophthalmologist (GWC).

The average normal disc diameter is 1.5 mm. Retinal vessel diameter at disc entry is 0.1 mm. Therefore, if the observer uses vessel diameter as a reference, 15 vessels should span the disc in a normal subject. A disc less than 0.8 mm is considered to be hypoplastic. Other signs of ONH are lack of nerve fiber layer reflex manifested as an excessive internal vitreoretinal reflex, broadened retinal vessel reflex and tortuous vessels. A double ring sign is also helpful (Fig. 1).

Subjects were excluded from the study when the ocular examination revealed retinopathy of prematurity, microphthalmia, pigment retinopathy and other chorioretinal lesions known to be associated with an abnormal ERG. The control groups consisted of age-matched subjects with no history or evidence of eye disease on examination.

The pupils of the eyes tested were dilated with 1.0% tropicamide and

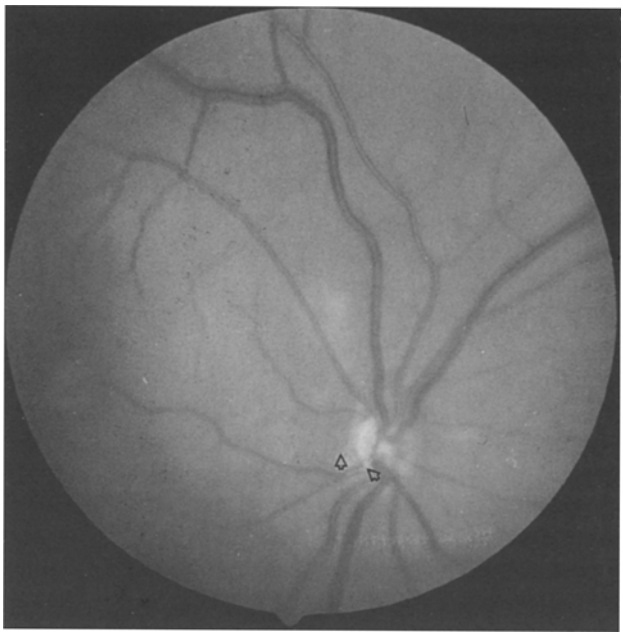

Fig. 1. Optic nerve hypoplasia. A double ring sign (arrows) is present.

2.5% phenylephrine hydrochloride drops. The patients' eyes were dark adapted for 45 minutes. Children under the age of 3 years and uncooperative patients were sedated with 50–75 mg/kg of oral chloral hydrate syrup after parental consent. The cornea was anesthetized with 0.5% proparacaine hydrochloride, and the contact lens electrode was inserted under dim long-wavelength illumination. The eyes were tested simultaneously.

After dark adaptation, stimulus flashes of short wavelength (blue) (Wratten filters 47, 47A and 47B in combination, Eastman Kodak, Rochester, NY, USA), long wavelength (red) (Kodak Wratten 26) and white (xenon) were presented in a ganzfeld bowl (Nicolet, Madison WI, USA) under scotopic conditions. Flash luminance was attenuated by means of internal strobe settings and neutral-density filters (Wratten). In the photopic conditions, a rod-desensitizing background field of 10 foot lamberts was used to isolate the cone response. The stimulus flash was white (xenon). Flash and background luminances were calibrated with a photometer (model 350, United Detector Technology, Hawthorne, CA USA).

The ERGs were recorded with a monopolar 'jet' contact lens electrode (Universo, Lausanne, Switzerland), referenced to the patient's ipsilateral mastoid with a forehead ground. Recordings were performed with a signal-averaging system (CA-1000, Nicolet). The conventional ERGs were recorded with a bandpass frequency setting of 1–1500 Hz (−3 dB points). Oscillatory potentials were recorded with bandpass frequency settings of

30–1500 Hz (−3 dB points). Responses were stored on floppy disks for later analysis.

