Ophthalmologic Disorders in Children With Syndromic and Nonsyndromic Hearing Loss

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Objective: To determine the rate of ophthalmologic anomalies among patients with syndromic and nonsyndromic, congenital sensorineural hearing loss (SNHL) to assess the need for comprehensive ophthalmologic evaluation in these children.

Design: Retrospective medical chart review of children with SNHL who underwent comprehensive evaluation by pediatric ophthalmologists and geneticists.

Setting: Tertiary care pediatric hospital.

Patients: Seventy-seven patients with SNHL.

Main Outcome Measures: Degree of hearing loss (HL) and presence of ophthalmologic and genetic disorders.

Results: The overall rate of ophthalmologic disorders was 32% (25 of 77 patients). When children with multisystem genetic disorders known to be related to visual loss were excluded, the rate fell to 23% (12 of 53 vs 13 of 24; \( P = .006 \)). There was no statistically significant difference in the degree of HL between patients with and without eye disorders (mean [SD], 46.5 [29.9] vs 49.1 [32.3] dB HL; \( P = .75 \)). Patients with eye disorders were significantly more likely to have a multisystem genetic disorder (13 of 25 [52%] vs 11 of 52 [21%]; \( P = .006 \)). No patients with ocular abnormalities had isolated otologic disorders, but 9 of 52 (17%) of those patients without ocular abnormalities did.

Conclusions: Comprehensive ophthalmologic examination revealed a rate of ophthalmologic disorders in children with SNHL in the lower end of the previously reported rates of 31% to 61%. Children with nonsyndromic SNHL have an approximately 2- to 3-fold increase in ocular abnormalities compared with the general pediatric population. Ophthalmologic and genetic consultations are warranted in patients with congenital SNHL.


The incidence of sensorineural hearing loss (SNHL) is approximately 3 in 1000 children (0.3%), and the incidence of ophthalmologic disorders in children has been reported to be 2% to 11%.\(^2\) The combination of multisensory deficits can seriously affect cognitive and language development. Therefore, early identification of a visual system abnormality is essential in a child with SNHL to maximize rehabilitative and therapeutic efforts.

A recent literature review on the prevalence rate of ophthalmic disorders in children with SNHL reported a range of 40% to 60%.\(^2\) The authors note a high degree of methodologic variability between studies: namely, variability in the type and comprehensiveness of eye examinations and inconsistent definitions of ophthalmic disorders. Very few studies on children with SNHL have included a comprehensive eye examination by a pediatric ophthalmologist.\(^3^6\)

The most recent study of the incidence of eye disorders in children with SNHL, by Sharma et al,\(^7\) identified a rate of 21.7%. Each of their patients underwent ophthalmologic examination, but a unified approach may have been lacking, resulting in a degree of uncertainty in their final rates. Their study\(^7\) offers strong insight into what percentage of children with SNHL have \(GJB2\) mutations, because 144 of their 226 patients were tested, revealing 38 patients (26%) with either single or biallelic mutations. One in 27 children with biallelic \(GJB2\) mutations (4%) had an ocular abnormality.

The goal of our study was to identify the rate of eye disorders through a comprehensive ophthalmologic and genetic examination in our children with syndromic and nonsyndromic congenital SNHL and no other clinical history suggestive of ophthalmologic disease. For this
reason, children with well-defined risk factors for ophthalmologic and auditory impairment (ie, prematurity; meningitis; and congenital infections such as rubella, cytomegalovirus, syphilis, or toxoplasmosis) were excluded from the study. A genetic evaluation by a pediatric clinical geneticist was included in the evaluation protocol to identify both syndromic and nonsyndromic hearing loss. A genetic evaluation was also helpful in diagnosing conditions that are known to have a risk of eye disorders. This information may assist in determining the necessity of ophthalmologic evaluation in children with apparently isolated congenital sensorineural hearing loss.

METHODS

We conducted an institutional review board–approved retrospective review of all pediatric patients from June 2001 to May 2006 with a diagnosis of congenital SNHL within the Department of Otolaryngology who received formal ophthalmologic examinations. A total of 408 patients with congenital SNHL had a comprehensive ophthalmologic examination. For a variety of reasons, many patients either declined or failed to complete the genetic evaluation. Patients without a formal genetic examination were then excluded, resulting in a final study population of 77 patients.

