Genetic Testing in Children With Epilepsy

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ABSTRACT
Genetic testing is now available clinically for several epilepsies. Neurologists increasingly face decisions about diagnostic testing in affected patients and should carefully deliberate the ethical considerations associated with genetic testing. The merits of ordering a genetic test are largely based on the utility for guiding clinical care, providing a prognosis, estimating recurrence risk, and identifying comorbidities. At the same time, a decision to pursue any genetic testing also requires evaluation of associated ethical concerns. This case illustrates ethical challenges that arise when considering genetic testing for a pediatric patient with epilepsy.

Case

Note: This is a hypothetical case.

A 1-year-old girl was brought to the clinic after her fourth hospital admission for prolonged status epilepticus. Her first three episodes were in the setting of fever, but the most recent episode was not associated with fever or other illness. Each episode resulted in several days of inpatient management. Results of metabolic, neuroimaging, and CSF studies were normal. The patient was otherwise well and developmentally typical. She was accompanied by her parents and 6-year-old sister.

The family history was significant. Her father stated that his mother remembered him having “fits” during fevers as a baby, but he had had no seizures since infancy and was otherwise well. Two of the father’s cousins had febrile seizures, and a paternal nephew had seizures and significant developmental delay. The patient’s mother and sister were in good health; neither had ever had a seizure.

During the last hospitalization, the family received information about a possible diagnosis of genetic epilepsy with febrile seizures plus (GEFS+). The history led to a reasonable suspicion that the patient could have a paternally inherited SCN1A mutation as the basis for her seizures. The parents understand that a test for pathologic mutations in the SCN1A gene could be performed to confirm their daughter’s diagnosis. The parents requested genetic testing for their 1-year-old daughter.

This case presents the following questions:
1. Is it ethically permissible to perform genetic testing for an SCN1A mutation in a child at her parents’ request?
2. What considerations must the neurologist address in counseling the family before testing?
DISCUSSION

While a clear genetic basis is not identified for most patients with epilepsy, over two dozen clinically available gene tests for various epilepsy syndromes now exist. Neurologists can anticipate increasingly frequent inquiries about genetic testing from patients who have epilepsy or their families. The US Centers for Disease Control and Prevention (CDC) has proposed the ACCE model (analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications) to guide the process of making decisions about ordering genetic tests. A practical tool for the model's application is available at the CDC website (www.cdc.gov/genomics/gtesting/ACCE/index.htm). Clinicians are encouraged to proceed stepwise through each of the four ACCE domains to decide whether ordering a particular test is appropriate for a patient. Analytic validity refers to how well the test can assess the genotype in question; for example, whether the test has technical limitations that might lead to false-positive or false-negative results. Clinical validity is whether the test is useful in diagnosing or predicting the clinical condition of interest. For example, a test with high analytic validity may still have limited clinical validity if environmental or other modifying factors significantly influence whether the gene mutation will produce clinical disease. Clinical utility is whether the information gained from the test might be clinically useful for the patient, such as indicating whether an intervention should be offered. Finally, the associated ethical, legal, and social implications of potential results must be considered before performing a test. The ethical implications of testing are addressed here.

In the case above, the family requested genetic testing for a clinical condition, GEFS+, that has been associated with mutations in the SCN1A gene. The ethical dilemma illustrated by this case is whether it is appropriate for the clinician to order the genetic test the parents requested. The physician must consider when genetic testing in a child is appropriate. Also, before ordering this genetic test, the physician should use the first three steps of the ACCE model to determine if it is medically indicated. Finally, before testing, pretest counseling should be provided to the family, particularly to ensure ethical factors are addressed.