The ERGs were recorded to a series of stimuli, first to the dark-adapted eye at 15-second intervals. We used one blue flash (−1.00 log cd-sec/m^2); one red flash (0.66 log cd-sec/m^2); and two separate white flashes, the first being the conventional ERG (1.72 log cd-sec/m^2) and the second the oscillatory potential (1.72 log cd-sec/m^2), recorded at the filter settings described earlier. The eyes were then light adapted to a rod-desensitizing background of 20 foot lamberts for 10 minutes. The light-adapted stimuli were presented with a 10-foot lambert background and consisted of one white flash (1.72 log cd-sec/m^2) followed by a 30-Hz flickering white light (0.79 log cd-sec/m^2).

Brain imaging was done whenever possible. In some cases it was not clinically indicated. Data were analyzed by means of a two-tailed t-test ($\alpha = 0.05$).

Results

Amplitude and implicit times of all ERG responses were compared to those of normal age-matched control groups. Those subjects whose ERG values were greater than 2 standard deviations from normal were labeled group 1 (n = 12, 35%). The remaining subjects were labeled group 2 (n = 22, 65%). A two-tailed t-test comparing amplitude and implicit time values of group 2 against the normal control groups revealed no statistically significant difference. A two-tailed t-test was then performed comparing the values of groups 1 and 2. This yielded significant differences between groups for both amplitude and implicit times for all test conditions (Figs. 2 and 3). While both amplitude and implicit times were affected, there seemed to be a greater effect on amplitude. In group 1 there was a 42% incidence of unilateral ONH compared to 18% in group 2 (Table 1). Surprisingly, the ERG was abnormal in both eyes in four of the five cases of unilateral ONH in group 2.

Brain imaging was done in 83% of the subjects in group 1 compared to 55% in group 2 (Table 2). Ten of the subjects in group 2 did not undergo imaging studies because of lack of parental consent or the absence of clinical evidence to warrant computed tomography or magnetic resonance imaging. Those subjects in group 1 had a higher incidence of neurologic findings (seizures, developmental delay), and only two subjects (17%) did not undergo imaging studies. Of the remaining subjects, nine (75%) had evidence of brain anomalies, while one subject (8%) had a normal imaging study. Brain anomalies were found in five (23%) of the subjects imaged in group 2, while seven (32%) were normal. The malformations detected in group 1 included one case of unilateral ONH with absence of the septum pellucidum and hypoplasia of the corpus callosum, another case of unilateral

