Binocular Sensory Outcomes in Accommodative ET

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Purpose: To review what is known about the normal maturational sequence for fusion and stereopsis and the binocular sensory deficits associated with accommodative esotropia (ET) and to explore the clues that accommodative ET provides about critical periods for binocular sensory function. Methods: Studies of binocular sensory function during infancy and early childhood are presented. Results: Most of the maturation of binocular sensory function occurs during the first year of life, yet a later abnormal visual experience—such as the onset of accommodative ET—can profoundly and permanently disrupt fusion and stereopsis. Conclusions: Some binocular sensory deficits may exist before the onset of accommodative ET, but others may result directly from abnormal binocular experience. The functional organization of the maturing visual system appears to be maximally sensitive to disruption by abnormal visual experience during the first months of life, but susceptibility continues until at least 4 years of age. (J AAPOS 2003;7:369-73)

In the past two decades, there has been an explosion of new information about the maturation of binocular sensory function during infancy and early childhood. One of the most intriguing outcomes from this research effort is that most of the maturation of binocular sensory function occurs during the first year of life, yet a later abnormal visual experience—such as the onset of accommodative esotropia (ET) at 2 years of age—can profoundly and permanently disrupt stereopsis. This article (1) summarizes data from my laboratory on the normal maturational sequence for fusion and stereopsis and on binocular sensory deficits associated with accommodative ET and (2) explores the clues accommodative ET provides to help define critical periods for binocular sensory function.

GROWTH CURVES FOR BINOCULAR SENSORY FUNCTION

The maturation of two aspects of binocular sensory function, fusion and stereopsis, have been studied. One approach to assessing fusion has been the four–prism diopter (4PD) base-out test. In this test, the infant is encouraged to fixate on a small toy, and then a 4PD base-out prism is introduced in front of one eye. If the infant appreciates the small shift in the image position away from the center of the fovea in one eye and makes a sequence of eye movements to re-establish bifoveal fixation, this is considered evidence of sensory fusion. The growth curve for this paradigm is presented in Figure 1. Few normal infants demonstrate fusion before 8 weeks of age, whereas most infants age 16 weeks or older readily produce the fusional vergence response.

Sensory fusion also has been evaluated directly using both forced-choice preferential-looking and visual evoked potential (VEP) test protocols. Growth curves for sensory fusion from all three protocols for assessing sensory fusion are shown in Figure 1. In each protocol, few infants < 4 weeks of age demonstrate fusion; however, by 12 to 16 weeks virtually all infants demonstrate sensory fusion.

Growth curves for stereopsis have been determined using a wide variety of stimuli, including static line stereograms and both static and dynamic Randot (Stereo Optical, Chicago, IL) stereograms. Both forced-choice preferential-looking protocols, in which the infant’s fixation preference for disparate over zero disparity patterns was assessed, and VEP protocols, in which cortical responses to changes in disparity are recorded, have been employed. Despite the wide variety of stimuli and response measures used, there is general agreement across studies that the onset of stereopsis occurs at approximately 15 weeks of age (Figure 2). After the abrupt onset of stereopsis, the rate of stereoaucuity maturation is rapid, with the infant achieving stereoaucuity of 30 to 100 arc sec by 40 weeks (Figure 2). Further slow improvement in stereoaucuity continues through 18 to 24 months of age.
ACCOMMODATIVE ESOTROPIA

Accommodative ET is a form of strabismus characterized by convergent misalignment of the visual axes that is associated with hypermetropia and/or abnormal accommodative convergence-to-accommodation ratio. Typically, accommodative ET initially presents as an intermittent esodeviation at age 1.5 to 4 years. The prevalence of accommodative ET has been estimated to be 1% to 2% in the United States. Treatment with optical correction (hypermetropic correction and/or bifocal correction) usually is successful in re-establishing alignment, but surgical correction is necessary in approximately 30% of cases.

PREEXISTING BINOCULAR SENSORY ABNORMALITY IN ACCOMMODATIVE ESOTROPIA

Despite the relative maturity of fusion and stereopsis by 18 to 24 months of age, approximately 10% of children with hypermetropia ≥ +4.00 PD develop accommodative ET at 18 to 48 months. The late onset of esodeviation, along with the finding that not all children with hypermetropia ≥ +4.00 PD are affected, suggests that there may be a pre-existing abnormality in binocular sensory function in some children.

A study of inheritance patterns in accommodative ET was conducted because many parents report a positive family history. Eighty-six families were interviewed. Siblings were examined, and adult relatives were carefully questioned about type of deviation, age of onset, and refractive error during early childhood. Adults’ medical records were consulted whenever available. Current eye examinations were not obtained from adults because many of the adults with a positive history for accommodative ET reported that they “outgrew” the condition and no longer wore hypermetropic correction. We developed a standardized questionnaire to verify accommodative ET by asking specific questions about the age of onset, the type of spectacle correction, and other treatment to verify to the best of our ability that the adult did have a positive history of accommodative ET rather than another form of strabismus.

