ABSTRACT

Purpose: To determine the clinical characteristics and long-term outcomes of infants who presented with isolated vertical nystagmus.

Methods: The medical records of 114 infants who were diagnosed as having nystagmus from 1996 to 2016 were screened. Patients with vertical nystagmus within the first year of life who had unremarkable magnetic resonance imaging of the brain and demonstrated age-appropriate visual behavior were included. The parents of patients in the final study cohort were contacted by telephone to obtain long-term follow-up information.

Results: Eight patients comprised the final cohort. Vertical nystagmus was first observed at a mean age of 1.4 months (range: 1 to 2.5 months) and resolved in 87.5% of patients at a mean age of 3.8 months (range: 2 to 10 months). Vertical nystagmus was intermittent in 62.5%, upbeat in 62.5%, and pendular in 37.5% of patients. One patient's nystagmus did not resolve. Seventy-five percent of patient guardians participated in the telephone questionnaire. The mean age of patients at follow-up was 3.5 years (range: 0.5 to 8.1 years). Isolated iris transillumination was discovered in one patient without other features of albinism. Fifty percent of patients had speech delay requiring intervention. No other developmental delay or general medical conditions were identified.

Conclusions: Nystagmus resolved in 87.5% of patients, all before the first year of life, and speech delay was later identified in half of the patients.

INTRODUCTION

Vertical nystagmus in infancy has a broad differential diagnosis that includes disorders of the anterior visual pathway and lesions affecting the cerebellum and brainstem. Benign intermittent upbeat nystagmus has been described in otherwise healthy infants without a known cause, but the long-term ophthalmic, neurologic, and developmental outcomes for these children are not known. We describe the clinical characteristics and long-term outcomes of infants who presented with isolated vertical nystagmus in infancy, age-appropriate visual behavior, and unremarkable neuroimaging studies.

PATIENTS AND METHODS

Institutional review board approval was granted. Potential participants for the retrospective portion of the study were identified by searching through a single clinician's (GTL) electronic patient database. Eligible study participants included infants who were evaluated in the pediatric neuro-ophthalmology clinic at the Children's Hospital of Philadelphia between 1996 and 2016 and were diagnosed as having vertical nystagmus within the first year of life. The medical records of 114 patients from 1996 to 2016 were screened for inclusion in the study. Inclusion criteria comprised infants younger than 1 year with vertical nystagmus, age-appropriate visual behavior, no obvious neurological abnormalities at presentation, and unremarkable magnetic resonance imaging (MRI) of the brain. The most common reasons for exclusion were the presence of associated neurologic signs, significant intracranial abnormalities on neuroimaging (eg, neoplasms), hydrocephalus, developmental or...
syndromic abnormalities, sequelae of infectious processes, prior hemorrhage or ischemia, reduced visual behavior, and ophthalmic lesions including media opacities, fundus, or optic nerve pathology.

Charts were reviewed for the following information: date of initial visit, sex, medical conditions, preterm status, age at onset of nystagmus, age when nystagmus resolved if applicable, and results of additional investigations such as electroretinogram (ERG), visual evoked potentials, and electroencephalogram (EEG) if performed. Neuro-ophthalmic examination findings were recorded, including visual acuity, motility, the waveform of the nystagmus, and anterior segment and dilated posterior segment examination. MRI results were considered unremarkable if they were reported as normal or if incidental abnormalities (ie, cysts; small, non-enhancing, non-periventricular white matter lesions; or venous abnormalities) were discovered and no mass lesions, infarcts, malformations, or hemorrhages were found.

For the prospective portion of the study, telephone contact information was obtained and informed consent for enrollment by the parents or guardians was conducted via telephone. Enrolled participants were then asked a brief, pre-drafted telephone questionnaire. Parents were asked to report whether the diagnosis of nystagmus had changed, the child’s motor and speech development was normal, the child had been diagnosed as having other ophthalmic, neurologic, or general medical conditions were identified. None of the patients had a history of prematurity. No other developmental delay or general medical conditions were identified. None of the patients had a known family history of nystagmus, and other investigations had been performed after the initial diagnosis.

This study was conducted in full accordance with all applicable Children’s Hospital of Philadelphia research policies and procedures and all applicable federal and state laws and regulations, including 45 Code of Federal Regulations part 46.

RESULTS

Eight patients who presented with isolated vertical nystagmus within the first year of life and had age-appropriate visual behavior, no other obvious neurological findings, and a normal MRI of the brain were included in the retrospective portion of the study (Table 1). No patients had a history of prematurity. At initial presentation, all patients either “grimaced to light” or “blinked to light.” At the follow-up visits, all patients demonstrated normal “fix and follow” behavior with each eye tested. Three patients (37.5%) underwent Teller quantitative visual acuity testing, which was normal. Vertical nystagmus was first observed at a mean age of 1.4 months (range: 1 to 2.5 months), which resolved in 87.5% of patients at a mean age of 3.8 months (range: 2 to 10 months). Vertical nystagmus was intermittent, upbeat, and pendular in 62.5%, 62.5%, and 37.5% of patients, respectively. Provocation of the nystagmus could be achieved when the patient was laid down or fixated at near or distance. Additional testing was ordered by the treating physician for 3 patients: 1 patient received both an EEG and ERG because this was the original patient to present with vertical nystagmus and the clinician (GTL) felt compelled to perform an exhaustive evaluation, 1 patient received an EEG because there was a history of a prior febrile seizure, and 1 patient received an ERG to exclude a retinal dystrophy because the nystagmus did not resolve. All were normal studies.