Each electronic medical record was reviewed to record the following: age at time of hearing evaluation, sex, degree of hearing loss, presence of a clinically significant ophthalmologic disorder, and presence of a known genetic disorder. Age at time of hearing evaluation was used instead of age at diagnosis because many patients were referred from outside institutions, and the age at diagnosis was unavailable.

The audiogram used to calculate the degree of hearing loss was the most recent and comprehensive test available obtained in a standardized manner at our institution. Conventional audiometry, play audiometry, visual reinforcement audiometry (VRA), and auditory brainstem response (ABR) were included. For VRA, the speech awareness threshold was recorded. For ABR testing, the average ABR response levels to clicks and tone bursts were recorded. In conventional and play audiograms, a 4-tone, pure-tone average over the frequencies of 500, 1000, 2000, and 4000 Hz was calculated. If there was asymmetric SNHL, the degree of hearing loss in the worse ear was recorded.

The pediatric ophthalmologic examination consisted of age-appropriate evaluation of vision, external structures, pupils, alignment and motility, anterior segment, optic nerve, retina, and cycloplegic refraction (to determine refractive error). Ophthalmologic disorders were defined as clinically significant if they would lead to amblyopia and would require an intervention with corrective lenses or surgery. Refractive disorders were considered clinically significant if they met the following criteria for bilateral eyes: hypermetropia correction of at least 5 diopters (D), myopia correction of at least 10 D, or astigmatism correction greater than 3 D. For unilateral eye disorders or a difference between 2 eyes (defined as anisometropia if a clinically significant difference exists between 2 eyes), the following refractive disorders were considered clinically significant: hypermetropia correction greater than 3 D, myopia correction greater than 1 D, and astigmatism correction greater than 1 D. These cutoff values are based on the 2007 American Academy of Ophthalmology Pediatric Ophthalmology and Strabismus Panel Preferred Practice Pattern Guidelines.8

The genetic evaluation consisted of obtaining a detailed family and medical history and a physical examination by a clinical geneticist. The family history interview was used to generate a 3-generation pedigree specifically addressing hearing loss and features suggestive of hearing loss syndromes. The patient history included detailed prenatal and neonatal histories, a complete review of systems, medical history, and a developmental history. The physical examination included a general detailed examination with attention to morphologic features; measurements of height, weight, head size, ear size, interocular distances, hands, and feet; and minor or significant dysmorphic features.

Patients with apparent nonsyndromic bilateral SNHL were offered molecular testing of the GJB2 and GJB6 genes (connexin 26 and connexin 30 DFNB1). Those with an inner ear anomaly (including Mondini or other anomalies) or enlarged vestibular aqueduct (EVA) were offered molecular testing of the SLC26A4 gene (Pendred syndrome; DFNB4). A urine cytomegalovirus (CMV) study was recommended for patients younger than 4 months. Although CMV urine culture after age 3 to 4 weeks is now known to be at best "indeterminant," it was decided in the early years of our program that the category of "indeterminant" could be helpful. Patients with documented exposure to gentamicin were offered testing for the mitochondrial mutation (A1555G) associated with aminoglycoside-induced hearing loss. Patients with findings suggestive of other hearing-loss syndromes were offered the appropriate follow-up studies and genetic tests that were clinically available. These included urinalysis, thyroid function studies, renal imaging, high-resolution chromosome studies, and array comparative genomic hybridization. Additional studies were considered when clinically indicated. Children with multiple anomalies had high-resolution chromosome studies, and many had subtelomeric fluorescence in situ hybridization or microarray comparative genomic hybridization studies.

All patients underwent inner-ear imaging, either by computed tomography or magnetic resonance imaging. Statistical analysis was performed using Microsoft Excel software (Redmond, Washington). The comparison of degree of hearing loss between groups was accomplished by t-test.

RESULTS

A clinically significant ophthalmologic disorder was identified in 25 of 77 patients, resulting in an overall rate of 32%. There was no statistically significant difference in age (mean [SD] age, 7.3 [4.9] vs 6.7 [4.7] years; P = .63) or sex between the group with SNHL and a clinically significant ophthalmologic disorder and the group without a clinically significant ophthalmologic disorder.

