Visual-evoked Potential Evidence of Chiasmal Hypoplasia

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Purpose: To show that chiasmal hypoplasia or aplasia need not be an isolated developmental anomaly and to examine the spectrum of associated clinical findings to explore the possibility that these patients may represent a phenotypic manifestation of a developmental gene anomaly.

Design: An observational case series.

Participants: Five infants, between several weeks and 7 months of age, in whom the electrophysiologic characteristic of chiasmal hypoplasia had been noted were included.

Methods: Flash electroretinography and flash and pattern visual-evoked potentials (VEPs) were elicited from all patients. Clinical ophthalmologic examinations, including funduscopy, were performed, and all patients had magnetic resonance imaging (MRI) brain scans.

Main Outcome Measures: The occipital distribution of monocular VEP response peaks was studied. The symmetry of lateral channel responses was compared for monocular stimulation.

Results: All five patients had a crossed asymmetry in the monocular VEP occipital distribution, which is consistent with a paucity of fibers crossing at the chiasm. The MRI findings supported this electrophysiologic observation, illustrating degrees of chiasmal hypoplasia and variable coincidence of other midline abnormalities of the brain. Optic disc appearances varied from normal to hypoplastic and colobomatous.

Conclusions: The ophthalmologic and MRI findings of five patients who showed a crossed asymmetry in monocular flash VEPs are consistent with a paucity of axons crossing at the chiasm. The similarities between achiasmia in humans and mice due to a Pax2 gene anomaly are discussed.

Achiasmia,1 or “non-decussating retinal fugal fibre syndrome,”2 has only recently been recognized. It was first described by Williams et al (Soc Neurosci Abstr 1991;17: 187) in a group of Belgian sheepdogs who manifested see-saw nystagmus. Williams et al1 reported that the optic nerves, in seven of eight dogs studied, did not approach each other to form a chiasm. In the eighth dog, only a small decussating retinal projection was observed. Apkarian et al2 described asymmetries in the distribution of the monocular, pattern-onset, visual-evoked potentials (VEPs) in two children who presented with poor distant vision and see-saw nystagmus. The polarity of VEP distribution across the occiput was the reverse of the crossed asymmetry that has been described in albinism,3,4 a condition in which there is excessive decussation at the chiasm. The findings by Apkarian et al2 suggested a chiasmal anomaly that subsequent magnetic resonance imaging (MRI) scans revealed a lack of a chiasm. There was neither MRI nor clinical evidence of abnormality of other midline structures. Apkarian et al2 suggested naming the condition “non-decussating retinal fugal fibre syndrome.” The only other report in the literature is of a girl who presented to our hospital with a midline cleft, nasal encephalocele, and see-saw nystagmus.5 Monocular flash VEPs showed the crossed asymmetry in scalp distribution indicative of compromise of chiasmal crossing fibers, and subsequent MRI scanning showed achiasmia.

Since then, we have recorded a further four patients who show this form of crossed asymmetry of monocular VEP distribution. In two patients, this VEP finding directly led to MRI scans. These demonstrated chiasmal hypoplasia in one patient and almost total achiasmia in the other patient. Neither of these patients showed any other midline abnormalities. The other patients had other widespread midline abnormalities, which included de Morsiers syndrome, with optic nerve hypoplasia and hypopituitarism, and frontonasal
dysplasia, with midline cleft and bilateral colobomatous “morning glory discs.”

Methods

The VEPs to both flash and pattern stimuli were recorded from three occipital electrodes: one placed 3 cm above the inion at Oz and the other two positioned midway between the mastoid and Oz, approximately 4 cm right and left depending on head size. Mixed rod/cone flash electroretinograms (ERGs) were recorded from active skin electrodes positioned close to the inferior eyelid margin. These are recorded under scotopic conditions to a grass intensity-4 flash, both rod and cones contribute to the response, and the b-wave latency occurs around 39 msec. The VEP and ERG active electrodes were referred to a common midfrontal electrode (Fz 10–20 system). Pattern VEPs were recorded to a range of check sizes (2.5 to 40.0 minutes of arc) phase reversing at 3 reversals/second in a field subtending 28° horizontally and 21° vertically. A total of 128 responses were averaged over 300 msec, which included a 15-msec prestimulus interval. Closed-circuit television was used to monitor fixation, and signal acquisition was carried out only when viewing behavior was satisfactory. The amplitude of the responses to different check sizes is used to give a qualitative assessment of acuity level (a fuller description is given in the study by Kriss and Thompson).6