Overall, 25% of first-degree relatives (eg, siblings and parents) were affected, and 12% of second-degree relatives (eg, grandparents, aunts, uncles) were affected. Only 2% to 3% of third- and fourth-degree relatives (eg, aunts, uncles, grandparents) were affected, similar to the prevalence in the general population. This high prevalence of accommodative ET among first- and second-degree relatives is consistent with a genetic basis and, possibly, a pre-existing sensory abnormality (Figure 3).

As a complementary approach to evaluating the hypothesis that a pre-existing binocular sensory abnormality may be associated with accommodative ET, binocular sensory function was evaluated in the earliest stage of the
disease, i.e., in newly diagnosed patients who still had only intermittent esodeviations.19 Despite the intermittency of their esodeviations, 40% of the children exhibited abnormal stereopsis, consistent with a possible congenital deficit. In contrast, three separate measures of fusion (4PD base-out test, Worth Four-Dot test at 33 cm, and motion VEP) were normal at this early stage of the disease.

It is important to note that although 40% of patients with newly diagnosed esodeviations already had profound deficits in stereopsis, the other 60% had normal stereopsis. Longitudinal data from six patients with accommodative ET who were representative of the range of binocular sensory function encountered at follow-up are shown in Figure 4. In the top row, two patients who had constant esodeviation on the initial visit are shown. As expected, in the presence of ET, neither patient showed evidence of stereopsis. Although both of these patients achieved orthoposition with spectacle correction within 2 months of their initial visit, neither showed improvement in stereopsis. The experience of these two patients is consistent with the theory that a congenital deficit in binocular sensory function may predispose some children to accommodative ET, although it is also possible that the initial brief period of constant esodeviation was sufficient to profoundly disrupt stereopsis.

The other patients shown in Figure 2 initially did not have profound deficits in stereopsis, consistent with an initially normal binocular sensory system that is susceptible to abnormal visual experience but also responsive to treatment. In the second row are two patients who initially presented with intermittent ET and subnormal stereopsis (3000 arc sec). After being treated with spectacles, both patients showed marked improvement in stereopsis to near-normal (left) or normal (right) stereopsis. Finally, two patients who initially presented with intermittent esodeviations and normal stereopsis are presented in the third row. Both of these patients initially achieved orthophoria with spectacle correction but had such poor compliance with spectacle wear that a constant esodeviation developed. Constant orthoposition was achieved in both patients with full-time spectacle wear only after a long period (>3 months) of constant esodeviation. Both developed marked deficits in stereopsis that did not improve after surgical alignment. Just these few cases clearly demonstrate the diversity of binocular sensory function in accommodative ET. Because it is not yet possible to determine which patient with subnormal stereopsis may show full recovery with treatment, prompt re-establishment of orthoposition is a priority for all patients with accommodative ET.
TABLE 1. Relative risk for accommodative ET after successful surgery for infantile ET

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk for Accommodative ET (95% CI)</th>
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<tbody>
<tr>
<td>Onset of infantile ET &lt;4 mo</td>
<td>1.2 (0.6–1.6)</td>
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<tr>
<td>Initial deviation &gt;50 PD</td>
<td>1.0 (0.1–1.7)</td>
</tr>
<tr>
<td>Hyperopia ≥+3.50 PD</td>
<td>1.2 (0.2–1.7)</td>
</tr>
<tr>
<td>Aligned at ≤6 mo</td>
<td>1.4 (0.6–1.9)</td>
</tr>
<tr>
<td>Aligned at ≤12 mo</td>
<td>1.4 (0.8–1.7)</td>
</tr>
<tr>
<td>Duration of misalignment &gt;3 m</td>
<td>2.1 (1.4–2.6)</td>
</tr>
<tr>
<td>Increased hyperopia after surgery</td>
<td>2.3 (1.8–2.6)</td>
</tr>
<tr>
<td>Postoperative stability of alignment</td>
<td>1.1 (0.2–1.6)</td>
</tr>
<tr>
<td>Amblyopia treatment</td>
<td>1.4 (0.5–1.9)</td>
</tr>
<tr>
<td>Fail Worth 4-dot at near</td>
<td>1.2 (0.2–1.5)</td>
</tr>
<tr>
<td>Nil stereopsis</td>
<td>2.1 (1.5–2.4)</td>
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CI: confidence interval; ET: esotropia; PD: prism diopters.

TABLE 2. Relative risk for accommodative ET among children with low to moderate hypermetropia

<table>
<thead>
<tr>
<th>Spherical Equivalent</th>
<th>Increased Relative Risk for Accommodative ET (95% CI)</th>
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<tr>
<td>+2.00 PD</td>
<td>7.8 (4.5–8.4)</td>
</tr>
<tr>
<td>+3.00 PD</td>
<td>2.1 (1.4–2.1)</td>
</tr>
<tr>
<td>+4.00 PD</td>
<td>1.3 (0.9–1.5)</td>
</tr>
</tbody>
</table>

CI: confidence interval; ET: esotropia; PD: prism diopters.

risk factors for accommodative esotropia in low hypermetropia

Although many children who develop accommodative ET have hypermetropia ≥+4.00 PD and/or abnormal accommodative convergence-to-accommodation ratio, some children with hypermetropia <+4.00 PD also develop accommodative ET. The identification of risk factors for the development of accommodative ET in this population could provide insight about the etiology of strabismus.

