Importance: We devised the optokinetic uncover test to examine the role of peripheral retinal motion input in generating horizontal optokinetic responses in patients with infantile strabismus.

Objective: To ascertain whether subcortical visual input contributes to the asymmetrical monocular optokinetic responses that characterize infantile esotropia.

Design and Setting: Observational study in an academic research setting.

Participants: Ten patients with infantile esotropia.

Intervention: Optokinetic uncover test.

Main Outcome Measures: Optokinetic testing was performed in 7 patients with isolated infantile esotropia (5 untreated and 2 previously treated) and in 3 patients with infantile esotropia syndrome associated with mild neurological disease.

Results: All patients showed poor temporally directed optokinetic responses that instantaneously improved when the occluded esodeviated eye was uncovered, exposing it to nasally directed optokinetic motion. This improvement in optokinetic responses did not necessitate a fixation shift to the contralateral eye.

Conclusions and Relevance: Nasally directed optokinetic input to the esodeviated eye can supplement temporal monocular optokinetic responses in the fixating eye under binocular conditions. This nonfoveal optokinetic contribution suggests that monocular nasotemporal optokinetic asymmetry is partly attributable to subcortical visuovestibular responses mediated by nonfoveal retina.

Infantile esotropia is characterized by the idiopathic onset of crossed eyes within the first 6 months of life. It is often accompanied by crossed fixation, primary oblique muscle overaction, latent nystagmus, and dissociated vertical divergence. This constellation of findings is also seen in the setting of prematurity and other neurological disorders.

Patients with infantile esotropia retain a monocular nasotemporal optokinetic asymmetry (MNTA) characterized by brisk monocular optokinetic responses to nasally moving optokinetic targets and poor monocular optokinetic responses to temporally moving optokinetic targets. The phenomenon of MNTA is believed to underlie latent nystagmus. In primates and humans, MNTA is normally seen during the first several months of life. Its spontaneous resolution coincides with maturation of binocular cortical pursuit pathways that provide the temporal component for the optokinetic reflex from each eye. Accordingly, the persistence of MNTA in infantile strabismus has been attributed to a cortical pursuit deficit caused by early failure of cortical binocular vision to develop.

CME available online at jamanetworkcme.com and questions on page 713

Video available online at www.jamaophth.com

Neonates show poor pursuit responses to focal moving stimuli but demonstrate strong optokinetic responses to large full-field rotating stimuli. These full-field responses are attributed to the activation of subcortical optokinetic pathways that modulate full-field rotational optokinetic responses and remain active until maturation of binocular cortical pursuit pathways within the first 6 months of life. This MNTA is seen in laterally-eyed afoveate animals during turning...
 movements, in which the full-field velocity of the nasalward optokinetic stimulus to one eye determines optokinetic rotation of both eyes. Because MNTA antedates development of the visual cortex both phylogenetically and ontogenetically, debate has been waged as to whether the persistent MNTA in humans with strabismus is caused by a cortical pursuit defect, a persistent activation of subcortical optokinetic pathways, or a combination of both.3,8,10,19,25

Cortical pursuit movements in foveate animals require foveal (or perifoveal) stimulation, while subcortical optokinetic movements in afoveate animals are generated by full-field optic flow detected by peripheral retina.26 If the persistence of MNTA in humans with infantile strabismus is caused solely by defective cortical pursuit, its activation should necessitate foveal (or parafoveal) fixation. We devised the optokinetic uncover test to examine the role of peripheral retinal motion input in generating horizontal optokinetic responses in patients with infantile strabismus.

METHODS

Ten patients had a history of infantile esotropia confirmed by MNTA on optokinetic testing using a handheld rotating drum (Figure 1). Patients ranged in age from 1 to 38 years, and all underwent full ophthalmological examinations with special attention to signs of crossed fixation, latent nystagmus, primary oblique muscle overaction, and amblyopia assessed by the inability to maintain fixation with one eye (Table). Seven of 10 patients had no history of neurological disease, developmental delay, or prematurity. Two of these patients had undergone previous strabismus surgery and had residual esotropia. Three of 10 patients had mild neurological disease. Two patients with mild prematurity and speech and fine-motor delays, as well as 1 patient with Down syndrome, were included because their clinical findings otherwise conformed to those of infantile esotropia.