The types of hearing evaluation were standard audiometry (32 of 77), play audiometry (19 of 77), visual reinforcement audiometry (13 of 77), and auditory brainstem response (13 of 77). The average hearing loss in all patients was 48.3 dB. There was no significant difference in hearing loss between the groups with and without clinically significant eye disorders (mean [SD], 46.5 [29.9] vs 49.1 [32.3] dB hearing; P = .75).

The most common types of ophthalmologic disorders were motility (52%), refractive (48%), structural (32%), and neuro-ophthalmologic (25%) (Table 1). Motility disorders included esotropia (inward eye deviation) in 7 of 25 patients (28%) and exotropia (outward eye deviation) in 6 of 25 (24%). Refractive disorders included hypermetropia (far-sightedness) in 7 of 25 patients (28%), myopia (near-sightedness) in 4 of 25 (26%), anisometropia (difference in refractive properties of the 2 eyes) in 5 of 25 (20%), and astigmatism (refractive error in which lens converges light on 2 separate points)
From an embryologic standpoint, critical development of some neurologic components of the ear and eye develop concurrently from ectoderm, starting at the fourth embryonic week. Genetic insults occurring at this time may result in simultaneous otologic and ocular manifestations. Children with hearing loss and visual loss may encounter considerable barriers to communication and interaction, limiting critical early childhood development.

Our study is one of few in the literature to include a detailed ophthalmologic evaluation by a pediatric ophthalmologist for children with SNHL and is, to our knowledge, the first in the literature to also include a comprehensive evaluation by a pediatric clinical geneticist. When compared with rates in the literature, our rate of ophthalmologic disorders in children with SNHL was lower (32% vs 40%-60%). In the few studies of children with SNHL (including congenital and acquired) who underwent comprehensive ophthalmologic examination, our rate of eye abnormalities was at the low end (32% vs 31%, 44%, 46%, and 61%). Our sample size was roughly equivalent to these studies (77 vs 54, 49, 83, and 110). The difference in our rate may be due to our decision to exclude patients with known prematurity; a history of meningitis; and those with a history of congenital infection with rubella, cytomegalovirus, syphilis, or toxoplasmosis. This was not performed in 3 of the 4 comparative studies. These patients were removed because it is general clinical practice to obtain an ophthalmologic examination in these children given their risk for eye disease, and we were interested in ascertaining whether those children presenting with SNHL but no obvious risk factors for eye disease required ophthalmologic examinations.

Our study is similar to a recent study by Sharma et al in which 226 children with SNHL were examined for ophthalmologic disorders. Although the extent of the eye examination is uncertain in each of their patients, the prevalence rate of eye disorders is similarly lower than the prior literature (21.7%). Syndromic hearing loss was present in 4.9% of their patients, which is roughly one-sixth of the number in our study (19 of 77 [25%]). We speculate that their rate of syndromic diagnosis may have

### Table 1. Ophthalmologic Disorders in Patients With Sensorineural Hearing Loss

<table>
<thead>
<tr>
<th>Type of Abnormality</th>
<th>Affected Patients, % (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motility</td>
<td>52</td>
</tr>
<tr>
<td>Refractive</td>
<td>48</td>
</tr>
<tr>
<td>Structural, anterior or posterior</td>
<td>32</td>
</tr>
<tr>
<td>Neuro-ophthalmologic</td>
<td>25</td>
</tr>
</tbody>
</table>

- A patient can have more than 1 category of abnormality but not multiple disorders within each category.

