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Comprehensive Diagnostic Battery for Evaluating Sensorineural Hearing Loss in Children

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Abstract

Objective—Selection of diagnostic tests for children with sensorineural hearing loss (SNHL) is influenced by clinical suspicion. Testing results reported in the literature are similarly biased. We evaluate the usefulness of a comprehensive diagnostic battery for each child.

Study Design—Retrospective review.

Setting—Tertiary care university hospital.

Patients—A total of 270 children referred for severe to profound SNHL between January 2002 and June 2009.

Interventions—Results of the following were reviewed: magnetic resonance imaging, computed tomography, renal ultrasound, electrocardiography, fluorescent treponemal antibody absorption test, connexin 26 sequencing, genetic consultation, and ophthalmologic consultation.

Main Outcome Measure—Diagnostic yield of each test was determined.

Results—Each diagnostic test or consultation was completed by at least 95% of patients for whom it was ordered. Magnetic resonance imaging revealed abnormalities explaining SNHL in 24% of patients. Computed tomography showed inner ear anomalies in 18% of patients. Biallelic connexin 26 mutations were found in 15%. Renal ultrasound found anomalies in 4% of patients. Electrocardiography found 1% of patients with prolonged QT intervals. Fluorescent treponemal antibody absorption test result was positive in 0.5%. Genetic consultation found a genetic cause for hearing loss in 25%. Ophthalmologic consultation found abnormalities associated with hearing loss in 8%.

Conclusion—Diagnostic radiologic imaging is the highest yielding test for evaluating children with SNHL. Connexin 26 sequencing identifies a nearly nonoverlapping subset of children compared with imaging. Specialty consultations, particularly from a clinical geneticist, can improve diagnostic yield. Other tests, although of lower diagnostic yield for SNHL, can identify important diseases that significantly affect patient health.

Keywords

Congenital hearing loss; Neonatal hearing loss; Pediatric otology

Hearing loss is the most common sensory disorder in the United States, with an incidence of approximately 1 per 1000 (1). Approximately 25% of the cases of neonatal sensorineural hearing loss (SNHL) are attributed to identifiable prenatal or postnatal disease or trauma (2). Two significant risk factors for congenitally acquired SNHL are perinatal infections and prematurity. Neonatal intensive care unit admission itself also portends significant risk for hearing loss (3,4). The remainder of cases of neonatal hearing loss is thought to be genetic in nature: 18% attributed to undiagnosed genetic factors, 15% to autosomal-dominant genetic mutations, 40% to autosomal-recessive genetic mutations, and 2% to sex-linked genetic mutations (5).

The ability to hear during the early years of life is critical for the development of speech, language, and cognition. Prelingual deafness is particularly worrisome as it can engender many other disabilities. Early identification and intervention can prevent severe psychosocial, educational, and linguistic repercussions (6–8). The prevalence of congenital hearing loss is greater than twice that of all other diseases and syndromes routinely screened at birth combined (9). Hence, universal newborn hearing screening programs have been implemented in most states across the country.

Once a child has been formally diagnosed with hearing loss and appropriate intervention has been implemented, clinical efforts are then directed toward finding the cause of hearing loss. Presently, no formal consensus exists regarding which specific diagnostic tests ought to be ordered, and therefore, the workup may vary significantly between physicians. Several studies in the literature report diagnostic yields for various tests, but these results may be biased by specific selection criteria used to determine which tests were ordered for each particular child (10–12). In this study, we attempted to avoid any bias by uniformly ordering a comprehensive diagnostic battery of tests for each child with profound to severe SNHL. Eliminating diagnostic test stratification allowed us to compare the diagnostic yields of these tests across the same population of children. In addition, the comprehensive diagnostic battery identified anomalies in other organ systems that may not have been useful for determining the cause for hearing loss but had significant effect on patient health.