RESULTS

On optokinetic testing, all patients showed brisk responses to nasally directed monococular optokinetic targets and poor responses to temporally directed optokinetic targets with each eye. During attempted pursuit of temporally directed optokinetic targets, removal of the occluder from the contralateral eye produced an immediate improvement in optokinetic responses (video; http://www.jamaophth.com). In 3 patients with alternating fixation, this improved optokinetic response produced a fixation shift to the contralateral eye, allowing the optokinetic response to be foveally driven by the eye receiving the nasally directed stimulus. In 7 patients with a fixation preference for one eye, this improved optokinetic response was accompanied by an immediate or delayed fixation shift when the preferred eye was uncovered and by maintenance of fixation when the nonpreferred eye was uncovered. In 3 patients, 3-dimensional video-oculography (Sensorimotoric Instruments) was performed using a full-field optokinetic stimulus projected on a flat surface (stripe width of 2.2" and velocity of 15° per second with the patient viewing at 3 m). These recordings confirmed that uncovering the contralateral eye produced improvement in the optokinetic waveform regardless of whether a change in fixation occurred (Figure 1). In 3 patients with mild neurological disease or prematurity, the optokinetic uncover test produced results identical to those in 7 patients with idiopathic infantile esotropia. Six of the untreated patients...
subsequently underwent strabismus surgery to correct their infantile esotropia. Other clinical findings are summarized in the Table.

### Table. Profiles of 10 Patients Manifesting Monocular Nasotemporal Optokinetic Asymmetry

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Latent Nystagmus</th>
<th>Dissociated Vertical Divergence</th>
<th>Fixation Preference</th>
<th>Amblyopia</th>
<th>Angle at Near&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Systemic or Neurological Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/4</td>
<td>No</td>
<td>No</td>
<td>Right eye</td>
<td>Yes</td>
<td>30</td>
<td>No</td>
</tr>
<tr>
<td>2/M/4</td>
<td>Yes</td>
<td>Yes</td>
<td>Left eye</td>
<td>Yes</td>
<td>20</td>
<td>Speech and fine-motor delay</td>
</tr>
<tr>
<td>3/M/2</td>
<td>No</td>
<td>No</td>
<td>Left eye</td>
<td>Yes</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>4/F/27</td>
<td>Yes</td>
<td>No</td>
<td>Left eye</td>
<td>Yes</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>5/F/6</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>No</td>
<td>40</td>
<td>Mild speech and motor delay</td>
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<td>6/F/38</td>
<td>Yes</td>
<td>Yes</td>
<td>Left eye</td>
<td>Yes</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>7/M/6</td>
<td>Yes</td>
<td>Yes</td>
<td>Left eye</td>
<td>Yes</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>8/M/2</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>No</td>
<td>50</td>
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<td>9/F/1</td>
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<td>45</td>
<td>No</td>
</tr>
<tr>
<td>10/M/4</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>No</td>
<td>45</td>
<td>Trisomy 21</td>
</tr>
</tbody>
</table>

<sup>a</sup>Prism diopter esotropia unless otherwise indicated.

In all patients with infantile esotropia, defective temporalward monocular optokinetic responses in the fixating eye improved when the esotropic nonfixating eye was uncovered, allowing it to receive naswards optokinetic input under binocular conditions. From a practical viewpoint, this observation shows that the examiner should not test for MNTA when the patient has both eyes open in the patient and assume that the suppressed eye will not contribute to the optokinetic response in a patient with infantile esotropia. At a mechanistic level, this observation challenges the long-standing assumption that MNTA in humans with infantile esotropia can be attributed solely to defective cortical pursuit. In our patients, the modulation of horizontal optokinetic responses by the nonfoveal retina of the esotropic eye suggests that subcortical optokinetic pathways must continue to modulate peripheral optic flow in humans with infantile strabismus. This improvement of optokinetic waveform is consistent with the clinical observation that patients with manifest latent nystagmus show a visible worsening of their nystagmus when the deviated eye is covered.25

In a 1936 publication, Ter Braak showed that afoveate animals, such as the rabbit, generate optokinetic nystagmus in response to movement of large objects, despite the fact that they did not track small objects. In the monkey, these full-field optokinetic responses persisted after decortication, suggesting that they were mediated by a subcortical optokinetic system.29,30 In the rabbit, each eye is driven by mainly forward (nasalward) optokinetic motion, which provides the stimulus for the optokinetic responses of both eyes.31 These asymmetrical subcortical optokinetic responses are now known to be modulated by the contralateral nucleus of the optic tract (NOT) and dorsal terminal nucleus (DTN) of the accessory optic system within the mesencephalon, which respond only to ipsilateral optokinetic stimulation (nasalward for the viewing eye).32 In rabbits and in monkeys, these pathways project down to the inferior olive and contralateral flocculus and then on to the vestibular nuclei to modulate visuovestibular responses to full-field optokinetic rotation during turning movements (Figure 2).33,35

