Prelingual Siblings of Children With GJB2 Hearing Loss

Issues to Consider

NEWBORN HEARING screening is currently being implemented in the United States and other countries, allowing early identification of and intervention for hearing loss in neonates. Also, genetic testing is clinically available for the GJB2 gene, which codes for the connexin 26 protein, and the results have begun to explain the cause of a significant number of cases of hearing loss. However, the current limited knowledge about the natural history of GJB2-related hearing loss in the postnatal period, particularly as it relates to age at diagnosis of the hearing loss, raises important clinical and ethical questions that need to be addressed regarding the evaluation of prelingual siblings of children identified with GJB2-related hearing loss.

Approximately 50% of prelingual hearing loss has a genetic basis and approximately 70% of genetic hearing loss is nonsyndromic. Remarkably, the recently identified gene GJB2 accounts for a large proportion of nonsyndromic genetic hearing loss, with hearing loss variants in GJB2 accounting for up to 50% of autosomal recessive nonsyndromic hearing loss in many populations, as well as for some cases of syndromic hearing loss. This gene produces connexin 26, a gap junction protein that is abundantly expressed in the cochlea and is essential for hearing. More than 100 hearing loss variants in GJB2 have been identified so far (http://www.crg.es/deafness/), with a few variants, such as 35delG in white populations, 167delT in the Ashkenazi Jewish population, and 235delC in Asian populations, accounting for the majority of GJB2 alleles containing hearing loss–associated variants. Clinical genetic testing is available for GJB2 (see www.genetests.org or www.geneclinics.org for listing of laboratory services), and genetic testing is recommended in the context of genetic counseling for individuals with apparent nonsyndromic hearing loss.

Hearing loss–associated variants in each copy of GJB2 produces an autosomal recessive nonsyndromic sensorineural hearing loss that can range from mild to profound. To date, the majority of individuals exhibit a bilateral hearing loss, although there are a few case reports of unilateral loss. There is evidence of genotype-phenotype correlation, with protein nontruncating variants producing a milder phenotype than protein truncating variants. However, some variability in the audiology phenotype exists, mainly involving protein nontruncating variants making it difficult to offer prognostic information in some cases.

Our current state of knowledge of GJB2-related hearing loss comes predominantly from cross-sectional or retrospective studies of individuals with documented prelingual bilateral sensorineural hearing loss that were conducted before universal hearing screening of neonates was available. Because of the timing and nature of these research designs, very little is known about the audiometric characteristics of GJB2-related hearing loss in the postnatal or infancy period. Studies performed in conjunction with recently implemented early hearing, detection, and intervention programs clearly demonstrate that GJB2-related hearing loss can be congenital. However, it is also possible that variants in this gene may produce hearing loss that may not be detectable in the immediate postnatal period. Evidence for later detection of GJB2-related hearing loss comes from a published report involving 2 neonates who had documented normal hearing before 6 months of age—one by automated auditory brainstem response screening of newborns and one by sound-field audiometry at the age of 5 months—who were later identified as having severe or profound hearing loss, one at the age of 15 months and the other at the age of 9 months. GJB2 testing was subsequently performed on both children, and both were found to be homozygous for the 35delG mutation. These cases are noteworthy, but it is yet unknown whether they are truly exceptional, whether they represent errors in the original audiometric testing, or whether they in fact represent a nontrivial subset of individuals with biallelic GJB2 variants who will pass newborn hearing screening and be diagnosed with hearing loss some time after birth. Only through empirical studies of infants whose hearing status at birth is documented through newborn hearing screening will clinicians be able to determine which infants or children who are later identified with hearing loss have a postnatal or progressive condition. In those cases, it will be possible to determine if GJB2 variants lead to a postnatal or a progressive hearing loss. This information will ultimately play a critical role in determining the appropriate evaluation of prelingual siblings of a child with documented GJB2-related hearing loss.

In light of the paucity of empirical data on age of identification of GJB2-related hearing loss, siblings of a child with documented GJB2-related hearing loss who pass newborn hearing screening may be viewed as being at risk for hearing loss, necessitating appropriate atrisk evaluation. For these children, there currently are 2 assessment options: audiologic assessment to de-
termine hearing status and GJB2 testing to determine genetic status. Both of these options, which are not necessarily mutually exclusive, raise clinical or ethical issues.