For the purposes of identifying anomalies at the chiasm, monocular flash testing is essential in children. Crossed asymmetry occurs when an asymmetric occipital scalp distribution of a VEP is reversed for comparison of left and right eye findings.7 In achiasma, this asymmetric distribution is opposite to that found in albinism.2,3 Figure 1 illustrates these differences schematically, and Figure 2 illustrates the actual recordings from patient 2. In a healthy infant, the maximum positivity is expected on the midline electrode, and the lateral channels have smaller symmetric responses.

Results

Table 1 summarizes the pertinent patient details. Additional clinical findings are described here for each case.

Patient 1

This patient was born at 38 weeks' gestation and weighed 6 lb. The mother’s pregnancy had been normal and the delivery uneventful. This patient is the youngest of three boys. There was no family history of eye problems. His parents noted that he was not fixing or following by 8 weeks of age, and he had wandering eye movements. He had a manifest horizontal nystagmus and head shake at 7 months of age and was referred to our department for visual electrodiagnostic assessment. There was no significant refractive error, and his optic discs appeared healthy. Eye movement studies showed a horizontal pendular nystagmus and no demon-
Ipsilateral and contralateral peaks represent a crossed asymmetry in occipital scalp distribution consistent with a chiasmal anomaly. A computed tomographic scan at this time was reported as normal. When he was examined again 3 months later, the patient’s electrophysiologic findings were unchanged, and an MRI scan did not identify a chiasmal lesion. Subsequent review of the scans showed a blood flow artifact obscuring the chiasmal detail in coronal section. This artifact often confounds chiasmal imaging and, indeed, is described by Apkarian et al. However, a sagittal section clearly showed a relative hypoplasia of the chiasm judged with respect to the size of the neighboring mamillary body (Figure 3). At his last follow-up at 5½ years of age, this patient read N4.5 print held 10 cm from his nose and had Cardiff card acuity of 6/18 in the right eye and 6/36 in the left eye, with a somewhat variable convergent strabismus. His development was globally moderately delayed in the first 3 years but accelerated to age-appropriate levels in the fourth year.

Patient 2

This patient was born by Caesarean section at 35 weeks after some fetal distress. His birth weight was 4 lb, 13 oz. He required facial oxygen, and the Apgar score was 9 at 10 minutes, but he spent time in a neonatal unit for poor respiratory effort. He is the youngest of three siblings and had an older sister with mild phenylketonuria. His parents noted that he had “wobbly eyes.” At 7 weeks’ corrected age, a pediatrician noted a strabismus but not nystagmus. At 7 months of age, he was examined by an ophthalmologist because of nystagmus. He fixed and followed well, and the fundi were normal. No significant refractive error was noted. At this time, concern was raised about a general developmental delay. His cognitive development continued at approximately two-thirds speed with a more severe motor delay but with no motor signs. (He walked at 2 years and remained immature in gross motor skills.) He was referred to our hospital to see whether the nystagmus was acquired and whether his failure to sit unsupported was caused by a related ataxia. At 14 months, he had visual electrophysiologic tests to investigate a possible sensory basis for his nystagmus. His irides did not transilluminate, he fixed and followed well, and he did not object to occlusion of either eye. A pigmented ring was noted around each optic disc, but they were otherwise normal. The flash mixed rod/cone ERG was normal, and the monocular flash VEP showed a crossed asymmetry consistent with an achiasmal anomaly (Figure 2). Pattern VEPs to a range of check sizes suggested moderate acuity levels. Eye movement studies showed the nystagmus was mostly pendular with no other defining characteristics. The absence of optokinetic nystagmus and vestibular ocular response suggested that this was compatible with a congenital nystagmus; no see-saw nystagmus was observed. An MRI scan at 18 months described normal caliber optic nerves and tract, but the chiasm was not clearly distinguished. Another scan carried out at 23½ years reported an absence of a normally formed chiasm with a small amount of tissue connecting the posterior aspects of the optic nerves (Figs 4A, B). There were also nonspecific signal abnormalities in the white matter of both hemispheres, a deficiency of the falx anteriorly, but no other cranial midline abnormalities were found. He attends another hospital for hearing difficulties and has had ventilation tubes inserted.

