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The Evaluation of Children With Sensorineural Hearing Loss

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Hypothesis: Molecular genetic testing should be part of the initial evaluation of children with sensorineural hearing loss (SNHL).

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BACKGROUND

Hearing impairment is the most common [1]sensory deficit in children, and SNHL is the most common form of congenital hearing impairment. It is also a significant health care problem. More than 40 000 children are born in the United States with significant hearing impairment, including about 4000 who are profoundly deaf. The incidence is estimated at about 1 in every 1000 live births.[1] Therefore, the otolaryngologist will frequently be challenged to determine the appropriate diagnostic regimen for this subset of children, a difficult and controversial procedure.

It is well accepted that a careful history, physical examination, and audiological evaluation are the first and most crucial tools used to diagnose the cause of hearing loss.[1-4] Many syndromes associated with SNHL can be diagnosed with these 3 methods. Subsequent testing remains controversial. The debate hinges on the yield and cost-effectiveness of specific tests vs the risks of failing to identify a potentially significant disorder. Possible diagnostic tests include various urine and blood tests, electrocardiograms, and imaging studies. Recent articles have suggested that high-resolution computed tomography (CT) has the best record of identifying underlying disorders contributing to SNHL.[5]

After performing a complete history, physical examination, and audiological evaluation, the physician must decide between 2 distinct diagnostic paradigms.[6] The first includes performing extensive laboratory and radiographic evaluation and soliciting opinions from other consultants in fields such as ophthalmology and genetics. The **Table** lists the laboratory tests traditionally considered and the diagnoses they will help determine. Radiographic studies, in conjunction with laboratory tests, have also been recommended as important components of evaluation. Specifically, fine-cut CT of the temporal bone can demonstrate abnormalities of bony labyrinthine formation such as an enlarged vestibular aqueduct or an incomplete partition (ie, Mondini dysplasia).[7]

The second paradigm involves a more modest evaluation dictated only by abnormal findings on the history and/or physical and audiological evaluations. Proponents of this strategy take a more conservative approach to ordering special studies. Full laboratory and radiographic evaluations are expensive (nearly $2000 per patient) and produce a relatively small likelihood of determining the precise cause of the hearing loss. No matter how many tests are ordered, the diagnosis rate may still be less than 40%, although some studies have reported a higher rate of diagnoses (68%) with a more comprehensive diagnostic evaluation.[8]

Molecular genetic testing, a relatively new diagnostic technique, promises to improve the diagnosis of SNHL in children. The ability to unlock genetic information associated with hearing impairment is truly a revolutionary development. Any means to diminish the number of affected children who remain undiagnosed would seem to offer a distinct improvement in current medical care. In addition, the demands on our diagnostic acumen will increase as universal infant hearing screening programs become a reality. Otolaryngologists will begin to diagnose hearing impairment in children in the first several months of life, and parents will want to understand the cause of the problem.

In light of the hundreds of mutations in dozens of genes found to be associated with hearing impairment, the identification of the high

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Diagnosis and Cost Data for Sensorineural Hearing Loss Tests

Test	Diagnosis	Cost, $*
Complete blood count with differential	Anemia, sickle cell disease, polycythemia, macrothrombocytopenia (Epstein syndrome)	19.25
Thyroid function tests (thyroxine, thyrotropin)	Hypothyroidism (isolated or Pendred syndrome)	76.94
Urinalysis	Proteinuria (Alport syndrome)	9.57
Sedimentation rate	Autoimmune disease	20.46
Renal function/electrolytes	Renal failure, Alport syndrome	15.77
Glucose	Diabetes	17.67
Cholesterol/triglycerides	Hyperlipidemia	17.67
Fluorescent treponemal antibody	Syphilis	47.36
TORCH titers	Congenital infection (toxoplasmosis, rubella, cytomegalovirus, herpes simplex)	211.60
Consultations (genetics and ophthalmology)	Syndromes and retinitis pigmentosa	Genetics 80-300 Ophthalmology 150-300
Electrocardiogram	Prolonged QT syndrome (Jervell and Lange-Nielsen syndromes)	138
Computed tomography of the temporal bones	Enlarged vestibular aqueduct, incomplete partition	1319.70

*Charges at Children's Hospital, Cincinnati, Ohio.

frequency of 35delG mutations in the *GJB2* gene in this population has allowed for the creation of an excellent screening test. The proper role of this and other genetic tests has yet to be determined. Therefore, a review of our current knowledge of molecular testing as a screening tool for SNHL is justified.

PRO

Genetic testing of children with hearing impairment holds the promise of diagnosing SNHL in a large cohort of patients whose condition we cannot currently diagnose. The role for the different genetic techniques that may be used to uncover the causes of SNHL is evolving as the classification of pediatric hearing loss changes and develops.[9] With improved medical therapy and the advent of molecular genetic research, the incidence of infectious causes of hearing loss has diminished as the incidence of hereditary hearing loss has relatively risen. The current literature ascribes 50% of severe to profound SNHL equally to acquired and genetic causes[10,11] (estimates concerning the proportion of hearing loss due to genetic causes range from 20% to 76%[12-14]).