### Table 2. Systemic Genetic Disorders or Other Multiple System Anomalies of Unknown Cause in Patients With Clinically Significant Ophthalmologic Disorders

<table>
<thead>
<tr>
<th>Systemic Genetic Disorder or Multiple Congenital Anomalies of Unknown Cause</th>
<th>Affected Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21 syndrome (Down syndrome)</td>
<td>2</td>
</tr>
<tr>
<td>Waardenburg syndrome</td>
<td>2</td>
</tr>
<tr>
<td>CHARGE syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Asperger syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Hemifacial microsomia</td>
<td>1</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Multiple congenital abnormalities</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. Systemic Genetic Disorders in Patients Without Clinically Significant Ophthalmologic Disorders

<table>
<thead>
<tr>
<th>Systemic Genetic Disorder</th>
<th>Affected Patients, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple congenital abnormalities</td>
<td>2</td>
</tr>
<tr>
<td>Currarino Triad/Townes-Brock syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Charcot-Marie-tooth disease</td>
<td>1</td>
</tr>
<tr>
<td>Mitochondrial myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Hemifacial microsomia</td>
<td>1</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Pendred syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Leopard syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia</td>
<td>1</td>
</tr>
</tbody>
</table>

- Disorders known to have association with ophthalmologic disorders.
been similar to our findings if a comprehensive genetics evaluation were a part of their protocol. Importantly, both of our studies determined that the prevalence of ocular anomalies in children with nonsyndromic SNHL was not predictive of the presence of ocular anomalies.

An interesting finding in our study was that children without nonsyndromic SNHL had a lower rate of ophthalmic disorders (23%) but still had a rate 2 to 3 times that found in the general pediatric population.1 For this reason, we believe ophthalmologic evaluation is warranted in children with apparently isolated SNHL. In addition, our data show that many of the patients with SNHL and eye disorders will have a diagnosable genetic anomaly; thus, comprehensive evaluation by a pediatric clinical geneticist is also warranted.

In 1992, Leguire et al13 found that children with greater than 80 dB hearing loss had a statistically higher prevalence of retinal abnormalities compared with those with less than 80 dB hearing loss, but differences in refractive and overall ocular disorders did not reach statistical significance. This may have been influenced by the fact that their group with retinal disease contained a significantly higher number of patients with rubella, who had a greater degree of hearing loss. In our study, the degree of hearing loss was not predictive of the presence of ocular disorders, perhaps because we excluded patients with prematurity and congenital infections. Our findings suggest, however, that the degree of hearing loss should not stratify patients into groups that should or should not undergo ophthalmologic evaluation.

Twenty-four of our 77 patients were diagnosed as having a genetic abnormality. Interestingly, Usher syndrome, which is the most common cause of congenital deafness and ocular findings,12 was not identified in any child. Because the clinical presentation of hypermetropia and myopia may occur before the hallmark anatomic finding in Usher syndrome, it is possible that some of our patients with refractive errors may go on to develop retinitis pigmentosa.13 In addition, none of the patients with significant ocular abnormalities had isolated otologic genetic disorders. Indeed, the yield rate of the genetic evaluation in patients with any type of eye disorder was 52%, suggesting that all children with SNHL and eye disorders should undergo a genetic evaluation.

The major limitation in our study was the absence of universal genetic evaluations. Even though this evaluation is a standard recommendation to all patients identified as having congenital SNHL, not all families elect to follow this recommendation. This shortcoming perhaps added an overall overreporting of genetic disorders in these patients because parents who felt that their children did not have a disorder may have been less likely to undergo evaluation.

Future studies will be focused on prospective demonstration of the cost benefit of including ophthalmologic evaluation in the care of children with congenital SNHL.

In conclusion, identifying and remediating the sensory deficits of children with hearing and visual loss is critical to physical, intellectual, and social development. Routine and comprehensive ophthalmologic evaluation should occur in children with congenital SNHL because of the several-fold increase in prevalence rate of ocular abnormalities when compared with the general pediatric population. Furthermore, many children with SNHL have identifiable syndromic and nonsyndromic causes, justifying a comprehensive genetic evaluation, especially in those with an associated ophthalmologic diagnosis.

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Analysis and interpretation of data: Johnston, Curry, Morlet, Lehman, Ennis, and O’Reilly.

Drafting of the manuscript: Johnston, Newborough, and O’Reilly.

Critical revision of the manuscript for important intellectual content: Johnston, Curry, Morlet, Bartoshevsky, Lehman, Ennis, and O’Reilly.

Statistical analysis: Johnston.

Administrative, technical, and material support: Curry, Newborough, Bartoshevsky, Lehman, and O’Reilly.

Study supervision: Morlet, Bartoshevsky, Lehman, and O’Reilly.

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REFERENCES