METHODS

We performed a chart review of 413 consecutive children with severe to profound SNHL who were referred to The Hearing Center at Texas Children's Hospital for evaluation between January 2002 and June 2009. Institutional review board approval of this study was obtained through Baylor College of Medicine. Of these children, we excluded those who had previously undergone a diagnostic workup for their hearing loss at another institution or who already had a confirmed cause for their hearing loss. Also excluded were those children for whom a routine comprehensive diagnostic battery had not been ordered. We noted that during the 7.5-year period reviewed, additional tests were added to the diagnostic battery as our understanding of neonatal hearing loss evolved. Therefore, earlier patients may not have undergone each component of the routine diagnostic battery as it presently stands. After exclusions, we identified 270 children (135 boys and 135 girls) with severe to profound SNHL for whom every component of the diagnostic battery had been ordered. The diagnostic battery consisted of 6 tests: fluorescent treponemal antibody absorption (FTA-ABS) test, connexin 26 gene mutation analysis (performed by sequencing the entire gene rather than polymerase chain reaction screening for specific mutations), electrocardiography (ECG), computed tomography (CT) of the temporal bone (inner ear malformations including cochlear dysplasia, semicircular canal, or vestibular dysplasia, enlarged vestibular aqueduct, and abnormalities of the internal auditory canal [IAC] and cochlear aperture [CA, the bony opening by which the cochlear nerve passes from the modiolus into the IAC] were evaluated

using criteria detailed by Swartz and Mukherji [13]), magnetic resonance imaging (MRI) of the brain and IACs (cochlear nerve hypoplasia or aplasia were evaluated using criteria detailed by Glastonbury [14]), and renal ultra-sound (US). Clinical notes from consultations to the clinical genetics and ophthalmology departments were also reviewed. The data were tabulated and analyzed with Microsoft Excel 2003 (Microsoft Corp., Redmond, WA, USA). Statistical significance was determined using the Student *t* test function of Microsoft Excel 2003.

RESULTS

Each patient underwent nearly all of the tests or consultations that were ordered (Fig. 1). Compliance was achieved at least 95% of the time for each component of the diagnostic battery. The diagnostic yields for each test or consultation are summarized in Table 1.

Imaging

Anomalies in the temporal bone were found in 43 (18%) of 245 patients imaged by CT scan. The most frequently observed anomalies were cochlear dysplasia (*n* = 25) and semicircular canal/vestibular dysplasia (*n* = 25); other pathologic findings included IAC/CA anomalies (*n* = 18) and enlarged vestibular aqueducts (*n* = 13). In isolation, the most frequently observed anomaly was narrowing of the IAC and/or CA (*n* = 12).

Abnormal MRI result was identified in 98 (40%) of 242 patients. Of these, 41 patients had inner ear anomalies that could explain hearing loss. Another 16 patients had a constellation of MRI findings consistent with congenital cytomegalovirus (CMV) infection including dilated lateral ventricles, oligo/pachygyria, white matter disease, and intracerebral calcifications. Therefore, 57 (24%) of 242 patients demonstrated MRI abnormalities that could explain hearing loss. Overall, 26 patients were noted on MRI to have either cochlear nerve hypoplasia or aplasia, of which only 15 were also found to have a correlated narrow/absent IAC or a narrow/absent CA on CT. Conversely, of 18 patients with abnormalities of the IAC or CA on CT, 3 were not found to have an associated cochlear nerve anomaly on MRI. The remaining findings on MRI were nondiagnostic for hearing loss but certainly could have explained other cognitive disabilities observed in the patients: leukomalacia (*n* = 19), encephalomalacia (*n* = 14), dysplasia (*n* = 4), Chiari malformation (*n* = 3), and microcephaly (*n* = 2).

Of the 43 patients with inner ear anomalies on CT, 42 were also imaged by MRI. The MRI studies generally corroborated the findings of the CT scans. The only exceptions included 3 patients with enlarged vestibular aqueducts on CT reported as normal on MRI as well as 3 patients with narrow IACs on CT reported as having normal cochlear nerves on MRI.