In primates, development of binocular corticopretectal pathways to the NOT and the DTN of the accessory optic system, which provide ipsilateral pursuit re-
Responses (temporalward for the viewing eye), are necessary to cancel this optokinetic asymmetry within the first year of life (Figure 3). These corticopretectal projections to the NOT-DTN come predominantly from the middle temporal area and the medial superior temporal area, as well as from V1 and V2, while those to accessory optic nuclei (lateral terminal nucleus and medial terminal nucleus) come exclusively from the middle temporal area and the medial superior temporal area. Within the superior temporal sulcus, the middle temporal area is involved in motion detection and is responsible for pursuit movements, while the medial superior temporal area modulates pursuit and visuovestibular detection of optic flow. As normal binocular cortical pursuit pathways become established within the first 6 months of human life, visuovestibular responses to full-field optokinetic stimulation become “encephalized” as they are incorporated into the cortical pursuit system (Figure 3).

In humans, these same subcortical optokinetic pathways retain their nasalward directional predominance and are believed to mediate the full-field horizontal optokinetic responses that are observed in early infancy until they are rendered inactive by the establishment of binocular cortical pursuit pathways (Figure 3). However, the general notion that they can retain function in the absence of cortical input has been controversial. For example, it has been suggested that the relative preservation of responses to nasally directed stimuli in patients with incomplete bilateral occipital lobe destruction could be owing to remnants of the subcortical projection to the NOT-DTN that may have been released from cortical control. Ter Braak and Schenk described a patient with acquired cortical blindness who retained some preservation of full-field optokinetic responses, but subsequent studies have found no evidence of this effect. These findings suggest that subcortical optokinetic pathways, once “shut off” after the first few months of life, are incapable of reactivating. However, they do not address the question of whether specific derangements in binocular cortical development can act to preserve their function.

Our finding that peripheral retinal optokinetic input can override defective foveal pursuit suggests that infant-
tile strabismus allows these subcortical optokinetic pathways (which rely on peripheral retinal input) to remain operational. Unlike “decortication,” infantile strabismus may maintain the function of the subcortical visual pathways in a way that prevents them from being shut off. In 1983, Schor suggested that selective maldevelopment of cortical binocular vision could provide a competitive advantage to reinforce the activation of direct subcortical projections from the nasal retina of each eye to the contralateral NOT-DTN and thereby potentiate their function. According to Hoffmann and colleagues, the Hebbian mechanism of synaptic formation predicts that only neurons firing in a correlated manner (in this case, sharing the same direction sensitivity) become consolidated during development. Through this activity-dependent mechanism, the ipsilateral direction sensitivity of the NOT-DTN would preferentially allow crossed nasal retinogeniculate pathways that connect monocularly through the visual cortex to establish corticofugal connections to the ipsilateral NOT-DTN, enabling these latent subcortical pathways to remain functional in infantile esotropia (Figure 4). In this way, infantile esotropia could remodel the cortical motion pathways to selectively maintain the nasally biased subcortical gateway through which unbalanced binocular visual input can turn the gears on these evolutionarily ancient eye movement control systems (Figure 4). The fact that cortical suppression can elicit latent nystagmus, and that peripheral retinal input can also drive this response, suggests that selective preservation of crossed corticopretectal connections may allow these latent subcortical mechanisms to be expressed in infantile esotropia.

This explanation has several implications for the MNTA that characterizes infantile esotropia. First, a selective preservation of crossed monocular nasal retinal projections from the contralateral eye would eliminate the temporal retinal projections subserving cortical pursuit from the ipsilateral eye, explaining why the cortical component of the optokinetic asymmetry can be monocularly driven in infantile esotropia and binocularly driven with a hemi-