Diagnostic Genetic Testing in Pediatric Patients

In providing care to children, clinicians have a duty to serve the best interests of the child (ie, beneficence) while minimizing harm (ie, nonmaleficence). Young children are unable to provide informed consent for diagnostic studies, including genetic testing, because their cognitive development is not yet sufficient to have decision-making capacity. Therefore, a child cannot provide consent, so a child's parents make decisions and provide informed consent on his or her behalf. The American Society of Human Genetics recommends that genetic testing should be performed if it will promote the well-being of the child. For example, a genetic diagnosis confirming suspected cystic fibrosis might be very beneficial in guiding appropriate surveillance and intervention for a child. In contrast, in some situations genetic testing has no clear benefit and may have potential harms for a child. For example, identification of BRCA2 mutations in a child may reveal an increased risk for cancer in adulthood, prompting anxiety in the family and child. BRCA2 testing does not facilitate the care of the child because preventive treatment does not need to begin until
adulthood. The American Academy of Pediatrics cautions, “In the absence of clearly beneficial treatments or effective preventive strategies, genetic testing of children and adolescents may not be justified.” However, if “the balance of benefits and harms is uncertain the provider should respect the decision of competent adolescents and families.”

In the case, testing the patient for an SCN1A mutation has some clinical utility. A negative result excludes a common cause of Dravet syndrome, a severe epilepsy syndrome. If a pathologic mutation is present, there will be some prognostic information, although with very limited precision. Identification of a pathologic mutation would help the parents to understand the cause of their daughter’s seizures. Furthermore, because the patient is a child, consideration must be given to the possibility that she may or may not want to know her SCN1A genetic status when she becomes an adult. Despite legal protections against discrimination, some patients with epilepsy still have anxiety that a genetic diagnosis would be used as a basis for discrimination. As such, at least some people with epilepsy might prefer not to have genetic testing. It is not possible to know with certainty what the child in the case would want.

Finally, if a mutation is identified in the child, the question arises of whether to test her father to confirm the nature of inheritance. This would open additional points of discussion for the family to consider that are beyond the scope of this discussion. Genetic testing in children is fraught with complicating factors of identifying the child’s best interests when the child is unable to participate in the decision. Parents must act as surrogate decision makers for the child. For these reasons, the balance of potential benefits and harms will largely depend on the family’s perceptions and priorities as clarified during pretest counseling.

**Pretest Genetic Counseling**

Respect for patient autonomy is a fundamental principle of medical ethics. The process of informed consent ensures that the patient is provided with all the necessary information to make well-informed decisions about his or her own health care. In genetic testing, this information can be particularly challenging to communicate and must be tailored to issues relevant to the individual patient. Genetic counseling “is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.” As part of this process, pretest genetic counseling aims to educate patients so that they have adequate information regarding whether to accept or decline the testing. This may be provided by a geneticist, genetic counselor, or other physicians who are knowledgeable about counseling, ordering, and interpreting the relevant genetic tests.

In the case, as part of pretest counseling, the physician can apply the ACCE framework to explain why the test may or may not be indicated. GEFS+ is a clinical syndrome that is classically characterized by family members with febrile seizures or epilepsy who can be affected with varying severity. Inheritance is autosomal dominant, but penetrance is incomplete (about 70%). De novo mutations can also occur. A wide spectrum of phenotypes exists; some patients may have isolated simple febrile seizures while others may have refractory epilepsy. The analytic validity for SCN1A testing is high; that is, most labs testing for mutations do so with high accuracy and reliability. The clinical validity of
testing is lower because not all people with GEFS+ will have a SCN1A mutation, and conversely SCN1A mutations are implicated in other disorders, such as Dravet syndrome (also called severe myoclonic epilepsy of infancy). Likewise, the clinical utility is imperfect. The physician should explain that a clinical diagnosis of GEFS+ is not identical to a genetic diagnosis of SCN1A mutation. The family may need further education about the implication of a negative SCN1A mutation test for the clinical diagnosis and particularly whether additional testing would be indicated or if treatment would change based on the result. Conversely, the physician should also explain that finding an SCN1A gene mutation would be consistent with having GEFS+, but that SCN1A gene mutations are also seen in patients with Dravet syndrome. Patients with Dravet syndrome may present initially with prolonged febrile seizures but then develop other types of seizures and have significant developmental difficulties. Genotype-phenotype correlation is limited, and therefore identification of a mutation in SCN1A will not necessarily predict how severely the patient will be affected.