Patient 3

This patient was referred for an electrophysiologic assessment of visual function after optic nerve hypoplasia had been noted during an ophthalmic examination for nystagmus. The flash mixed rod/cone ERG was normal, but the monocular flash VEP showed the crossed asymmetry in occipital scalp distribution consistent with a reduction in chiasmal crossing fibers reaching the contralateral hemisphere. The VEP acuity was estimated to be moderate. His nystagmus was not formally recorded. His MRI scan at 4 months showed chiasmal hypoplasia (Figs 5A, B) and an absent septum pellucidum. Having presented with persistent neonatal jaundice, he was found to have hypopituitarism and was treated with thyroid and cortisone supplements; thus, the diagnosis of septo-optic dysplasia was proposed. His development was significantly, moderately, globally delayed.

Patient 4

This patient has been reported by Leitch et al as a case study. She presented with a midline facial cleft lip and palate and see-saw
nystagmus and was found to have a nasosphenoidal encephalocele, agenesis of the corpus callosum, and absent falx. Visual electrophysiologic analysis showed an achiasmic crossed asymmetry in monocular VEP distribution consistent with a deficit in crossing fibers. The VEP acuity was estimated to be moderate. Mixed rod/cone ERGs were normal. Although the patient’s optic discs were originally reported as normal, a more recent examination while the patient was asleep revealed somewhat small discs (see Fig 6 for a photograph of the left fundus). Her cognitive and motor development was entirely normal despite the extensive brain malformation and need for endocrine supplementation. An MRI demonstrated mild holoprosencephaly, a nasosphenoidal encephalocele involving the chiasmal area, and a complete absence of a chiasm.

### Patient 5

This patient was one of an in vitro-fertilized twin. He presented at birth with frontonasal dysplasia, cleft lip and palate, with a nasoencephalocele (Fig 7A). He had panhypopituitarism and bilateral colobomatous “morning glory” optic discs. He had see-saw nystagmus and a vertical gaze palsy. The flash mixed rod/cone ERG was normal, and the monocular VEPs showed a crossed asymmetry consistent with the MRI finding of absent chiasm (Fig 7B). The VEP acuity was estimated as poor. He had meningitis secondary to a cerebrospinal fluid communication, with seizures in the acute phase. His development was globally delayed with the assessment by the Griffiths scale (Test Agency, Henley-on-Thames, Oxon, England) showing a scatter of attainments between 13 and 15 months at 35 months of age. His behavior (crying and negative) was a problem, and he needed a gastrotomy for failure of adequate nutrition.

### Discussion

Monocular flash VEP-crossed asymmetry can reveal “achiasmia” well. Achiasmia was first described as an isolated structural brain abnormality, clinically presenting as see-saw nystagmus. Although acquired see-saw nystagmus is closely associated with chiasmal anomalies, other midline abnormalities (e.g., lesions of the thalamus and rostral midbrain) have often been cited as contributory factors. However, a patient has been recently described with a progressive cone-rod dystrophy who acquired see-saw nystagmus without MRI signs of rostral midbrain abnormality.
The identification of see-saw nystagmus in sheepdogs by Dell’Osso was instrumental in linking these findings to achiasma in humans. He subsequently hypothesized that isolated interruption of the chiasmal crossing fibers is enough to cause congenital see-saw nystagmus. Our patients show a phenotype ranging from chiasmal hypoplasia to complete achiasmia, which can occur in isolation or in association with a spectrum of optic disc appearances (hypoplasia, coloboma) and other developmental cranial midline abnormalities. It is interesting to note that those patients who had chiasmal hypoplasia and no other apparent midline anomalies on MRI scans had pendular nystagmus, while those patients with other midline abnormalities had see-saw nystagmus.

