Co-Development of VEP Motion Response and Binocular Vision in Normal Infants and Infantile Esotropes

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PURPOSE. To determine the maturational course of nasotemporal asymmetry in infantile esotropia and to define the relationships among the symmetry of the motion visual evoked potential (MVEP), eye alignment, fusion, and stereopsis.

METHODS. Sixty healthy term infants and 34 infants with esotropia participated. Nasotemporal MVEP asymmetry was assessed by the presence of a significant $F_1$ response component with an interocular phase difference of approximately 180° and by an amplitude “asymmetry index.” Fusion was evaluated using the 4 p.d. base out prism test. Random dot stereocuity was assessed in infants with forced-choice preferential looking (FPL) using the Infant Random Dot Stereocards. Eye alignment was assessed by the alternate prism and cover or the modified Krimsky test.

RESULTS. Normal infants 2 to 3 months of age exhibited marked nasotemporal MVEP asymmetry, which rapidly diminished by 6 to 8 months. Neonates did not exhibit MVEP asymmetry. There was good concordance between fusion and MVEP symmetry and between stereopsis and MVEP symmetry; the concordance between MVEP symmetry and orthoposition of the visual axes was significantly poorer. The same proportion of normal and young esotropic infants showed symmetrical MVEPs. Regardless of the age at surgery, most patients with infantile esotropia had asymmetrical MVEPs after surgery.

CONCLUSIONS. These data support a strong link between fusion and MVEP symmetry during both normal maturation and in infantile esotropia. Furthermore, the finding that the youngest infants with esotropia do not differ significantly from normal suggests that the nasotemporal asymmetry found in older patients with infantile esotropia does not represent an arrest of maturation but, rather, a pathologic change of the motion pathways. (Invest Ophthalmol Vis Sci. 2000;41:1719–1723)

The maturation of motion processing in the human visual cortex can be assessed by means of the motion visual evoked potential (MVEP), which appears to selectively access binocular motion pathways. An initial study of the MVEP in 11 normal infants 6 to 26 weeks of age reported nasotemporal asymmetries that diminished as the visual system’s response to motion matured.1 A subsequent cross-sectional study of 22 infants 25 to 104 weeks of age verified that normal infants over 25 weeks of age show little residual asymmetry.2

“Persistence” of nasotemporal asymmetry was reported in 15 patients with infantile esotropia who had been surgically aligned after 2 years of age.3 Unlike esotropic patients with infantile onset, those with late onset do not show pronounced nasotemporal asymmetries in the MVEP.3 Treatment of infantile esotropia with full-time alternate occlusion and surgery during the first 2 years of life has been shown to decrease or abolish the nasotemporal asymmetries in most patients, whereas later treatment had little or no effect on nasotemporal asymmetry.1,2,4 Taken together, these data are consistent with an early critical period during which abnormal binocular experience can interfere with the maturation of the binocular motion pathways tapped by the MVEP.

Although the association between early abnormal binocular experience and nasotemporal asymmetry is clear, it is not known whether the asymmetry truly represents persistence of an infantile state or, rather, a pathologic change due to prolonged abnormal experience. In addition, the interrelationships among eye alignment, fusion, stereopsis, and the MVEP have not been well defined. All show rapid development during the first months of life, all are sensitive to disruption by early abnormal sensory experience, and all are responsive to treatment during the first 2 years of life. The aims of the present study were to determine the maturational course of nasotemporal asymmetry and to define the relationships among the symmetry of the MVEP, eye alignment, fusion, and stereopsis.

METHODS

Subjects
Sixty healthy term infants 0.5 to 10 months of age participated in study 1. None had a family history of strabismus or heredi-
Thirty-four infants with infantile esotropia participated in studies 2 and 3. All of the patients were diagnosed with constant esotropia of at least 30 p.d. at 3 to 6 months of age, and the angle of deviation was found to be maintained or increased during follow-up before surgery. All were otherwise healthy infants. None of the infants had significant refractive errors. Only nonamblyopic infants were recruited for the study because phase delays in VEP responses associated with amblyopia might confound measurement of interocular phase differences associated with nasotemporal asymmetry. Twenty of the infants were tested before surgery and 28 infants after surgery (14 infants were tested both pre- and post-surgery). No treatment other than surgery was provided to these patients.