Renal US anomalies were noted in 20 (9.6%) patients. Of the abnormal USs, 8 (4%) contained findings that could be associated with branchio-oto-renal (BOR) syndrome; these included hypoplastic kidney (*n* = 3), dysplastic kidney (*n* = 2), vesiculoureteral reflux (*n* = 2), and hydronephrosis (*n* = 1). Ultimately, none of the 8 patients were diagnosed with BOR syndrome. The remaining 12 patients demonstrated renal findings that have not been associated with BOR syndrome such as renal stones, ectopic kidney, duplex kidney, and horseshoe kidney. These patients were each referred to a consulting nephrologist, but these findings ultimately had no significant consequence for the patients' health.

Laboratory Testing

Only 1 (0.5%) of 204 patients who underwent FTA-ABS testing was found to be positive. This patient was reported to the Centers for Disease Control and Prevention and referred to an infectious disease specialist. Ultimately, this patient was not treated for syphilis because

the cause for seropositivity was determined to be a result of more than 20 blood transfusions this patient received during her lifetime because of multiple medical problems.

Biallelic mutations in the connexin 26 gene were found in 33 (15%) of 220 children. Gene sequencing demonstrated that 18 mutations were homozygous 35delG mutations, 1 was a homozygous W44X mutation, 1 was a homozygous E147K mutation, and 13 were compound heterozygous mutations. All 33 patients with connexin 26 mutations underwent a CT temporal bone, and only 1 patient was found to have an inner ear anomaly (lateral semicircular canal dysplasia). Of these 33 patients, 29 also underwent MRI imaging, and again the only temporal bone anomaly was the single corroboration of the patient with lateral semicircular canal dysplasia.

Electrocardiography

Electrocardiographic abnormalities were found in 7% (10/143) of patients tested, and 3 of these patients were found to have a prolonged QT interval. Of these 3 patients, 1 had multiple atrial and ventricular septal defects and was already being observed by a cardiologist. The 2 remaining children were newly referred to cardiologists and were both ultimately diagnosed with Jervell and Lange-Nielsen syndrome by gene sequencing analysis. Other ECG abnormalities included sinus bradycardia, right bundle branch block, and left ventricular hypertrophy.

Consultation

A genetics evaluation was completed in 107 patients and revealed genetic abnormalities in 38 (36%), 27 (25%) of which were associated with SNHL. The most common finding was abnormally coded connexin 26 (n = 16). Other findings included CHARGE association (n = 3), Waardenburg syndrome (n = 2), Usher syndrome (n = 2), mitochondrial disorder (n = 2), and Jervell and Lange-Nielsen syndrome (n = 2).

Ophthalmologic evaluation was completed in 120 patients, and abnormalities were observed in 47 (39%) of 120 children. Overall, the most common finding was myopia (n = 10). Abnormalities associated with syndromic hearing loss were found in 9 patients (7.5%), the most common of which was coloboma (n = 7). The remaining 2 patients were found to have retinitis pigmentosa and were ultimately diagnosed with Usher syndrome by gene sequencing analysis.

Overall Diagnostic Yield

Overall, 106 patients underwent all diagnostic tests and specialty consultations. The diagnostic yield of the entire battery consisting of 6 diagnostic tests and 2 specialty consultations was 43% (46/106; Fig. 2). Computed tomography and MRI had diagnostic yields of 14% (15/106) and 21% (22/106), respectively. Combined, their diagnostic yield was 24% (25/106). These yields were comparable to those achieved in our larger population of children who had not necessarily undergone all 8 components of the diagnostic battery. The addition of connexin 26 mutation testing to CT and MRI significantly increased the diagnostic yield to 38% (40/106). As noted earlier, the subset of children found to have connexin 26 mutations was complementary to the subset of children with imaging abnormalities with virtually no overlap between subsets. The addition of a genetic consultation further improved the diagnostic yield to 42% (44/106). The remaining 1% of diagnoses was achieved by a combination of renal US and ophthalmologic consultation. Electrocardiography and FTA-ABS testing did not contribute to the cumulative diagnostic yield in this set of patients.

Diagnostic Yields Stratified by Hearing Screening Results

The original 270 patients were separated into 2 subsets based on whether they passed their newborn hearing screening test. The diagnostic yields of each component of the battery were determined for each subset of children and compared with the yield for the overall group (Table 2). The only significant finding was that the CT temporal bone identified fewer inner ear anomalies in those who passed newborn hearing screening.