The neurodevelopment concomitants in these children are nonspecific, but four of the five children had significant early global developmental delay. This was transient in patient 1. Interestingly, one of the two children with the most obvious midline forebrain malformations was developmentally normal. No specific neurologic syndrome as distinct from septo-optic dysplasia (which is composed of a group of rather heterogeneous conditions labeled de Morsier syndrome) is described. Although moderate global developmental delay is compatible with other reports, it is quite nonspecific. The possibility that early poor functional vision may exaggerate the degree of early developmental problem is suggested by the data of patient 1, but not conclusive, and most of the children had fixed developmental impairments.

The spectrum of structural phenotypes associated with achiasmia allows us to speculate about a common defect underlying these developmental anomalies. A wealth of current research indicates there are several possible mechanisms of disrupting normal chiasmal development: a disruption of ganglion cells’ retinotopic reference, a disruption of chronotopic order in the retina, and a disturbance of transiently expressed cues to chiasmal formation. In addition, it is becoming clear that PAX developmental control genes can have an important role in the development of midline structures. Recent reports describe abnormalities of the optic chiasm in mouse Pax2 mutants and zebrafish noi mutants (homologous to Pax2) with optic nerve effects that are similar to the phenotypic range manifest in our patients.

The family of 9 PAX genes in humans (Pax in mouse) are transcription factors, which have dynamic and restricted expression patterns. They direct cell differentiation and regionalization in the neuroprimordium. PAX genes are highly conserved sequences of DNA that have been identified in Drosophilia, hedgehog, mouse, human, zebrafish, rat, and chicken. In the developing mouse eye, Pax2 is exclusively expressed in the optic stalk and Pax6 in the eyecup. They are each under the influence of other regulators. In mice, at least one of these appears to be Shh (sonic hedgehog), a member of the hedgehog family of signaling proteins that has patterning activity in a range of organisms. An inverse relationship between Pax2 and Pax6 has been illustrated when Shh is ectopically overexpressed. This leads to overexpression of Pax6 and downregulation of Pax2 in zebrafish, 24 causing hypertrophy of the optic stalk and reduction of retinal pigment epithelium and neural retina. In humans, PAX2 defects are commonly associated with coloboma, and PAX6 defects are associated with aniridia.

PAX2 is also expressed in the central nervous system. In the mouse, Pax2 appears to have morphogenetic functions, such as closure of the cephalic neural tube and optic fissure, but also has a role in regional specification (e.g., determining the axonal composition of the chiasm). 21 Pax2 mutant murine brains show agenesis of the optic chiasm with the optic tracts remaining completely ipsilateral. In addition, pigmented retina extends into the optic stalks, and there are colobomata, a failure of the optic fissure to close. 21 To investigate why this should happen, Torres et al compared the expression of Pax2 and Shh in normal and Pax2

![Figure 4. A,B, magnetic resonance imaging scans showing a thin strand of tissue connecting the posterior aspects of the optic nerves (T1-weighted tilted axial [A] and coronal [B] images).](Image)
mutant brains. The distribution pattern of Pax2 expression was the same in normal and mutant mice until the first axons were due to migrate out of the retina. At this time, in normal mice, the expression of Shh splits in two, leaving a gap through which Pax2 can extend. This gap is the optic recess through which the first retinal axons pass. In the Pax2 mutants, this gap is lost and the retinal neurons cannot cross through the optic recess to form the future chiasm. The mutual regulation of Shh and Pax2 appears important in chiasmal formation. Pax2 is the first Pax family member to demonstrate a role in axonal guidance.22