Informed consent was obtained from one or both parents before the child’s participation. This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

**Quadrature Motion VEP**

MVEPs were elicited by jittering 1 c/deg sinus wave gratings ± 90° in phase at 6 Hz. Each trial had a duration of 10 seconds, with a minimum of 5 trials per eye. The presence of significant F₁ and/or F₂ components in the vector averaged response was assessed via the $t_{95}$ statistic. Two methods were used to determine the presence of a nasotemporal asymmetry: the presence of a significant F₁ response component in the same channel(s) for both eyes with an interocular phase difference of 180 ± 40° (a “bow tie” on a polar plot of amplitude and phase) and the amplitude “asymmetry index,” which is calculated as the ratio $[F_1/(F_1 + F_2)]$. Only infants and children who tolerated the electrodes and looked at the stimulus display for a minimum of 10 trials (5 per eye) were included in analyses.

**Fusion**

Fusion was evaluated using the 4 p.d. base out prism test. Only infants and children who gave consistent responses on four tests (two for each eye) were included in analyses.

**Stereoacuity**

Random dot stereoacuity was assessed in infants (1.5–24 months) with forced-choice preferential looking (FPL) using the Infant Random Dot Stereocards. Only infants and children who wore the polarizing spectacles well and examined the test plates were included in the analyses.

**Eye Alignment**

Eye alignment was assessed by the alternate prism and cover test whenever possible. For some of the youngest infants, the modified Krimsky test was used instead.

**Study 1: Early Maturation of the MVEP in Normal Infants**

Data were grouped by age into 8 categories: newborns (<1 month old) and 1.5, 2.5, 3.5, 4.5, 5.5, 8, and 10 months. Between 5 and 10 infants contributed data to each age group. Sample MVEP records for three infants are shown in Figure 1. Response amplitude and phase are plotted in polar coordinates for each of the 10-second trials obtained for each eye. The youngest infant shown has small response amplitudes overall, variable first harmonic responses, and small but reliable second harmonic responses with similar phase for the two eyes. The 2.5-month-old infant has a sizeable first harmonic component, which is approximately 180° out of phase for the two eyes, and a small but reliable second harmonic response with similar phase for the two eyes. The 4.5-month-old infant had little first harmonic response and a robust second harmonic response with similar phase for the two eyes.

Mean data are summarized in Figure 2. Both measures of asymmetry (the “bow tie” and the asymmetry index) show rapid change from asymmetry toward symmetry between 1.5 and 8 months. Also shown in Figure 2 are data from 9 infants who were tested longitudinally on 4 to 6 visits between 1.5 to 6 months of age; these asymmetry index data show the same general trend as the group averages. In contrast to the monotonic decline during months 1.5 to 8, the group of 5 neonates aged 0.5 to 1 month showed a qualitatively different pattern of response (namely, robust F₂ responses). None of the 5 neo-
FIGURE 2. Two measures of MVEP asymmetry in 55 normal infants 1.5 to 10 months of age (squares and thick line). Tolerance limits were constructed to encompass 95% of the area of the normal distribution (thin lines). The mean (±1 SD) asymmetry index from a group of 5 neonates 0.5 to 1 month of age is shown as a filled circle. Asymmetry index data from 9 normal infants tested longitudinally during months 1 to 6 are also shown.

nates showed evidence of a “bow tie,” and their asymmetry indices ranged from 0.17 to 0.38, with a mean of 0.26.