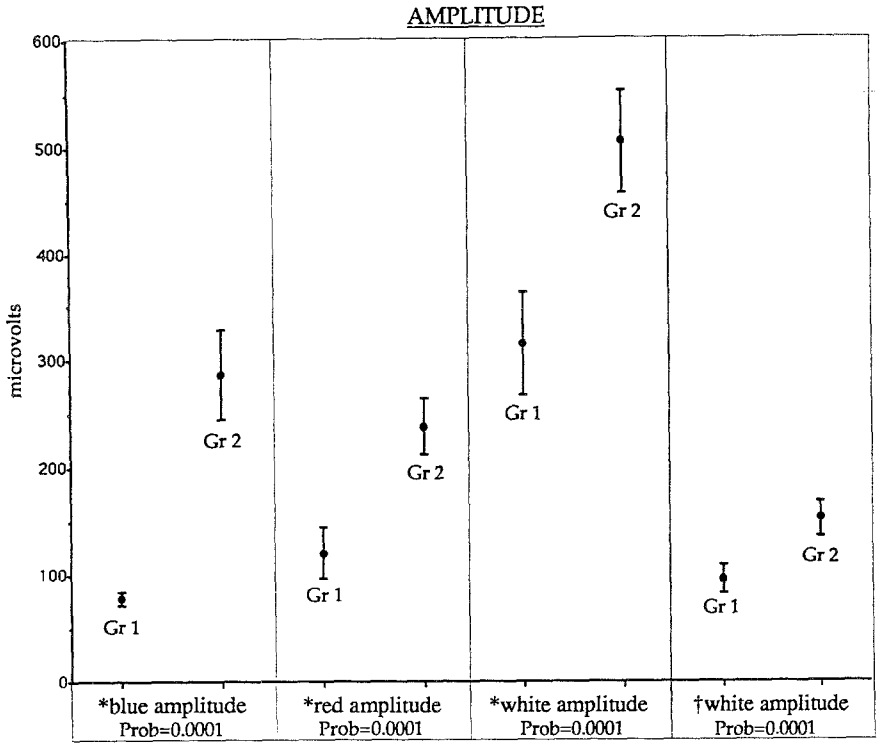

Fig. 2. ERG amplitudes of group 1 (Gr 1) and group 2 (Gr 2). Both scotopic and photopic values are represented. The error bars represent 95% confidence intervals. A two-tailed T-test between groups shows statistically significant differences for all values ($\alpha = 0.05$).
*scotopic testing conditions;
†photopic testing conditions.

ONH with an absent septum pellucidum and a porencephalic cyst, two bilateral ONH cases with ventriculomegaly and cerebellar hypoplasia, one bilateral case with a porencephalic cyst (Fig. 4), one bilateral case with cerebellar atrophy and cerebral dysgenesis and one bilateral case with leukomalacia, porencephaly, atrophy of the corpus callosum and cerebellar atrophy (Fig. 5). One bilateral case was true DeMorsier syndrome. One unilateral case with unilaterally abnormal ERG had a temporal lobe vascular malformation on the side of the ONH. Three subjects were microcephalic. The ERGs associated with the imaging shown in Figs. 4 and 5 are compared with that of normal control in Fig. 6. Imaging studies in group 2 revealed three bilateral cases with DeMorsier syndrome, while the remaining two bilateral cases had hypoplasia of the corpus callosum associated with cerebellar and cortical hypoplasia. A summary of clinical and other findings in all subjects is presented in Table 3.

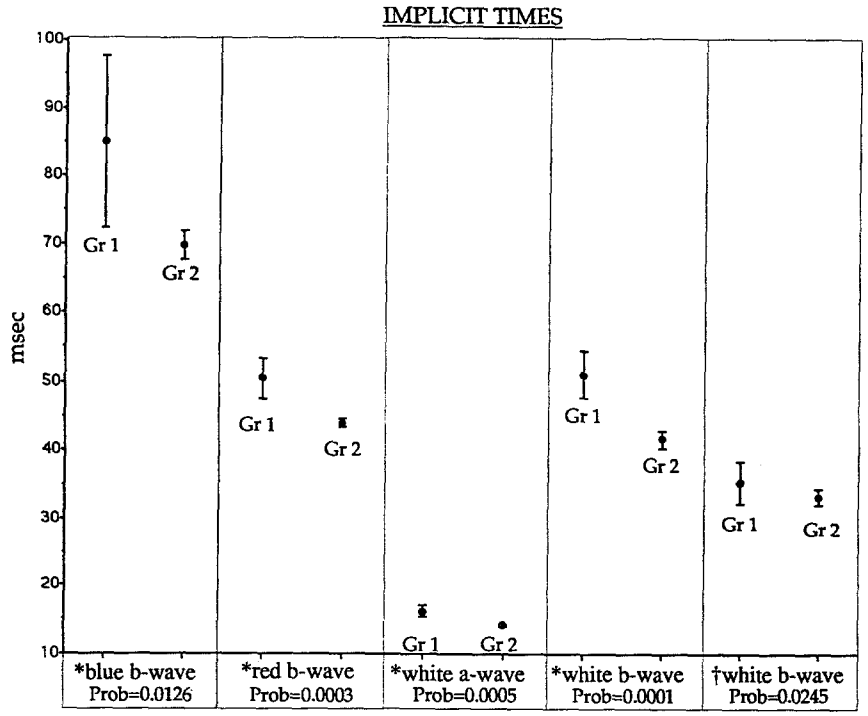

Fig. 3. ERG implicit times of group 1 (Gr 1) and group 2 (Gr 2). Both scotopic and photopic values are represented. The error bars represent 95% confidence intervals. A two-tailed T-test between groups shows statistically significant differences for all values ($\alpha = 0.05$).
*scotopic testing conditions;
†photopic testing conditions.