One strategy is to perform audiologic assessments on all prelingual siblings of a child with GJB2-related hearing loss. If a hearing loss is diagnosed, GJB2 testing could then be performed to confirm the role of this gene in the sibling’s hearing loss. Although this strategy appears to be innocuous, there are several questions about an assessment strategy that is based primarily on the results of audiologic assessment. How often should a young sibling who may be at heightened risk for GJB2-related hearing loss undergo audiologic assessment? For how many years should this sibling receive audiologic assessments (ie, at what age is it safe to presume that the child is not at risk for GJB2-related hearing loss)? This issue is even more vexing when very young siblings are involved, as audiologic diagnostic assessments for children between about 3 months and at least 6 months of age must involve diagnostically automated auditory brainstem response testing, generally with sedation, which puts the infant at a potentially unnecessary risk. There are also cost considerations that accompany repeated audiologic assessment, as well as the potential of creating a situation in which parents experience prolonged uncertainty about their child’s hearing status.

An alternative strategy is first to perform GJB2 testing in the context of genetic counseling on prelingual siblings who pass newborn hearing screening, and then to perform audiologic assessment on those who are identified as being at genetic risk for hearing loss. Although this strategy does not answer the questions about how to implement audiologic assessment, it does have the attractive feature of reducing the number of siblings on whom audiologic assessment is performed.

The genetic testing strategy could be justified as presymptomatic genetic testing for a later-onset condition for which audiologic surveillance provides the opportunity for earliest possible intervention if the result is positive or for which audiologic surveillance can be stopped if the result is negative. Genetic testing that leads to early identification of hearing loss and early intervention would presumably have a tremendously positive impact on the development of language skills of prelingual siblings who are identified as being truly at risk for GJB2-related hearing loss. However, testing also would identify the carrier status of many siblings who truly are not at risk for GJB2-related hearing loss. In fact, the chance that a sibling will be found to be a carrier is between one half (if hearing status truly has not been determined) and two thirds (if the sibling truly has normal hearing). Therefore, carrier status is the most likely outcome of genetic testing, which raises ethical issues pertaining to genetic testing in children.

Guidelines established by the American Academy of Pediatrics, the American Society of Human Genetics, and the American College of Medical Genetics pertaining to appropriate uses of genetic testing have been published, with special consideration for the testing of minors. According to these published guidelines, genetic testing is considered appropriate in children for diagnostic purposes, to refine prognosis if genotype-phenotype correlations are strong, for predicting later-onset conditions in presymptomatic at-risk children when surveillance is associated with effective treatment, and to allow a reduction in surveillance for later-onset conditions.

Testing healthy minors to determine carrier status for autosomal recessive conditions, eg, cystic fibrosis or GJB2-related hearing loss, generally is not recommended for reasons that include the fear that knowledge of a child’s carrier status will alter family dynamics and child rearing, that there will be confusion about the difference between being an asymptomatic carrier and having a condition, that the information is not clinically relevant, and that the child ought to be able to make an autonomous decision as an adult to seek this information, which could have reproductive ramifications. Moreover, hearing loss per se is not considered a disease entity by members of the Deaf community. Performing genetic testing on minors that produces information that most likely could relate only to their future reproductive decision making may be construed as a pejorative to the Deaf community, which views hearing loss or deafness to be a personal trait but not a medical condition. Because GJB2 testing will incidentally reveal carrier status, there should be careful consideration about whether or how to include genetic testing as a primary evaluation option for prelingual siblings of a child with GJB2-related hearing loss.

A possible solution to resolving the conflicting outcomes of genetic testing of prelingual siblings is to perform presymptomatic genetic testing for familial mutations and to report either that the sibling has the same GJB2 results as the child with GJB2-related hearing loss and hence is at heightened risk for hearing loss or that the sibling does not have the same genotype as the child with GJB2-related hearing loss and hence is not at heightened risk for hearing loss. This procedure would enable parents to ensure appropriate audiologic follow-up for hearing children who have an at-risk molecular test result, while allowing those children who are not at genotypic risk for hearing loss to engage in independent decision making about determining carrier status when they are older. There are 2 additional levels of complexity that need to be considered, however. First, it has been noted that significantly more individuals with apparently nonsyndromic hearing loss have only 1 identified pathogenic GJB2 allele than is predicted by the carrier rate, even after complete GJB2 sequencing and testing for the 2 reported deletions in GJB6, making it impossible to distinguish carrier status from the possibility that the single identified pathogenic allele is contributing to the hearing loss in those individuals. Although present in a minority of cases, a GJB2 heterozygous result occurs frequently enough that it may need to be considered an at-risk molecular result for a sibling. The second level of complexity involves results that are sometimes inconclusive because of limited information about the role of particular GJB2 variants in hearing loss, even if such variants are identified in a child with hearing loss. Such gaps in our knowledge may argue against GJB2 testing in prelingual siblings.

There is at least 1 precedent for tailoring molecular tests to accommodate conflicting agendas. The concept of exclusion testing was developed in the context of Hunting-
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Financial Disclosure: None.

Funding/Support: This commentary was supported in part by grant R01DC005663 from the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, Md.

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