Early genetic testing for neonatal epilepsy

When, why, and how?

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The incidence of seizures is greatest during the neonatal period, with an estimated rate of 2–4 per 1,000 live births. Although the majority of seizures in the newborn are due to acquired brain disorders, a substantial proportion are due to metabolic and genetic disorders causing neonatal- and infantile-onset epilepsies. For decades, genetics has played a critical role in identification and treatment of seizures in the newborn and infantile period.[1,2] With newborn screening, disorders such as phenylketonuria and biotinidase deficiency can be identified before patients develop seizures. Early identification and treatment prevents the development of often severe epilepsy syndromes and associated comorbidities. Detection and early treatment will continue to improve as newborn screening methods advance, whether based in genetics or clinical observation: the first channelopathy that causes epilepsy was identified in families with benign familial neonatal convulsions in the 1990s, before completion of the human genome project and modern genomics.[3]

Advances in genomic technologies such as microarray-based comparative genomic hybridization and DNA sequencing have revealed hundreds of heterogeneous pathogenic variants in patients with neurodevelopmental disorders, including epilepsy. Large-scale studies investigating the molecular basis of human epilepsy syndromes using modern genomic methods have identified many previously unknown causes of epilepsy.[4] The highest yield in many of these studies has been in patients with early-onset epilepsy syndromes. The genetically determined early-onset epilepsy syndromes can be divided into groups based on underlying mechanisms and pathways. A modification of one such scheme divides these into synaptopathies, channelopathies, mTORpathies, and other genetic disorders causing malformations of brain development and chromosomal anomalies.[5] Many of these patients have what are described as epileptic or developmental encephalopathies. These disorders are associated with persistent EEG abnormalities and are frequently resistant to treatment with conventional pharmacotherapy for seizures.

Clinical application of modern genomic technologies has many challenges. Multiple phenotypes may be associated with pathogenic variants in a single gene, whereas single phenotypes can be associated with changes in multiple genes. Our understanding and interpretation of the clinical import of any given sequence variant falls along a gradient, ranging from those in which the variant is almost certainly pathogenic for a disorder to those that are almost certainly benign. There are many tools, standards, and guidelines that aid in this process.[6] To aid in interpretation, genomic data from parents or other relatives are often required. Coverage and reimbursement for clinical genetic testing is complex and highly variable and influenced by several factors such as clinical setting, insurance coverage, and privacy concerns. There is substantial variation among health care systems throughout the world and in the United States there is also regional variation.

This issue of *Neurology*® reports an important study that identified a cohort of newborns with neonatal-onset epilepsy diagnosed through the use of modern neurodiagnostic guidelines.[7,8] From a group of over 600 newborns, the authors were able to separate acquired causes of seizures and identify 79 (13%) with neonatal-onset epilepsy. This cohort included patients with brain malformation, familial epilepsy syndromes, and epileptic encephalopathies. Despite using a heterogeneous approach to genetic testing, this study identified that nearly three-quarters of this cohort had pathogenic or likely pathogenic genetic causes for the epilepsies. The genetic causes identified included several patients with de novo pathogenic variants, which has important implications for family planning and genetic counseling. Also, many of the identified disorders have prognostic implications both for treatment and risk of comorbid neuropsychological and multisystem disorders. The authors did not identify any vitamin-responsive neonatal epilepsies, but identified patients with specific disorders that would allow enrollment in clinical research protocols.

This study begins to address the questions of when, why, and how genetic testing should be

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performed in early-onset epilepsies. The high yield shown in this study clearly demonstrates that genetic testing should be performed as early as possible in certain epilepsy phenotypes. The prospect for early diagnosis of potentially treatable disorders, the important prognostic and genetic information for family planning and patient care, and the potential to avert further unnecessary diagnostic testing are all reasons why. The "how" will continue to be challenging and dynamic. Continued work with our colleagues in genetics and development of guidelines for this population will be critical.

DISCLOSURE

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