Table 1. The ERG in Optic Nerve Hypoplasia

		No. of patients		
Group	ERG	Unilateral ONH	Bilateral ONH	Total
1	Abnormal	5	7	12
2	Normal	4	18	22
Total		9	24	34

Table 2. Brain imaging in Optic Nerve Hypoplasia

		No. of patients			
Group	ERG	Abnormal brain imaging	Normal brain imaging	Not tested	Total
1	Abnormal	9	1	2	12
2	Normal	5	7	10	22
Total		14	8	12	34

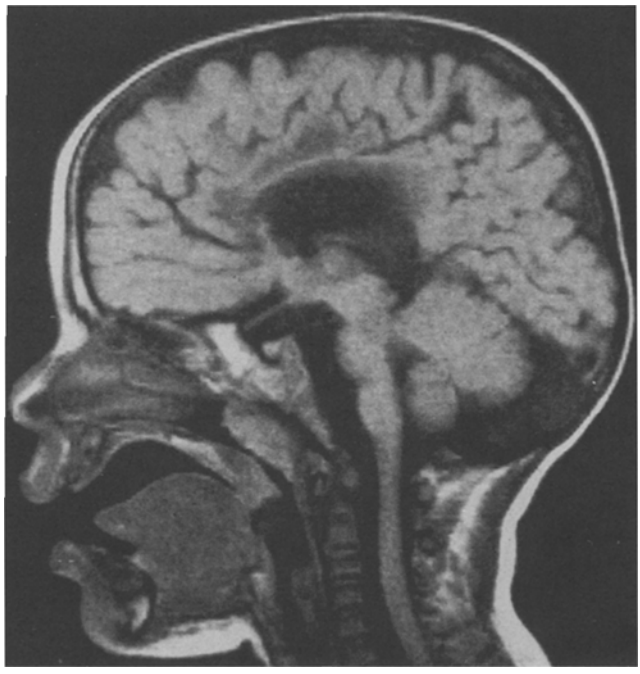

Fig. 4. Grossly abnormal magnetic resonance image of the brain with multiple abnormalities, including ventriculomegaly with periventricular leukomalacia or porencephaly. There is atrophy of the corpus callosum and the optic chiasm. There is diffuse severe cerebral and cerebellar atrophy. The septum pellucidum appears to be present.

Discussion

Many hypotheses surround the mechanism of ONH. Scheie and Adler [21] suggested a primary lack of ganglion cell development, citing histopathologic reports that showed a lack of ganglion cell formation with normal outer retina. However, Mosier et al. [1] pointed out that third-order neurons arise from the same precursor cells as amacrine and horizontal cells, and it would be unlikely that injury to the stem cells could affect only one of the differentiated cell types. They espoused the hypothesis that CNS injuries lead to a secondary, transsynaptic [22, 23] degeneration of ganglion cells and nerve fibers. On the basis of clinical appearance and associated CNS abnormalities, Frisen and Holmegaard [24] concluded that ONH indicates irreversible axonal damage to the eye or visual pathway sometime before full development. Novakovic et al. [2] deduced that ONH occurs embryologically from damage to any site in the developing visual pathway from retina to occipital lobe.

On the basis of their ERG findings in ONH, Francois and DeRouck [20] theorized retinal degeneration 'outside the ganglion cell layer'. Our findings of an abnormal ERG in both eyes in four of five cases of unilateral ONH

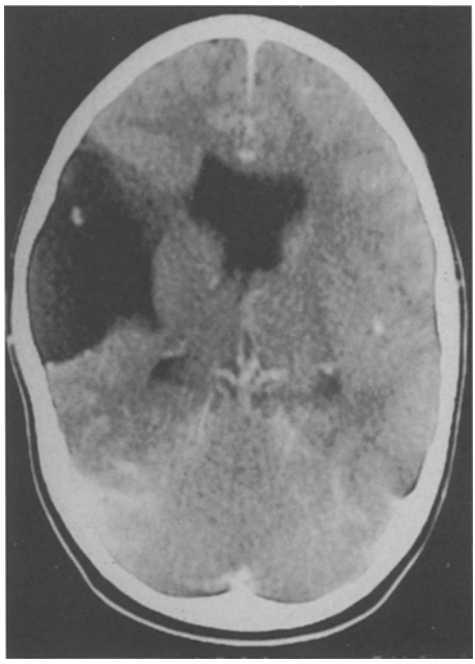

Fig. 5. Abnormal computed tomographic scan shows a large porencephalic cyst involving the right temporal region that communicates with the right lateral ventricle. Both lateral ventricles are enlarged. No septum pellucidum is identified.