Within the population of patients with low hypermetropia at risk for accommodative ET, two relatively homogeneous subgroups were identified: children with infantile ET and children with anisometropia. Most children with infantile ET have low hypermetropic errors (<+3.00 PD). Yet, after undergoing surgical alignment to correct infantile ET, 60% develop accommodative ET at approximately 3 years of age. Risk factor analysis of potential clinical, treatment, and sensory factors is summarized in Table 1 (adapted from Birch et al). Increasing hypermetropia after the initial surgery for infantile ET, duration of infantile ET > 3 months after onset, and absence of stereopsis were identified as factors that each doubled the risk for accommodative ET in this cohort. The last two factors are likely closely related because duration of infantile ET > 3 months has been shown to be related to poor binocular sensory outcomes. Thus, the high prevalence of accommodative ET among children treated for infantile ET may be the result of the disruption of binocular sensory function, which allows accommodative ET to occur at low levels of hypermetropic refractive error.

Disruption of binocularity associated with anisometropia also may allow accommodative ET to occur at lower levels of refractive error. Risk factor analysis of anisometropia as a function of amount of hypermetropia is summarized in Table 2 (adapted from Weakley and Birch). Anisometropia was found to increase the risk for accommodative ET by seven times in children with +2.00 PD refractive error and by two times in children with +3.00 PD refractive error. For children with hypermetropia ≥ +4.00 PD, anisometropia did not pose an additional risk for accommodative ET.

ACCOMMODATIVE ESOTROPIA AND CRITICAL PERIODS

Many children with accommodative ET have abnormal stereoaucity even after undergoing re-establishment of stable alignment by optical correction and/or surgery. For example, in a prospective cohort of 79 children with accommodative ET followed up for 4 to 11 years, we found that only 18% had normal Randot stereoaucity results at their most recent visit. The remaining children had subnormal (28%) or nil (39%) stereoaucity or could not be assessed because they never attained orthotropia (10%) or had deep amblyopia that precluded stereoaucity testing (5%). The pervasiveness of abnormal binocular sensory function in a cohort with onset of esodeviation after most of the maturation of fusion and stereoaucity is complete must give important clues about critical periods in binocular sensory development.

It is clear that the critical period for maturation is not the same as the critical period for susceptibility. Although fusion and stereoaucity are almost fully developed by 2 years of age, accommodative ET with onset after age 2 can result in profound impairment of binocular sensory function. A more detailed look at the critical period for susceptibility to abnormal visual experience was accomplished by constructing a mathematical model for a developmental weighting function to examine the relationship between age at onset and duration of abnormal visual experience and the long-term random dot stereoaucity outcome.

Using onset, duration, and stereoaucity data from a cohort of 90 children with infantile ET and 60 children with accommodative ET, various shapes for the developmental weighting function were evaluated. Specifically, the best-fit location of peak sensitivity, the rate at which sensitivity exponentially increases to the peak, and the rate at which sensitivity exponentially decreases after the peak were determined by the maximum correlation between amount of normal binocular experience and long-term stereoaucity outcome. The best fit to the data is shown in Figure 5. Stereoaucity is most susceptible to abnormal experience at 0.33 years (3.8 months) of age, ie, a relatively brief period of ET occurring at 3 to 4 months of age most...
profundely disrupts susceptibility. Susceptibility decreases slowly beyond the peak but never decreases to zero. Nonetheless, the end of the critical period can be arbitrarily set at the age point below which 95% of the area-under-the-curve falls, i.e., 4.8 years of age. Note, however, that in the model susceptibility does not decrease to zero at any age, and there is some evidence from studies of laser in situ keratomileusis monovision suggesting that prolonged anisometropia can induce stereoacuity deficits even in adults.24

Very little is known about the critical period for recovery and whether it extends beyond the critical period for susceptibility. Duration of abnormal visual experience may be an important factor in limiting the potential for recovery. There is some evidence that constant misalignment of the visual axes >3 months’ duration may result in permanent deficits in binocular sensory function regardless of the age at onset of ET or the age at which treatment is effective in restoring alignment.16,22

**CONCLUSION**

Maturation of binocular sensory function is nearly complete by 18 months of age, yet accommodative ET—which has an onset beyond this critical period for maturation—places the child at risk for permanent binocular sensory deficits. Some of these deficits may exist before the onset of accommodative ET, but others result directly from the abnormal binocular experience after the onset of the disease. The functional organization of the maturing visual system appears to be maximally sensitive to disruption by abnormal visual experience during the first months of life, but susceptibility continues until at least 4 years of age.

Colleagues and postdoctoral fellows who have made significant contributions to the studies summarized in this manuscript include Priscilla Berry, MD, Rain Bosworth, PhD, Sherry Fawcett, PhD, Brett Jeffrey, PhD, Joel Leffler, MD, Anna O’Connor, PhD, Marshall Parks, MD, Maria Pesceva, MD, Solange Salomão, PhD, David Stager Sr, MD, David Weakley, MD, and Weldon Wright, MD.

**References**