In a subset of 19 normal infants, eye alignment and fusion responses to 4 p.d. base out prisms were measured on 2 to 4 visits. At 1.5 and 2 months of age, 89% of infants had asymmetrical MVEPs and intermittent exotropia and failed to show fusional eye movements on the 4 p.d. base out prism test. By 4.5 months, 78% of the infants had symmetrical MVEPs, orthoposition of the visual axes, and fusional eye movements on the 4 p.d. base out test. There was good concordance between the response to the 4 p.d. base out prism and the symmetry of the MVEP, with only one discordant pair in 52 test pairs. The concordance between MVEP symmetry and orthoposition of the visual axes was significantly poorer (10 of 52 pairs discordant; χ² = 6.51, P = 0.011).

In a subset of 15 normal infants aged 3 to 5 months, both random dot stereopsis and MVEPs were measured. Of 8 infants who had random dot stereacuity ≤ 400 seconds, 7 had symmetrical MVEPs. Of 7 infants who had no random dot stereopsis, 6 had asymmetrical MVEPs. These proportions are significantly different by the Fisher exact test (P = 0.01).

Study 2: MVEP Asymmetry in Infantile Esotropia before Treatment

The prevalence of “bow ties” and the mean asymmetry index are shown in Figure 3 along with the normative data replotted from Figure 1. Infants tested at 4 to 6 months of age were evaluated at a mean of 1.2 ± 0.9 months after the initial diagnosis of esotropia by their pediatric ophthalmologist. Infants tested at 7 to 9 months of age were evaluated at a mean of 4.5 ± 1.1 months after the initial diagnosis of esotropia by their pediatric ophthalmologist. The proportion of esotropic infants with “bow ties” at 4 to 6 months and at 7 to 9 months of age was not statistically different from the proportion found in the normative cohort (Fisher exact test). The asymmetry index was borderline normal at 4 to 6 months of age but abnormal by 7 to 9 months of age. Asymmetry index data from 4 esotropic individuals tested on 2 or 3 visits before surgery are consistent with the mean data (i.e., borderline normal indices at the earliest ages but abnormal indices at older ages).

Study 3: MVEP Asymmetry in Infantile Esotropia after Surgery

The prevalence of “bow ties” and the mean asymmetry index at the first postoperative visit is shown in Figure 4 as a function of age along with the normative data replotted from Figure 1. Eleven of the infants had their first postoperative visit at 9 to 11 months of age (8.6 ± 1.1 weeks postop), 10 infants had their first postoperative visit at 12 to 14 months of age (20.7 ± 4.2 weeks postop), and 5 infants had their first postoperative visit at 15 to 24 months of age (34.1 ± 11.2 weeks postop). For all 3 groups, the proportion of treated esotropic infants with “bow ties” was statistically higher than the proportion found in the normative cohort (Fisher exact test; P < 0.008). For all 3 groups, the asymmetry index was significantly higher than normal as well (P < 0.001 by t-test). Similar trends can be seen in the longitudinal data sets from 11 infants who were tested on 2 to 4 visits postoperatively (Fig. 4); all but one of the asymmetry indices obtained from these infants during 29 visits were abnormal.

For 14 of the infants, both pre- and postsurgery data were available. Eleven infants had a “bow tie” presurgery; six retained the “bow tie” postoperatively. Of the three infants who had no “bow tie” presurgery, one developed a “bow tie” postoperatively. The mean change in the asymmetry index postoperatively was not significantly different from zero (−0.06 ± 0.28). Eight infants showed a decrease in their asymmetry index ranging from −0.05 to −0.69, whereas 6 infants showed an increase ranging from +0.01 to +0.63.