Diagnostic Yields Stratified by Cause of Hearing Loss

The original 270 patients were also separated into three subsets based on the suspected cause of hearing loss: syndromic, nonsyndromic, and acquired/nongenetic. Again, the diagnostic yields of each component of the battery were determined for each subset of children and compared with the yield for the overall group (Table 2). Diagnostic imaging and ophthalmologic consultation were found to be significantly higher yielding in the subset of children who were suspected of having a syndromic cause for hearing loss. In these children, connexin 26 sequencing did not identify any mutations in the *GJB2* gene. In contrast, connexin 26 testing was significantly higher yielding in the subset of children whose hearing loss was thought to be nonsyndromic. For those children with acquired/nongenetic hearing loss, only MRI was useful for determining a cause for hearing loss. In this subset, the majority of MRI findings were consistent with congenital CMV infection.

DISCUSSION

This study reports the effectiveness of applying a diagnostic battery without selection bias to determine the cause of hearing loss in children presenting with severe to profound SNHL. Although undergoing all tests in the battery certainly achieves the highest diagnostic yield, it requires many healthcare visits and considerable effort on the part of the child's caretakers. Furthermore, this approach does not represent efficient utilization of healthcare resources. The data from this study should not be interpreted to conclude that every deaf child needs a complete battery of tests. Rather, analysis of the data is used to determine the fewest diagnostic tests that can still provide a diagnostic yield that is comparable to that of the entire battery.

To that end, we confirm several studies in the literature that find diagnostic radiologic imaging to be effective in determining a possible cause for hearing loss. A CT of the temporal bone and an MRI of the brain and IAC with contrast are similarly effective in finding inner ear anomalies (18% and 17%, respectively). The inner ear anomalies identified by each study are nearly identical—with CT identifying a few enlarged vestibular aqueducts missed by MRI and MRI identifying a few hypoplastic or aplastic cochlear nerves missed by CT. Outside the inner ear, however, MRI also identified pathologic disease in the brain consistent with congenital CMV infection. Thus, the overall diagnostic yield of MRI is higher than that of CT (24% versus 18%).

If only 1 study can be chosen, the higher diagnostic yield of MRI must be weighed against its extra cost, the additional time required to perform the study, and the requirement for sedation. Our data suggest that in cases where the child has passed newborn hearing screening and/or has a suspected environmental cause of hearing loss, MRI may be more useful than CT in that it can identify a pathologic disease outside the temporal bone. Alternatively, if a syndromic hearing loss is expected, CT and MRI are similarly effective. Intracerebral anomalies identified by MRI, although they may not necessarily yield a definitive cause for hearing loss, might guide expectations regarding the success of future auditory rehabilitation and speech and language development. In 1 particular case in this study, MRI identified a medulloblastoma that would not otherwise have been discovered.

This patient required life-saving surgical intervention and then radiation therapy and chemotherapy. Thus, despite significant overlap of findings within the temporal bone, both CT and MRI are warranted as bases for a minimal diagnostic battery.

The finding in 1997 that 50% of autosomal-recessive nonsyndromic hearing loss were due to mutations in the *GJB2* gene that encodes connexin 26 significantly improved the prospects of genetic testing for hearing loss (15,16). The fact that connexin 26 anomalies were responsible for 5% to 10% of all pediatric hearing loss made genetic testing for *GJB2* mutations a reasonable option rather than just a “shot in the dark” (17). Our finding that connexin 26 sequence analysis has a diagnostic yield of 15% compares similarly to rates of connexin 26 mutations reported in the literature (18). A compelling finding was that the subset of children identified with connexin 26 mutations was almost completely distinct from the subset of children identified with inner ear anomalies by diagnostic imaging. Indeed, only 1 of 33 children with a connexin 26 mutation was found to have an inner ear anomaly. As might be expected, connexin 26 analysis was only useful in cases of nonsyndromic SNHL. Interestingly, connexin 26 mutations continued to be prevalent in children who passed newborn hearing screenings. A minimal diagnostic test battery consisting of connexin 26 gene sequencing analysis in conjunction with diagnostic imaging studies achieved an overall diagnostic yield of 38%, a 14% increment in diagnostic yield over imaging alone.