supports the theory of retinal dysgenesis as a cause. In these cases, retinal dysgenesis is the primary event, severe enough in some eyes also to cause ONH by lack of ganglion cell formation.

While we found a higher incidence of nonmidline brain anomalies in subjects with ONH with an abnormal ERG, most patients with DeMorsier syndrome with midline defects had normal ERG. This may represent primary failure of the ganglion cells to send out axons, as postulated by Scheie and Adler [21], or retrograde degeneration that does not extend past the ganglion cells. The rostral part of the neural tube is the earliest definable developmental field [25]. Teratogens or genetic aberrations acting at this early stage can influence both eye and brain development [26, 27]. We believe both developmental and mechanical disruption of brain formation can contribute to ONH associated with an abnormal ERG.

An abnormal ERG with ONH may be a clue to nonmidline developmental brain malformations. The association of developmental anomalies, such as hypoplasia of the corpus callosum, cerebellar hypoplasia and cerebral dysgenesis, with an abnormal ERG leads us to theorize a shared defect in brain and retinal cell embryology such as cell migration or synapse formation, a condition we call brain-retina neuroembryodysgenesis. We

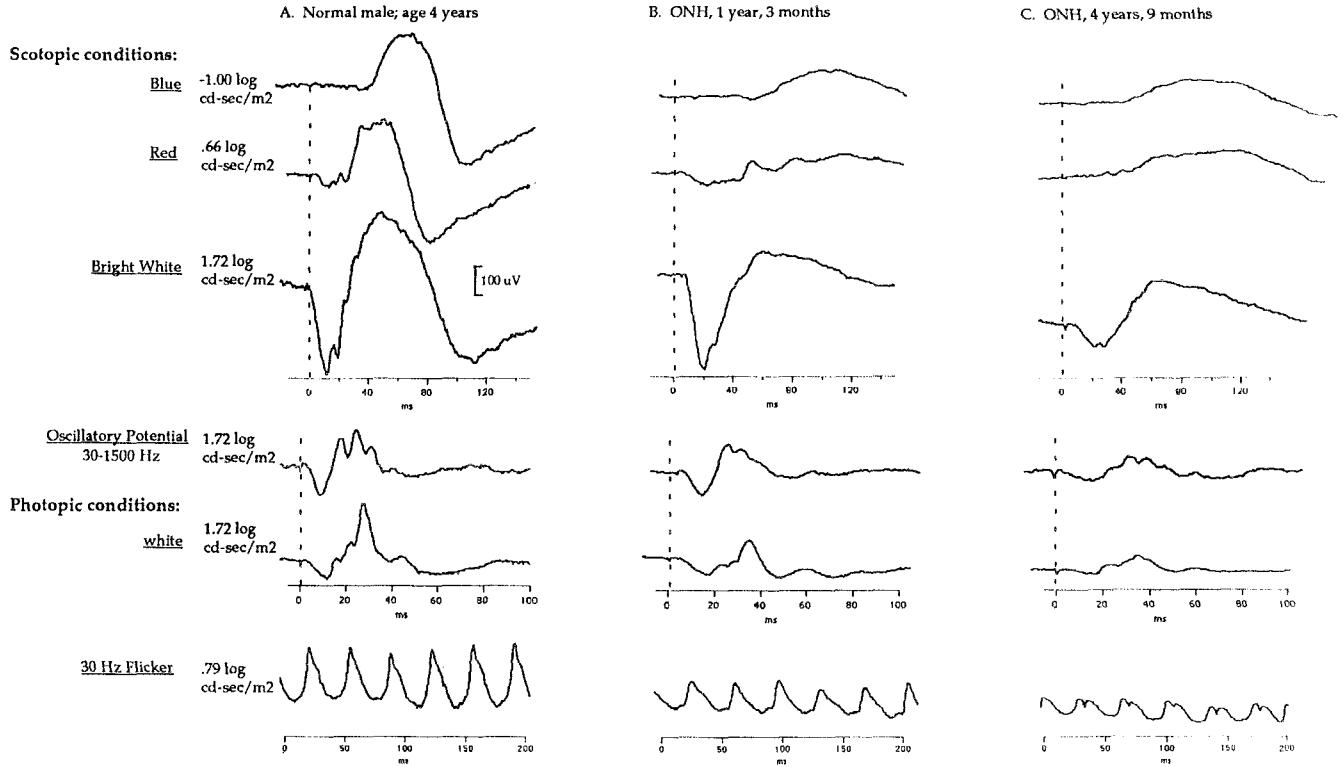

Fig. 6. (A) Normal ERG from a 4-year-old subject. (B) ERG of a child ages 1 year 3 months with bilateral ONH and leukomalacia, porencephaly, atrophy of the corpus callosum and cerebellar atrophy (Fig. 4). Note the prolonged implicit times of both a- and b-waves, decreased b-wave amplitude and an abnormal b/a amplitude ratio, which gives the response to bright white stimulus an almost negative appearance. Oscillatory potentials are poorly formed, and photopic amplitudes to a single flash and 30-Hz flicker are decreased (C). The ERG of a child aged 4 years 9 months with a porencephalic cyst (Fig. 5). Responses to scotopic blue and red stimuli are nearly extinguished, with very little cone contribution to the red flash. The response to bright white stimuli shows decreased-amplitude a- and b-waves. Oscillatory potentials and photopic responses are nearly extinguished. The dashed line represents stimulus onset.

Table 3. Acuity, clinical and other findings in 34 patients with ONH

Patient	Age	Acuity[a]	Clinical findings	ONH[b]	ERG[c]	Imaging[d]	Other[e]
1	8 mo	NA	Exotropia, anisometropia	U	A	A	Absent corpus callosum and septum pellucidum
2	7 mo	NA	Cataract OD	U	A	nd	PPHV (OS), morning glory syndrome (OD), developmental delay, seizures, microcephally