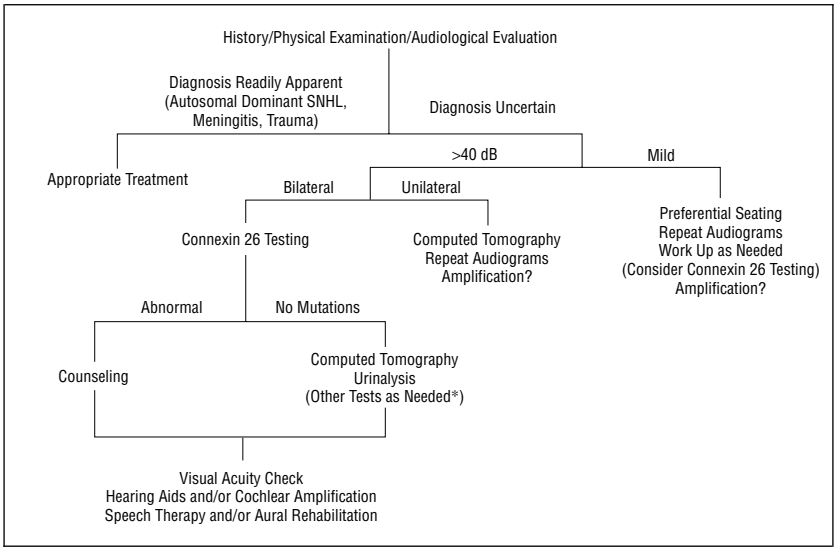
Currently, there are more than 60 loci for genes associated with nonsyndromic hearing impairment; an autosomal recessive pattern accounts for approximately 70% of cases. With current technology, testing for mutations at all these loci would not be practical. However, mutations in a single gene, *GJB2*, which encodes a connexin protein (Cx26), have been shown in approximately 40% of children with severe to profound SNHL.[15,16] Roughly two thirds of patients (primarily white) with a *GJB2* abnormality have a single variation, the so-called 35delG (also termed 30delG) mutation.[16,17] This robust yield argues strongly for the placement of genetic testing within the diagnostic algorithm for SNHL. It is more powerful than any of the more traditional tests, including blood tests, urinalysis, and imaging studies, and the risks of testing are minimal. Although blood sampling allows for a greater yield of DNA, buccal smears are an alternative and accepted means of obtaining DNA for testing.

One of the great advantages for targeted genetic testing such as examining for the 35delG mutation in *GJB2* is that it allows for an expedient means of diagnosis and therefore may limit further testing. Genetic testing should take into account the patterns of phenotypic presentation. The most common presentation for a child with the 35delG mutation is bilateral severe to profound SNHL. While other phenotypic presentations are possible, targeted genetic testing for these children seems warranted. If the mutations are identified, additional testing can be avoided. The incidence of children identified with a *GJB2* mutation having other concurrent diseases is exceedingly low. Moreover, since some laboratories are offering the genetic test free of charge, it would clearly be a cost-effective alternative. Of course, as more data are gathered and the genetic testing assumes a cost, further analysis for cost-effectiveness will be required to evaluate genetic testing as a practical diagnostic technique.

In addition to providing a cost-effective and timely means of diagnosis, genetic testing offers the opportunity to provide appropriate genetic counseling and share with the child's family meaningful information about this common form of hearing loss. In the Midwest, the carrier rate for the 35delG mutation is 2.5%, and for all Cx26 mutations, 3.0%,[16] rivaling the carrier rates of other common recessive diseases such as cystic fibrosis. While it is true that the phenotypic presentation is somewhat variable, there are certainly strong tendencies for severe to profound hearing loss. However, it is too early in the development of diagnostic genetic techniques to be able to predict the exact course of the hearing loss or the outcome of a surgery such as cochlear implantation for patients identified with a genetic mutation. More research is needed to gather sufficient data to address these questions. Nevertheless, for the family searching for the reason behind their child's hearing loss, genetic testing currently provides valuable information and holds the promise of helping physicians and parents determine appropriate treatment.

CON

There are several arguments against including genetic testing as part of



Diagnostic algorithm for sensorineural hearing loss (SNHL) in children. The asterisk indicates the following other tests: thyroid function; fluorescent treponemal antibody; erythrocyte sedimentation rate and/or Western blot analysis; platelet analysis, Pendred syndrome and bronchio-oto-renal syndrome genetic studies; and electrocardiogram.

the initial evaluation offered to children with severe to profound hearing. First is the concern for false-positive and false-negative findings. An ethical argument can be made that false-positive findings might adversely affect families' treatment decisions. The false-positive and false-negative rates for the 35delG mutation detection alone have been calculated as 2.6% and 3.1%, respectively,[16] and mutation screening of the entire coding portion of the gene by direct sequencing should detect nearly *all* mutations, 35delG and others. For example, in the Ashkenazi Jewish population, 167delT is the most prevalent mutation.