Clinical variables that might contribute to binocular vision outcomes were examined. Infants who were surgically aligned by 10 months of age had significantly lower postoperative asymmetry indices than those who were aligned at 11 to 18
months of age ($t = 2.64; P < 0.05$). There were no significant differences in asymmetry indices between infants who developed a dissociated vertical deviation and those who did not (Mann-Whitney test; $P = 0.22$). The proportion of treated esotropic infants who demonstrated fusion with “bow ties” was statistically lower than the proportion found among infants who failed to demonstrate fusion (Fisher exact test; $P = 0.008$). Infants who demonstrated fusion after surgery ($n = 4$) also had significantly lower postoperative asymmetry indices than those who did not demonstrate fusion ($t = 2.12; P < 0.05$). There were no significant differences in asymmetry indices between infants who developed stereopsis ($n = 4$) and those who did not develop stereopsis ($t$-test; $P = 0.54$).

**DISCUSSION**

The MVEP data from 60 normal infants aged 0.5 to 10 months provide a well-defined range for comparison with data from pediatric patients. As noted by others, infants aged 2 to 3 months exhibited marked nasotemporal asymmetry that rapidly diminished by 6 to 8 months. A novel finding in the present study is that neonates did not exhibit nasotemporal asymmetry. This finding is consistent with the report that neonates can detect motion but cannot discriminate its direction (i.e., direction selective mechanisms may not be present at birth). Given the concordance between MVEPs and fusion during normal development, the lack of nasal-temporal asymmetry in neonates is consistent with the observation that, despite the absence of stereopsis, simultaneous perception with two eyes may be present at birth. This finding suggests that substantial reorganization of directionally selective binocular pathways occurs postnatally.

The concordance of MVEP symmetry with sensory fusion and stereopsis but not with eye alignment supports a link between these aspects of binocular sensory function in normal infants. Although every attempt was made to obtain data only when the infant was alert and fixating, it is possible that eye alignment varied during the course of conducting multiple tests and that the eye alignment assessed during the alternate prism and cover test did not always reflect alignment status during the fusion and stereopsis tests. Thus, it is possible that the two infants who were judged to have intermittent exotropia during the alignment examination had straight eye during the fusion test. Likewise, the eight infants who were judged orthophoric on the alignment examination may have exhibited intermittent exotropia during the fusion test.

Among infantile esotropes evaluated during the first weeks after onset, the same proportion of normal and esotropic infants show symmetrical responses, and, in the youngest infants the asymmetry index is near normal. These data conflict with an earlier report of abnormal MVEPs before treatment, but patients in that study were evaluated at an average of 4 months after the onset of esotropia (all had onset by 4 months and were first evaluated at an average age of 8 months), whereas patients in the present study were evaluated at an average of 1 month after onset. The finding that the initial course of maturation of MVEPs in young esotropes appears to be normal is reminiscent of our earlier finding that the same proportions of normal and esotropic infants (aligned with prisms) are able to demonstrate stereopsis at 3 to 5 months of age. Both observations support the hypothesis that early treatment may be beneficial in preventing major abnormalities in this aspect of binocular sensory function.

Regardless of the age at surgery, most patients with infantile esotropia exhibited “bow ties” and abnormal asymmetry indices after surgery. These outcome data were gathered from patients at 5 to 60 weeks postoperatively, so it is possible that there may be further long-term changes in the asymmetry index. The rare patients who achieved symmetry after surgery had had surgery during the first 10 months of life, achieved good alignment outcomes, and exhibited fusion. Early surgery for infantile esotropia also has been reported to be associated with better stereoaucuity outcomes. In addition, a strong relationship between fusion (by the 4 p.d. prism test) and nasotemporal symmetry has been reported in a large group of older children treated for infantile esotropia, accommodative esotropia, intermittent strabismus, or other common pediatric eye disorders who had a wide spectrum of binocular sensory function.

Overall, the data presented here support a strong link between fusion and MVEP symmetry during both normal maturation and in infantile esotropia. Furthermore, the finding that pediatric patients with infantile esotropia do not differ significantly from normal immediately after the onset of strabismus suggests that the nasotemporal asymmetry found in such patients may not represent a persistence of the normal infantile state but, rather, a pathologic disruption of motion pathways as a result of prolonged abnormal binocular sensory experience.

**References**