Regarding the clinical use of genetic testing in epilepsy, the International League Against Epilepsy (ILAE) Genetics Commission found that the clinical utility of SCN1A testing is highly dependent on the clinical presentation of the patient. In patients with GEFS+, approximately 5% to 10% of families will have an SCN1A mutation, and, even in those cases, the wide phenotypic heterogeneity makes the gene test not useful in predicting outcome or guiding treatment. Conversely, 70% to 80% of patients with the clinical features of Dravet syndrome will have an identifiable SCN1A mutation. This information is very useful in establishing etiology and guiding treatment.

The clinical presentation of the patient in the case is more consistent with GEFS+; however, the patient’s young age means that Dravet syndrome cannot yet be ruled out. Thus, the clinical utility of genetic testing is less clear-cut, and this uncertainty warrants discussion during the pretest counseling.

Pretest counseling should include the potential benefits and drawbacks of testing. In the case above, a test result of no mutation would exclude only SCN1A mutations, not other less-common or yet unknown genetic etiologies. A positive test result could have a number of benefits. Identifying a mutation could be useful in establishing an etiology, which the family may be especially eager to know. In particular, a genetic explanation can be particularly useful for patients and families in refuting alternate theories about why they have epilepsy (eg, toxin exposures). A genetic diagnosis may also be useful in excluding alternate diagnoses (such as a metabolic disease or neurodegenerative condition) and preventing the need for further diagnostic testing, such as other genetic tests or repeat workups if she is hospitalized for status epilepticus in the future. For some—but not all—specific SCN1A mutations, a positive result might be helpful in providing a prognosis if genotype-phenotype correlation is possible. Finally, finding a mutation may empower the family to better understand the cause of the patient’s condition and identify community and family support resources for those with the same disease.

At the same time, potential drawbacks to testing must also be considered. Depending on their insurance coverage, the family may have significant out-of-pocket expenses. The test result may or may not change long-term management for the patient. While certain medications are avoided for patients with known SCN1A mutations, currently no interventions are available to modify the
disease course. Finally, identifying a genetic mutation may lead to feelings of blame or guilt in the parents, although in this case, the family may already suspect that the condition is inherited based on their history.

The clinicians should seek to learn what particular factors weigh into the parents' request for testing. Important considerations include whether a negative test result would bring relief by excluding the specific genetic diagnosis or worry because of continued uncertainty regarding the etiology. Similarly, consideration should be given to whether a positive result would be beneficial by providing certainty in diagnosis or whether it would cause worry by confirming the presence of a genetic condition. Finally, the physician should help the patient’s family understand that testing may reveal an equivocal result, such as a variation of unknown significance. Pretest counseling requires an exchange of information between clinician and family to ensure that the patient’s family comes to an informed decision about whether testing is the best choice for her.

CONCLUSIONS

In most cases, the order for genetic testing must be written by the physician caring for the patient. Therefore, the physician in the case above can decide whether to order the SCN1A genetic testing requested by the family. The physician may refuse to order the test if he or she believes it is not in the best interests of the child and the family, but in refusing the physician has an obligation to explain the reasons for refusing their request. Regardless of whether the physician refuses or agrees to the family's request for SCN1A genetic testing, careful discussion with the family is essential before proceeding. The family must be aware of the utility of the testing and the possible outcomes of the test for their decision to be adequately informed. At the same time, dialogue with the family may reveal benefits beyond simple diagnostic labeling and treatment choices. Identifying the family’s perceived value of the information that could be obtained is important. Communication can be facilitated by the involvement of a genetic counselor or epileptologist familiar with the genetics of epilepsy. The individual factors brought to light in dialogue would guide an accurate comparison of potential benefits and harms, allowing for the family to make an informed decision as to whether or not testing is in the best interest of their child.

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REFERENCES