In the prospective portion of the study, 6 (75%) of the patient guardians could be reached and completed the telephone questionnaire. The parents of 2 patients could not be contacted, and no parents refused to participate in the study. The mean age of patients who could be contacted for follow-up was 3.5 years (range: 0.5 to 8.1 years), and only 1 patient had less than a full year of follow-up. One patient who presented with upbeat nystagmus later developed a horizontal waveform and the nystagmus never resolved. No patients received an alternate diagnosis for the nystagmus. One patient was later found to have isolated iris transillumination that was not associated with other features of ocular albinism, but was being monitored by a pediatric ophthalmologist. A history of speech delay requiring intervention by speech therapy, occupational therapy, or a developmental pediatrician was elicited in 3 (50.0%) children, all of whom had had upbeat nystagmus. No other developmental delay or general medical conditions were identified. None of the patients had a known family history of nystagmus, but one father described a history of “eyelid twitching” that resolved in infancy.

DISCUSSION

We have described the clinical characteristics and follow-up of infants who presented with isolated vertical nystagmus but had age-appropriate visual behavior and an unremarkable MRI of the brain. Reports in the literature describe patients with benign, self-
### TABLE 1
Characteristics and Long-term Follow-up of Infants With Isolated Vertical Nystagmus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nystagmus First Identified (mo)</th>
<th>Nystagmus Resolution (mo)</th>
<th>Clinical Description of Nystagmus Waveform</th>
<th>Additional Tests</th>
<th>Able to Contact for F/U</th>
<th>Age at Time of F/U (y)</th>
<th>Other Ophthalmic Disease</th>
<th>Other Neurologic Disease</th>
<th>Other Major Medical Conditions/Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M)</td>
<td>1</td>
<td>4</td>
<td>Low amplitude, moderate frequency, vertical pendular nystagmus</td>
<td>None</td>
<td>Yes</td>
<td>8.0</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2 (M)</td>
<td>2</td>
<td>4</td>
<td>Intermittent; high amplitude, high frequency upbeat nystagmus provoked by leaning backward</td>
<td>EEG (normal), Teller acuity (normal)</td>
<td>Yes</td>
<td>2.9</td>
<td>Iris trans-illumination without other features of albinism</td>
<td>Speech delay requiring developmental pediatrician</td>
<td>Febrile seizure; father had “eyelid twitching” that resolved in infancy</td>
</tr>
<tr>
<td>3 (M)</td>
<td>2</td>
<td>10</td>
<td>Intermittent upbeat nystagmus in primary gaze</td>
<td>Teller acuity (normal)</td>
<td>Yes</td>
<td>3.2</td>
<td>No</td>
<td>Speech delay requiring 1 year of speech therapy</td>
<td>No</td>
</tr>
<tr>
<td>4 (M)</td>
<td>2.5</td>
<td>Did not resolve</td>
<td>Upbeat nystagmus in primary gaze, worsened in up gaze; down gaze preference; later evolved a horizontal pendular component</td>
<td>ERG (normal), Teller acuity (normal)</td>
<td>Yes</td>
<td>3.1</td>
<td>No</td>
<td>Speech delay requiring occupational therapy and early intervention</td>
<td>No</td>
</tr>
<tr>
<td>5 (M)</td>
<td>1</td>
<td>4</td>
<td>Intermittent upbeat nystagmus lasting a few seconds; nystagmus would occur when laid down or when fixating at near</td>
<td>None</td>
<td>Yes</td>
<td>3.1</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6 (M)</td>
<td>1</td>
<td>2</td>
<td>Upbeat nystagmus; provoked by distance fixation</td>
<td>None</td>
<td>Yes</td>
<td>0.5</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7 (M)</td>
<td>1</td>
<td>4</td>
<td>Intermittent, pendular vertical nystagmus with an occasional rotary and divergent component</td>
<td>EEG, ERG (both normal)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8 (M)</td>
<td>1</td>
<td>2</td>
<td>Intermittent shimmering vertical pendular nystagmus</td>
<td>None</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total</td>
<td>1.4</td>
<td>3.8 (87.5% resolved)</td>
<td>62.5% intermittent, 62.5% upbeat, 37.5% pendular, 25.0% provoked by leaning backward</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12.5%</td>
<td>50%</td>
<td>0%</td>
</tr>
</tbody>
</table>