Another scenario that makes the possibility of a false-positive worrisome is one in which further diagnostic studies were not done because genetic testing had already made the "diagnosis." Likewise, false-negative results could lead to unnecessary further diagnostic evaluations and persistent uncertainty of the proper diagnosis. To be effective, complete mutation screening should lessen the possibility of missing a disease-causing mutation.

Both the concerns about a second "hidden" diagnosis and ethical issues are present even when the results of genetic testing are accurate. Have enough data been collected to state with certainty that children with a *GJB2* gene mutation do not have another abnormality that might be identified if further diagnostic tests were pursued? Not absolutely. Further large-scale studies will be required to answer that question. One troubling ethical dilemma would be the possibility of parents opting to terminate a pregnancy after genetic testing for hearing impairment. Although this has been a controversial area since before the field of molecular genetics began to influence the practice of clinical medicine, practitioners must be prepared for these situations. Importantly, the needs and desires of the parents for this type of genetic information are not known. What would they do with this information? How should this information be presented to them? Since most busy otolaryngologists cannot spend sufficient time with families to address these issues in detail, involvement of genetic counselors knowledgeable in hereditary hearing impairment is warranted.

Finally, there are issues of which laboratories could provide these services and what the costs would be. Appropriate certification must be required of diagnostic laboratories to ensure quality data reporting. Without this certification, results cannot be shared with the practitioner or patient for use in clinical practice. It is likely that the offering of connexin genetic tests free of charge will not continue. As the tests become more available, the cost will be significant. Currently, our fee for Cx26 mutation screening is $265. The value of genetic testing must be measured from the diagnostic and economic standpoints.

BOTTOM LINE

What is the most appropriate diagnostic evaluation technique for children with SNHL? This is an important question that begs a proper answer. Children with SNHL represent a substantial population; various studies indicate that the incidence of undiagnosed bilateral SNHL ranges from 25% to 52%.[4,5,18,19] Apparently, a precise diagnosis was made in a significantly smaller cohort because the 25% to 50% figures included an unknown number of "probable" diagnoses (ie, perinatal factors). In populations in which the overall incidence of SNHL approximates 1:1000 live births,[10,11] this number of undiagnosed SNHL cases is substantial.

Our diagnosis of these patients now relies heavily on the incorporation of molecular testing. The flow diagram in the **Figure** summarizes our current paradigm for evaluating children with SNHL. All children with bilateral hearing impairment greater than 40 dB undergo Cx26 mutation screening. The application of this technology to mild hearing loss, however, is debatable: the likelihood of recessive deafness producing this phenotype is very low. It should be noted, however, that Wilcox et al[20] and Cucci et al[21] have recently demonstrated that non-35delG Cx26 mutations (ie, M34T) can cause mild forms of hearing impairment with a downsloping audiogram. A conservative approach would be to include molecular testing in the diagnostic regimen for children with mild hearing loss along with further testing to quantify the actual incidence of Cx26 mutations. Most cases of unilateral hearing impairment are not currently evaluated by molecular testing.

For those patients not harboring Cx26 mutations, we perform a modified evaluation including urinalysis, electrocardiogram (for bilateral severe to profound cases), and CT. More extensive evaluations are

performed on a case-by-case basis. This paradigm is supported by several studies.[5,6] Routine screening of Pendrin (*DFMB4*), the gene responsible for Pendred syndrome and some cases of enlarged vestibular aqueduct , is now also available. Its current role is for those patients with an obvious goiter, progressive hearing loss, and temporal bone anomalies (eg, enlarged vestibular aqueduct). Further studies are needed to evaluate its role in mass screening of all patients with SNHL.

The current economic benefit of genetic testing is obvious. If more than one third of all children with SNHL test positive for Cx26 mutations, further evaluations may not be necessary because no abnormal CT or laboratory findings have been associated with *DFNB1*. Other studies (eg, CT) may be needed as part of the preoperative evaluation for cochlear implantation, but these can be deferred from the time of initial diagnosis.

Besides being a more precise and potentially cost-effective method of diagnosis, genetic evaluation and understanding of the molecular mechanisms of hearing impairment offer the benefits of accurate prognosis and the potential for novel therapeutic approaches. Intense research efforts in the molecular genetics of hereditary hearing impairment will allow us to engineer novel regimens that can be used to better treat hearing-impaired children. As more deafness-causing genes are identified, the success of molecular diagnostic testing to identify the genetic causes of hearing loss should also increase. Despite the recent advances in this field, we are still in the infancy of our ability to diagnose genetic variations as causes of SNHL in children and adults. As DNA microchip technology expands, one can envision a single blood test that quickly screens not just one gene but dozens, and for hundreds of different mutations.

Appropriate patient counseling on the results of genetic testing is essential. If the clinician does not feel comfortable providing this, consultation with a professional experienced in genetic counseling should be sought. Further studies are required to explore the ethical and social issues of the impact of genetic testing in the diagnosis of our hearing-impaired population.

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