In addition to optic disc colobomata, some of our patients had optic nerve hypoplasia. There is some evidence to link this to Pax2.21 Netrins have been associated with optic nerve hypoplasia.26 Netrins comprise a family of lamina-related proteins that have chemotrophic, chemorepulsive, and growth-promoting actions. Both netrin and Shh expression are altered in noi mutants.27 Noi in zebrafish is homologous in sequence to Pax2 and shows similar expression domains. In normal zebrafish, as the optic stalks diminish, they are replaced by optic nerves with tightly packed axons. In mutants, the stalk is retained with large numbers of nuclei surrounding the fibers in disorganized clumps, and the axons are less tight. The relationship is less clear in mice. Mice, which are deficient in netrin-1 and DCC ("deleted in colorectal cancer"), have optic nerve hypoplasia and an absent corpus callosum, a feature seen sometimes in de Morsiers syndrome (e.g., px3). In netrin-1 mutant mice, the retinal ganglion cells successfully find their way to the optic disc, but their axons fail to exit from the disc. Pax2 and netrin-1 have similar patterns of expression, but Pax2 was still normally expressed in the cuff of cells at the optic disc in the netrin-1 mutant eyes.26

Thus, the disc appearances noted in our patients, ranging from colobomata to optic nerve hypoplasia, could be related to variation in the morphogenetic function of Pax2 in closing the optic fissure and to the reduced expression of proteins such as Shh and netrin, which are linked to Pax2 expression. It is relevant to note that Shh found at 7q36 is one of the genes that has been implicated in dominant holoprosencephaly28 (patient 4 had mild holoprosencephaly). Optic nerve hypoplasia has been reported in association with a spectrum of deformities that can vary widely in severity, including holoprosencephaly.29,30

Ten humans who have been described to date with known PAX2 mutations mostly have optic nerve and renal abnormalities (summarized by Schimmenti et al25), but they vary enormously in phenotypic expression and severity, even when they have the same mutation. Isolated eye and ear or renal defects have not been reported yet. Although an
unusual finding, aplasia of optic nerves chiasm and tracts with no other MRI abnormalities has been reported by Scott et al31 in a developmentally normal 3½-year-old child.

Within our patient group, the midline abnormalities range from de Morsiers syndrome to a nasosphenoidal encephalocele with a mild holoprosencephaly, to a midline facial cleft and morning glory colobomatous discs. It is not clear whether the encephalocele is part of the spectrum. Encephalocele pathogenesis is still poorly understood. It appears that encephaloceles contain brain with normal patterning and are prone to occur within a critical time window of rapid postneurulation brain growth. They are mechanistically associated with postneurulation defects and decompression of the primitive ventricle.32,33 Encephaloceles have been regarded as part of the dysraphic developmental lesions, primarily associated with axial mesodermal defects.34,35 Neural tube defects arise from genetic factors, interacting with environmental and dietary agents, and a multisite closure model allows for multifactorial influences and diverse manifestations.36 The craniofacial lesions associated with encephaloceles can vary from none to extensive.34 The extreme phenotypic variability could be difficult to reconcile with a common cause, but an embryonic transcription factor typically has a multiplicity of functions and can instruct cells into different pathways depending on the cell’s history and position in the embryo.37 Pax2 may have some involvement in neural tube closure, but it is haploinsufficient, and the neural phenotype in the heterozygous condition is extremely variable and background dependent.21 In addition, it is not yet known whether genetic modifiers can enhance different aspects of Pax2 function.

In summary, monocular VEP-crossed asymmetry can reveal achiasmia in the absence of see-saw nystagmus. Our evidence indicates a range from chiasmal hypoplasia (e.g., patient 2, who has a chiasmal strand of tissue connecting the posterior aspects of the optic nerves, as originally described by Williams et al1 in one of the mutant Belgian sheepdogs), to complete achiasmia. It can occur in isolation or in association with a spectrum of optic nerve hypoplasia and coloboma and other cranial midline abnormalities. See-saw nystagmus is not always present. An apparently uniform developmental defect such as achiasmia could arise in many different ways. Pax2 mutations may prevent the retinal axons from reaching the site of chiasmal formation, yet other defects may change ganglion cell behavior at the chiasm after they have arrived. However, developmental control genes, in particular PAX2, may provide a common substrate to understand the association of achiasmia with other midline abnormalities.

References