Current Literature

In Clinical Science

Two Studies, One Message: High Yield of Genetic Testing in Infants and Young Children With Severe Epilepsies

Neonatal Seizure Registry. Profile of Neonatal Epilepsies: Characteristics of a Prospective US Cohort.

Shellhaas RA, Wusthoff CJ, Tsuchida TN, Glass HC, Chu CJ, Massey SL, Soul JS, Wiwattanadittakun N, Abend NS, Cilio MR; Neonatal Seizure Registry. *Neurology* 2017;89:893–899.

OBJECTIVE: Although individual neonatal epilepsy syndromes are rare, as a group they represent a sizable subgroup of neonatal seizure etiologies. We evaluated the profile of neonatal epilepsies in a prospective cohort of newborns with seizures. METHODS: Consecutive newborns with seizures were enrolled in the Neonatal Seizure Registry (an association of 7 U.S. children's hospitals). Treatment and diagnostic testing were at the clinicians' discretion. Neonates with seizures related to epileptic encephalopathies (without structural brain abnormalities), brain malformations, or benign familial epilepsies were included in this analysis. RESULTS: Among 611 consecutive newborns with seizures, 79 (13%) had epilepsy (35 epileptic encephalopathy, 32 congenital brain malformations, 11 benign familial neonatal epilepsy [BFNE], 1 benign neonatal seizures). Twenty-nine (83%) with epileptic encephalopathy had genetic testing and 24/29 (83%) had a genetic etiology. Pathogenic or likely pathogenic KCNQ2 variants ($n = 10$) were the most commonly identified etiology of epileptic encephalopathy. Among 23 neonates with brain malformations who had genetic testing, 7 had putative genetic etiologies. Six infants with BFNE had genetic testing; 3 had pathogenic KCNQ2 variants, and 1 had a pathogenic KCNQ3 variant. Comorbid illnesses that predisposed to acute symptomatic seizures occurred in 3/35 neonates with epileptic encephalopathy versus 10/32 with brain malformations ($p = 0.03$). Death or discharge to hospice were more common among newborns with brain malformations (11/32) than those with epileptic encephalopathy (3/35, $p = 0.01$). CONCLUSIONS: Neonatal epilepsy is often due to identifiable genetic causes. Genetic testing is now warranted for newborns with epilepsy in order to guide management and inform discussions of prognosis.

Early-Life Epilepsies and the Emerging Role of Genetic Testing.

Berg AT, Coryell J, Saneto RP, Grinspan ZM, Alexander JJ, Kekis M, Sullivan JE, Wirrell EC, Shellhaas RA, Mytinger JR, Gaillard WD, Kossoff EH, Valencia I, Knupp KG, Wusthoff C, Keator C, Dobyns WB, Ryan N, Loddenkemper T, Chu CJ, Novotny EJ Jr, Koh S. *JAMA Pediatr* 2017;171:863–871.

IMPORTANCE: Early-life epilepsies are often a consequence of numerous neurodevelopmental disorders, most of which are proving to have genetic origins. The role of genetic testing in the initial evaluation of these epilepsies is not established. OBJECTIVE: To provide a contemporary account of the patterns of use and diagnostic yield of genetic testing for early-life epilepsies. DESIGN, SETTING, AND PARTICIPANTS: In this prospective cohort, children with newly diagnosed epilepsy with an onset at less than 3 years of age were recruited from March 1, 2012, to April 30, 2015, from 17 U.S. pediatric hospitals and followed up for 1 year. Of 795 families approached, 775 agreed to participate. Clinical diagnosis of the etiology of epilepsy were characterized based on information available before genetic testing was performed. Added contributions of cytogenetic and gene sequencing investigations were determined. EXPOSURES: Genetic diagnostic testing. MAIN OUTCOMES AND MEASURES: Laboratory-confirmed pathogenic variant. RESULTS: Of the 775 patients in the study (367 girls and 408 boys; median age of onset, 7.5 months [interquartile range, 4.2–16.5 months]), 95 (12.3%) had acquired brain injuries. Of the remaining 680 patients, 327 (48.1%) underwent various forms of genetic testing, which identified pathogenic variants in 132 of 327 children (40.4%; 95% CI, 37–44%): 26 of 59 (44.1%) with karyotyping, 32 of 188 (17.0%) with microarrays, 31 of 114 (27.2%) with epilepsy panels, 11 of 33 (33.3%) with whole exomes, 4 of 20 (20.0%) with mitochondrial panels, and 28 of 94 (29.8%) with other tests. Forty-four variants were

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identified before initial epilepsy presentation. Apart from dysmorphic syndromes, pathogenic yields were highest for children with tuberous sclerosis complex (9 of 11 [81.8%]), metabolic diseases (11 of 14 [78.6%]), and brain malformations (20 of 61 [32.8%]). A total of 180 of 446 children (40.4%), whose etiology would have remained unknown without genetic testing, underwent some testing. Pathogenic variants were identified in 48 of 180 children (26.7%; 95% CI, 18–34%). Diagnostic yields were greater than 15% regardless of delay, spasms, and young age. Yields were greater for epilepsy panels (28 of 96 [29.2%]; $P < .001$) and whole exomes (5 of 18 [27.8%]; $P = .02$) than for chromosomal microarray (8 of 101 [7.9%]). CONCLUSIONS AND RELEVANCE: Genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies regardless of key clinical features. Thorough genetic investigation emphasizing sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations and poor outcomes.