Figure 4. Optokinetic uncover test in infantile esotropia. A, When the right eye is covered and the left eye receives a leftward (temporal) optokinetic stimulus, the temporal retina is ineffective in generating a response. The absence of binocular cells within the visual cortex means that temporally directed stimuli cannot be transmitted to the ipsilateral nucleus of the optic tract–dorsal terminal nucleus (NOT-DTN) because maturation of this function requires an early directional match between action potentials originating from binocular cortical cells in the middle temporal area (MT) and the medial superior temporal area (MST) with those projecting from the right eye via the ipsidirectional subcortical pathway to the NOT-DTN. B, When the right eye is uncovered, the nasalward optokinetic stimulus to the right retina generates a leftward optokinetic response that could be mediated by crossed subcortical connections to the NOT-DTN (small red arrow) or through the retinogeniculate pathway to the monocular right eye cells within V1 of the left hemisphere to MT-MST, where corticofugal projections can establish connections with cells in the left NOT-DTN that share the same leftward direction preference (large red arrow). L indicates left eye monocular cells; LGN, lateral geniculate nucleus; R, right eye monocular cells; R + L, cortical binocular cells (that are absent in infantile esotropia); and SCC, semicircular canals.
spheric lesion involving the cortical pursuit pathways. Second, this neurodevelopmental derangement would help to explain how the cortical motion asymmetry in infantile esotropia is dictated the directionality of the NOT-DTN. Third, it suggests that infantile esotropia can arrest development of the nascent optokinetic system at a stage wherein MNTA can be generated from the visual cortex (top down) or from subcortical pathways (bottom up). Fourth, as divined by Schor 30 years ago, the associated monocular corticofugal projections from the motion centers in the middle temporal area and the medial superior temporal area to the other ipsilateral accessory optic nuclei that control cyclovertical rotations of the eyes would (by a similar Hebbian mechanism) explain the torsional optokinetic biases and complex cyclovertical movements that accompany latent nystagmus but remain conspicuously absent in a hemispheric (binocular) pursuit defect. Fifth, the ability of subcortical visual pathways (Figure 2) to be activated bidirectionally via subcortical and cortical visual pathways would render obsolete the debate about neuroanatomical localization in infantile esotropia. This study has several inherent limitations. First, we did not use a circular full-field optokinetic apparatus, which produces the sensation of circularvection (the false sensation of physical rotation) and is believed to be necessary to directly stimulate the visuovestibular system. Although this testing paradigm would have fortified our conclusions, we were only able to confirm our observation using a flat full-field optokinetic stimulus, which (like the optokinetic drum) probably elicits pursuit responses in healthy individuals. However, the enhancement of temporalward foveal optokinetic responses when peripheral retina of the nonfixating eye was exposed to nasaward optokinetic motion demonstrates that cortical pursuit cannot be the only system involved in the generation of MNTA (and latent nystagmus, by inference). A selective preservation of crossed cortical projections to the NOT-DTN from the nasal retina of the contralateral eye (Figure 4) would allow nasaward cortical pursuit pathways to generate subcortical visuovestibular eye movements (with their associated torsional components), rendering these 2 classes of eye movement indistinguishable in the setting of infantile esotropia. Second, some of the patients with infantile esotropia had undergone previous strabismus surgery. Consequently, the angle of the esotropic deviation was smaller than that seen in infantile esotropia. Therefore, it cannot be assumed that the optokinetic uncover test would have necessarily shown a positive response in these patients with infantile esotropia prior to surgery. Nevertheless, all of our patients with unoperated infantile esotropia showed this effect, and all of our patients had an angle of deviation large enough to preclude perifoveal fixation, confirming that this binocular optokinetic mechanism arises from the synthesis of foveal and peripheral retinal input. Third, the inclusion of some patients with mild neurological disease could potentially challenge the results of our study. However, given that all patients showed the same pattern of responses on the optokinetic uncover test, our results suggest that these patients share a common pathogenesis for their infantile esotropia. Fourth, because optokinetic motion is known to displace the eyes in the direction of the fast phase, it might be argued that this displacement could have led to the false conclusion that the uncovered esodeviated eye was not fixating when the eye receiving temporal optokinetic stimulation was uncovered. As shown in the video, however, the fixating eye was clearly evident in all patients, and videouculography confirmed that the nasal retina of the esotropic eye could drive the optokinetic response.

In conclusion, the results of this study provide evidence that human subcortical optokinetic pathways may remain active in the presence of infantile esotropia. Selective preservation of corticotectal projections from the nasal retina of the contralateral eye would enable these subcortical visual pathways to retain their original function in the setting of infantile esotropia. The optokinetic uncover test provides a unique insight into the role of peripheral motion detection under binocular conditions, allowing us to deconstruct the optokinetic system into its cortical and subcortical components. The intrinsic monocular optokinetic biases that define these subcortical pathways may be the proximate cause of MNTA, while failure of the binocular cortical pursuit pathways to develop may provide the permissive cause that allows these subcortical pathways to remain functional.

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