F/U = follow-up; EEG = electroencephalogram; ERG = electroretinogram; N/A = not available
limited intermittent vertical nystagmus in infancy. Good et al.\textsuperscript{3} described one infant with transient vertical nystagmus that disappeared within the first year of life. Goldblum and Effron\textsuperscript{3} described two healthy infants with tonic down gaze and upbeat nystagmus on attempted up gaze that was accentuated by the supine position. Transient tonic up gaze in infancy with downbeat nystagmus has also been described.\textsuperscript{4} Robert et al.\textsuperscript{1} elegantly described the largest series of five infants with benign intermittent upbeat nystagmus in infancy, two of whom had associated tonic down gaze. In their series, all patients had a normal neurological and developmental evaluation and had normal visual function, fundus examination, MRI of the brain, and neuro-otologic investigations.\textsuperscript{5}

Although all eight infants in our study population were male, only one of the five patients in Robert et al.'s\textsuperscript{1} study was male. Therefore, we do not have evidence for a strong sex predilection for isolated vertical nystagmus of infancy. The ages at nystagmus onset and resolution in our study cohort were similar to those described by Robert et al.,\textsuperscript{1} with the onset of nystagmus in the first 2 months of life and resolution prior to 1 year of age in all but one patient. In our cohort, the nystagmus did not resolve in one patient whose waveform was initially vertical upbeat but later evolved a horizontal component. It is possible that this infant's nystagmus represented atypical infantile nystagmus and, therefore, had a distinct etiology and long-term prognosis.\textsuperscript{5} Similar to the patients in Robert et al.'s\textsuperscript{1} study, upbeat nystagmus could be triggered or enhanced by leaning the child backward into a supine position in two of our patients.

Benign intermittent upbeat nystagmus is well recognized and is "benign" because the infants have no identifiable cause or associated neurologic illness. We identified speech delay that necessitated intervention by a specialist in 50% of patients, which has not been described in this population before, although the severity and nature of speech delay was not able to be further characterized in the prospective telephone questionnaire. This is higher than the prevalence of speech or language delay in the general pediatric population, which has been estimated to be less than 20%.\textsuperscript{6,7} The significance of this association is unclear and further investigation with a larger cohort is needed.

The current retrospective study has several limitations. Clinical observation of age-appropriate fixation behavior and structural ophthalmic examinations were demonstrated in all patients and excluded significant retinal or optic nerve pathology; therefore, further testing with ERG was not performed universally. Cases of mildly impaired visual acuity from subtle macular or optic nerve pathology that may have been identified with optical coherence tomographic imaging of the retina or optic nerve could have been missed.\textsuperscript{8} Although the presence of neurological signs and symptoms was elicited during the neuro-ophthalmologist's history and clinical examination, formal neurological examinations were not performed. All patients received an MRI of the brain, but an EEG was not performed universally.

Not all guardians could be reached for the questionnaire and the duration of follow-up varied substantially from a few months to 8 years. Parents of patients with limited follow-up would not have had sufficient time to report long-term neurological and developmental outcomes such as speech delay, and those with extended follow-up periods may have had limited recollection. Our prospective study relied on the recollection of parents and, therefore, is subject to error and recall bias.

The work-up for isolated vertical nystagmus in infancy (normal development at the time of presentation and normal general and neurologic examinations) should include a thorough eye examination by a pediatric ophthalmologist or neuro-ophthalmologist and an MRI of the brain with and without contrast to exclude a lesion of the optic chiasm, brainstem, or cerebellum, which may also be associated with vertical nystagmus. Further ophthalmic testing is not needed if imaging is normal, and the infant should have close follow-up with the ophthalmologist for monitoring of visual development.

It is imperative that benign isolated vertical nystagmus is distinguished from vertical nystagmus associated with afferent visual pathway disease or neurological disease. Vertical nystagmus in neonates has been associated with retinal dystrophies, macular hypoplasia, and optic nerve hypoplasia.\textsuperscript{8-11} Within this group, visual maturation is significantly impaired, abnormalities may be identified on ophthalmic examination, and the nystagmus does not typically resolve. In such patients, confirmatory studies such as ERG, visual evoked potentials, optical coherence tomographic imaging of the retina and optic nerve, visual field studies, and genetic testing may be essential in addition to neuroimaging to reach a diagnosis. Rarely, idiopathic infantile nystagmus may present with vertical nystagmus.\textsuperscript{9}
The pathophysiology of isolated vertical nystagmus in infancy is not well understood. Based on the ability of supine positioning to accentuate or elicit the nystagmus, Robert et al.\(^1\) proposed that inadequate wiring of the semicircular and otolithic first order vestibular neurons may be responsible and that continued motor activity causes recalibration of the vestibulo-ocular pathways, leading to resolution of the nystagmus at an older age. It is possible that immature development of the primary vestibular organs or pathways mediating the vertical vestibular-ocular reflex, brainstem neural integrators for vertical gaze, cerebellar pathways, or supranuclear influences could also be responsible.

In a cohort of otherwise neurologically intact male infants with vertical nystagmus but age-appropriate visual behavior and unremarkable neuroimaging studies, we found a high rate of resolution of nystagmus within the first year of life. There was no emergence of significant ophthalmic or neurologic impairment; however, speech delay was noted in half of the patients who could be reached for follow-up. Further studies that perform longitudinal ophthalmic and neurological assessments will be required to confirm these initial findings.

REFERENCES