3	2 yr 1 mo	NA	Amblyopia, Ptosis	U	A	nd	Normal development
4	1 yr	NA	Congenital anomalis	B	A	A	Ventriculomegaly, cerebellar hypoplasia
5	5 yr	NA	Exotropia	U	A	A	Porencephalic cyst, absent septum pellucidum
6	1 yr 1 mo	NA	Exotropia, amblyopia, head turn	B	A	N	Failure to thrive, microcephally
7	1 yr 3 mo	NA	Behaves blind, pale fundus	B	A*	A*	Leukomalacia, porencephaly, atrophy of corpus callosum and cerebellar atrophy
8	10 mo	NA	Pale fundus, poor jmacular reflex, esotropia	B	A	A	Cerebellar atrophy, cerebral dysgenesis, seizures
9	4 yr 9 mo	20/200 OD, 20/200 OS	Nystagmus	B	A*	A*	Developmental delay, porencephalic cyst
10	8 mo	NA	Nystagmus, poor reflex	B	A	A	Thinning of the corpus callosum, absent septum pellucidum
11	5 yr 11 mo	NA	Tortuous vessels, esotropia	B	A	A	Cerebellar hypoplasia, ventriculomegaly, microcephaly
12	7 mo	NA	Esotropia, nystagmus	U	A	A	Left temporal lobe venous angioma
13	3 yr 5 mo	20/60 OD, 20/30 OS	Normal OS, esotropia	U	N	nd	Normal development
14	11 yr 6 mo	LP OD, 20/200 OS	Esotropia, pale fundus	U	N	N	Normal development
15	1 yr 5 mo	NA	Esotropia	U	N	N	Normal development
16	8 mo	NA	Nystagmus, esotropia	U	N	N	Developmental delay
17	1 yr 11 mo	NA	Nystagmus, esotropia	B	N	N	Normal development
18	4 mo	NA	Esotropia	B	N	nd	Normal development
19	10 mo	NA	Pale fundus, tortuous vessels	B	N	nd	Congenital anomalies, developmental delay, renal failure
20	3 yr	NA	Pendular nystagmus, exotropia	B	N	A	CHARGE syndrome, cortical atrophy, prominent sulci and ventricles
21	13 yr	CF at 6 inches	Field loss, head turn	B	N	nd	Normal development
22	4 mo	NA	Strabismus	B	N	A	Small optic chiasm and tracts
23	5 yr 11 mo	NA	Nystagmus, exotropia	B	N	A	Absent septum pellucidum, thinning of corpus callosum, attenuated optic tracts
24	10 yr 4 mo	LP OD, 20/200 OS	Pendular nystagmus, exotropia	B	N	A	Right cerebral hemiatrophy, absent septum pellucidum
25	4 mo	NA	Horizontal nystagmus, myopia	B	N	A	Absent septum pellucidum
26	5 mo	NA	Poor reflex, tortuous vessels	B	N	nd	Maternal drug abuse
27	9 yr 6 mo	20/300 OD, 20/100 OS	Exotropia	B	N	N	Normal development
28	3 yr	NA	Nystagmus, Esotropia	B	N	nd	Failure to thrive, developmental delay
29	11 yr	20/200 OD, 20/100 OS	Field loss, color blind	B	N	nd	Normal development
30	8 yr	20/60 OD, 20/200 OS	Nystagmus, amblyopia	B	N	N	Normal development
31	5 yr	20/80 OD, 20/80 OS	Nystagmus	B	N	nd	Developmental delay
32	7 yr	LP OD, 20/70 OS	Field loss	B	N	nd	Normal development
33	7 yr	LP OD, 20/200 OS	Nystagmus	B	N	nd	Normal development
34	5 yr 1 mo	20/60 OD, 20/80 OS	Anisometropia, esotropia, amblyopia	B	N	nd	Developmental delay