Congenital hearing loss can result from 1 of more than 400 syndromes and be associated with defects in virtually any organ system (reviewed by Toriello et al. [19]). Therefore, collaboration between specialists may be essential in identifying a syndrome. The clinical geneticist has a familiarity with the constellation of physical findings beyond that of any one particular specialist; in addition, the geneticist is more knowledgeable regarding which particular gene mutation tests are available and can make recommendations regarding which specific gene tests may be most likely to yield a genetic diagnosis. We found that consulting a clinical geneticist could provide a diagnostic yield of 25% independently. However, including this consultation after both imaging and connexin 26 sequence analysis had been performed added a marginal increment of only 4% to the overall diagnostic yield.

Hearing loss is disproportionately associated with abnormalities of ocular structures. Therefore, every child in the study was also referred to an ophthalmologist. Certainly, identification of a subtle ocular abnormality such as retinitis pigmentosa could indicate Usher syndrome as the cause for hearing loss. We found that although an ophthalmologic consultation independently had a diagnostic yield of 8%, it contributed less than 1% to the overall yield of a minimal diagnostic battery. Thus, from a diagnostic perspective alone, an ophthalmologic consultation may not be warranted. One exception may be in the case of children with suspected syndromic hearing loss—in which the independent diagnostic yield is 42%. In any case, congenital hearing loss of all types has been associated with decreased visual reception skills with age (20). Therefore, at the very least, the child's visual acuity should be evaluated and optimized to minimize his or her sensory disabilities and maximize the potential for normal development. Indeed, myopia was the most common diagnosis resulting from ophthalmologic consultation in this study.

Renal US is a commonly performed diagnostic imaging procedure in the workup of pediatric hearing loss, but we found a renal anomaly consistent with BOR syndrome in only 4% of patients, and of these patients, not one was confirmed with BOR syndrome. On the other hand, several cases of previously undiagnosed renal anomalies were discovered, precipitating consultations to nephrologists for further management and follow-up. None of these findings were potentially life-threatening, however, suggesting that a more judicious use of renal US would be reasonable. Branchio-oto-renal syndrome, in the absence of

branchial arch findings or auricular deformities, occurs quite rarely, and the diagnostic yield of renal US might be improved significantly by limiting testing only to those patients with such clinical findings.

Electrocardiogram testing is similar to renal US in that it is another diagnostic procedure that is low in yield when applied to all children with congenital hearing loss. Analogously, recommendations have been made in the literature to limit ECG testing to patients with a previous history or a family history of syncope. Unlike BOR syndrome, however, Jervell and Lange-Nielsen syndrome and its prolonged QT interval is life-threatening and can present with an initial symptom of sudden death. Furthermore, in our testing, ECG serendipitously identified other cardiac conduction anomalies that may also have been dire and necessitated cardiology evaluations. Given the relatively low cost and short time required to perform the test, an ECG may be warranted within a diagnostic battery.

Several studies suggest that performing a standard battery of laboratory tests is not particularly useful in identifying the cause for congenital hearing loss (10–12). Abnormal laboratory findings for autoimmune serologies occur nearly 25% of the time but almost never correlate with clinical hearing loss (11). Testing for syphilis is often either overlooked or not performed; we therefore included this in our diagnostic test battery. We found this test to be low yielding (0.5%). We agree with previous recommendations that rather than blanketing all deaf children with multiple blood tests, specific laboratory tests be ordered on the basis of the patient's history and physical examination.