[a]NA = not applicable due to age or developmental delay of subject; OD = right eye, OS = left eye, LP = light perception, CF = counting fingers.
*ERG and imaging studies are illustrated in Figs. 4, 5 and 6.
[b]ONH: U = unilateral; B = bilateral.
[c]ERG: A = abnormal; N = normal.
[d]Imaging: A = abnormal; N = normal; nd = not done.
[e]Other: PPHV = primary persistent hyperplastic vitreous; CHARGE = cololoma, heart, atresion choanal, retarded growth and development, genital hypoplasia, ear anomalies, hearing loss.

conclude that an abnormal ERG associated with ONH and brain malformations may represent retinal dysgenesis or transsynaptic degeneration beyond the ganglion cell layer, implying a shared causative mechanism between retina and brain. Transsynaptic degeneration has been shown to be age dependent in monkey experiments showing more extensive degeneration in younger animals [23]. This raises the possibility of a simultaneous interplay of intrauterine brain and retinal embryodysgenesis with antegrade [24] and retrograde transsynaptic degeneration. Correlated with other clinical findings, the ERG may be helpful in establishing the pathogenic mechanism of ONH.

References

1. Mosier MA, Lieberman MF, Green WR, Knox DL. Hypoplasia of the optic nerve. Arch Ophthalmol 1978; 96: 1437–42.
2. Novakovic P, Taylor DSI, Hoyt WF. Localizing patterns of optic nerve hypoplasia: Retina to occipital lobe. Br J Ophthalmol 1988; 72: 176–82.
3. Lambert SR, Hoyt CS, Narahara MH. Optic nerve hypoplasia. Surv Ophthalmol 1987; 32: 1–9.
4. Gelbart SS, Hoyt CS. Congenital nystagmus: A clinical perspective in infancy. Graefes Arch Clin Exp Ophthalmol 1988; 226: 178–80.
5. Taylor D. Congenital tumours of the anterior visual system with dysplasia of the optic discs. Br J Ophthalmol 1982; 66: 455–63.
6. Mayer W, Sperl W. Porencephalie als ursache von ophthalmologischen symptomen. Klin Monatsbl Augenheilkd 1985; 187: 449–50.
7. Greenfield PS, Wilcox LM, Weiter JJ, Adelman L. Hypoplasia of the optic nerve in association with porencephaly. J Pediatr Ophthalmol Strabismus 1980; 17: 75–8.
8. Garg BP. Colpocephaly: An error of morphogenesis. Arch Neurol 1982; 39: 243–6.
9. Rogers GL, Brown D, Gray I, Bremer D. Bilateral optic nerve hypoplasia associated with cerebral atrophy. J Pediatr Ophthalmol Strabismus 1981; 18: 18–22.
10. Hoyt CS. Optic nerve hypoplasia: A changing perspective. Pediatr Ophthalmol and Strabismus: Transactions of the New Orleans Academy of Ophthalmology. New York: Raven Press, 1986: 257–64.
11. Boniuk V, Ho PK. Ocular findings in anencephaly. Am J Ophthalmol 1979; 88: 613–7.
12. Hotchkiss ML, Green W. Optic nerve aplasia and hypoplasia. J Pediatr Ophthalmol Strabismus 1979; 16: 225–40.
13. Herman DC, Bartley GB, Bullock JD. Ophthalmic findings of hydraencephaly. J Pediatr Ophthalmol Strabismus 1988; 25: 106–11.
14. Warburg M. Doyne Memorial Lecture. Retinal malformations aetiological heterogeneity and morphological similarity in congenital retinal nonattactment of falciform folds. Trans Ophthalmol Soc UK 1979; 99: 272–83.
15. Skarf B, Hoyt CS. Optic nerve hypoplasia in children: Association with anomalies of the endoctrine and CNS. Arch Ophthalmol 1984; 88: 613–17.
16. Ewald RA. Unilateral hypoplasia of the optic nerve. Radiologic electroretinographic findings. Am J Ophthalmol 1967; 63: 734–67.
17. Ouvrier R, Billson F. Optic nerve hypoplasia: A review. J Child Neurol 1986; 1: 181–8.
18. Margalith D, Jan JE, McCormick AQ, Tze W, Lapointe J. Clinical spectrum of congenital optic nerve hypoplasia, review of 51 patients. Dev Med Child Neurol 1984; 26: 311–22.
19. Harcourt B. Developmental abnormalities of the optic nerve. Trans Ophthalmol Soc UK 1976; 96: 395.

20. Francois J, DeRouck A. Electroretinographical study of the hypoplasia of the optic nerve. Ophthalmologica 1976; 172: 308–30.
21. Scheie HC, Adler FH. Aplasia of the optic nerve. Arch Ophthalmol 1941; 26: 61–70.
22. Gills JP, Wadsworth JAC. Retrograde transsynaptic degeneration of the inner nuclear layer of the retina. Invest Ophthalmol Vis Sci 1967; 6: 437–47.
23. Dineen JT, Hendrickson AE. Age-correlated difference in the amount of retinal degeneration after striate cortex lesions in monkeys. Invest Ophthalmol Vis Sci 1981; 21: 749–52.
24. Frisen I, Holmegaard L. Spectrum of optic nerve hypoplasia. Br J Ophthalmol 1978; 62: 7–15.
25. Warburg M, Friedrich U. Coloboma and microphthalmos in cromosomal aberrations and neural crest cell developmental field. Ophthalmic Paediatr Genet 1987; 8: 105–18.
26. Cook CS, Nowtony AZ, Sulik KK. Fetal alcohol syndrome: Eye malformations in a mouse model. Arch Ophthalmol 1987; 105: 1576–81.
27. Newman NM, Stevens RA, Heckenlively JR. Nerve fibre layer loss in diseases of the outer retinal layer. Br J Ophthalmol 1987; 71: 21–6.

Address for correspondence: Gerhard W. Cibis, MD, 4620 J.C. Nichols Parkway, Suite 421, Kansas City, MO 64112, USA
Phone: (816) 561 0306; Fax: (816) 842 7420