As our understanding of the molecular basis of hearing improves, a significant percentage of hearing loss that is presently idiopathic will likely be found to have a genetic basis. In the last 5 years, however, rapid escalation in the numbers of genes responsible for nonsyndromic hearing loss has made a definitive diagnosis of this disease process more likely. At present, however, aside from connexin 26, no consensus exists regarding which additional genes need to be tested. In an excellent review of the genetic approach toward diagnosing pediatric hearing loss, Rehm (21) proposes an algorithm that accounts for patterns of inheritance, timing of hearing loss, audiogram profile, and associated clinical findings in recommending specific genes to be tested. On the other hand, cost reductions in gene testing technology are likely to soon render obsolete any need for algorithmic testing. Gene-Chip microarray technology, which allows large numbers of genetic tests to be performed in parallel, will ultimately realize the goal of screening for every known mutation in every known gene associated with hearing loss. Thus, in the near future, after history, physical, and audiometric testing, a reasonable recommendation for ancillary tests in the workup of a congenitally deaf child might consist only of diagnostic radiologic imaging of the temporal bone and GeneChip microarray analysis.

CONCLUSION

Evaluation of a comprehensive diagnostic battery allowed for an unbiased analysis and comparison of the diagnostic usefulness of the various tests ordered for children with SNHL. In the course of analysis, we found that a subset of diagnostic tests could provide nearly the same diagnostic yield as the entire battery. These tests included diagnostic radiologic imaging, connexin 26 sequence analysis, and consultation with a clinical geneticist. Electrocardiography and ophthalmologist consultation, although of low diagnostic yield for SNHL, can identify important diseases that significantly affect patient health. The remainder of the tests in the battery should be reserved only for those patients in whom there is reasonable clinical suspicion.

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FIG. 1.
The percentage of each ordered test or consultation that was completed by patients.

FIG. 2.

The diagnostic yield achieved by the stepwise addition of each test or consultation is indicated. Testing began with CT temporal bone. Each additional row depicts the diagnostic yield achieved by adding the diagnostic test indicated in the row label to the cumulative testing battery consisting of tests indicated in the row labels of all rows above.

TABLE 1

Diagnostic yields of comprehensive diagnostic battery components

Test or consultation	Diagnostic yield
CT temporal bone anomalies	18% (43/245)
Total	
Cochlear dysplasia	10% (25)
Vestibule/semicircular canal dysplasia	10% (25)
IAC/cochlear aperture anomaly	7% (18)
Enlarged vestibular aqueduct	5% (13)
Isolated	
IAC/cochlear aperture anomaly	5% (12)
Enlarged vestibular aqueduct	3% (7)
Cochlear dysplasia	2% (5)
Vestibule/semicircular canal dysplasia	2% (4)
MRI brain and IAC with contrast	24% (57/242)
VIII nerve aplasia	7% (16)
VIII nerve hypoplasia	4% (10)
Connexin 26	15% (33/220)
Homozygous 35delG	8% (18)
Compound heterozygous	5% (11)
Other	1% (2)
Genetics consultation	25% (27/107)
Ophthalmology consultation	8% (9/120)
Coloboma	6% (7)
Retinitis pigmentosa	2% (2)
Renal US	4% (8/213)
ECG	1% (2/143)
FTA-ABS	0.5% (1/204)

Yields of diagnostic battery components stratified by hearing screening results and by cause of hearing loss

TABLE 2

	<u>CT</u>	<u>MRI</u>	<u>Connexin 26</u>	<u>Genetic</u>	<u>Ophthalmology</u>	<u>Renal US</u>	<u>ECG</u>	<u>FTA-ABS</u>
Total	18%	24%	15%	25%	8%	4%	1%	0.5%
Passed hearing screen (n = 65)	8% ^a	23%	12%	21%	4%	4%	3%	0%
Failed hearing screen (n = 159)	20%	23%	17%	27%	8%	5%	0%	1%
Syndromic SNHL (n = 33)	56% ^b	50% ^b	0% ^a	44%	42% ^b	4%	6%	0%
Nonsyndromic SNHL (n = 172)	16%	20%	22% ^a	28%	2% ^a	3%	2%	0%
Acquired SNHL (n = 65)		27%	0% ^a	0% ^c	0% ^a	5%	0%	2%

^a $p < 0.05$ versus diagnostic yield for total population.
^b $p < 0.001$ versus diagnostic yield for total population.
^c $p < 0.01$ versus diagnostic yield for total population.