Commentary

One of the primary goals in caring for a child with epilepsy is to find the cause of the seizures. Finding an etiology that leads to targeted and effective treatment is the ultimate goal. For many patients, the origin of their epilepsy remains a mystery and a constant reminder to physicians of how little we understand. In particular, patients with intractable epilepsy often experience a journey filled with repeated MRIs, laboratory tests, EEGs, and invasive procedures that too often fail to provide answers. Our clinical algorithms for diagnosis—especially as they pertain to the epileptic encephalopathies of infancy—are often based on approaches handed down over generations to cast a wide net when patient history and imaging fail to provide direction. The problem is, as our knowledge of disease has evolved, the net has become increasingly cumbersome to navigate, and the efficiency of finding a diagnosis among the myriad of tests degrades while the cost of care increases. Genetic testing has been late to arrive to the long list of possible investigations. The evolution of modern genetic testing—beginning with chromosomal microarray analysis and now including next-generation sequencing—has had a major impact on the way we approach the diagnosis of epilepsy, yet we must continue to define ideal utilization of these technologies. While often expensive at the outset, genetic testing has the potential to provide a diagnosis that can avoid unnecessary testing, shorten the time to diagnosis, reduce cost of care, and increase our ability to develop and pursue precision treatments.

Determining the diagnostic yield of genetic testing in epilepsy requires large-scale population-based studies to define which patients' epilepsies are attributable to a genetic cause. Two recent studies, conducted in tertiary care settings where genetic testing is now undertaken for some patients, begin to define the value of genetic testing in neonatal and early-life epilepsies. While there are no current guidelines governing which patients should undergo genetic testing, these reports identify important groups in whom genetic evaluation is not only of diagnostic utility but also likely to yield results that influence treatment of the most severely affected infants and children with epilepsy.

Through the multi-institutional collaborative Neonatal Seizure Registry (NSR), Shellhaas and colleagues evaluated 611 consecutive neonates with seizures of which 79 were diagnosed with neonatal epilepsy. Genetic testing was carried out at the discretion of the provider. The type of testing varied, over time and across institutions and providers, from single gene tests to broader chromosomal microarrays and whole exome sequencing. Fifty-eight percent of patients undergoing genetic testing had an identified genetic etiology for their epilepsy, underscoring the value of gene testing in this population. The highest yield was found in the evaluation of patients with neonatal epileptic encephalopathies, among whom 83% (24/29) had positive findings, most often variants in *KCNQ2* and *SCN2A,* that were considered disease-causing variants. This subgroup encompasses patients who often do not have an etiology established after imaging or common metabolic testing. In addition, early diagnosis of several etiologies (including *KCNQ2* and *SCN2A* as well as *ALDH7A1* and *PNPO*) may alter therapy to include treatments that have empirically improved efficacy in these syndromes and potentially improve long-term outcomes. Even when the etiology is clear from clinical or imaging evaluation, genetic testing plays an important role. Amongst neonates with epilepsy symptomatic of brain malformations, 26% had identifiable genetic etiologies. Finding a pathogenic or likely pathogenic variant in a gene associated with epilepsy can help parents by lifting the burden of determining what did or did not cause their child's epilepsy. Further, a genetic etiology can inform future reproductive decisions for parents; in some disorders it can aid the provider in screening for other comorbidities associated with gene mutations. These findings (albeit from a relatively small group of patients) not only suggest that genetic testing should be part of the evaluation of neonatal epilepsy but help narrow the types of neonatal epilepsy for which testing will prove most valuable.

Berg and colleagues took a similar approach examining a prospective cohort of 775 patients less than 3 years of age with new-onset epilepsy, including those with neonatal onset. Of these, 327/680 (48%) without acquired brain injuries underwent some form of genetic testing, and 40% were identified to have pathogenic genetic variants that explain their epilepsy. Within this cohort, the overall diagnostic yield of genetic testing compared favorably to that of imaging (38%) and better than metabolic testing (4%), though, as in the NSR study, the evaluation process was not standardized. Nonetheless, the high yield of genetic testing was similar to initial imaging done for new-onset seizures, which ranges from 21 to 50 percent (1,

2). Investigators assigned etiologies following clinical examination, imaging, and metabolic testing in 329 patients, but for the remaining 446, etiology remained unknown. For these, 180 underwent genetic testing, with genetic diagnoses made in 26%. Chromosomal microarray was most commonly used, followed by multigene sequencing panels, karyotypes, whole exome sequencing, mitochondrial gene tests, and disease-targeted testing (e.g., *TSC1* and *TSC2* testing for suspected tuberous sclerosis complex). Children with negative microarrays commonly had positive findings on sequencing-based testing, although the converse was not true.

These studies demonstrate the practical diagnostic utility of genetic testing in real-world hospital settings where infants and young children with severe epilepsy are typically treated, although practices still vary widely. The yields are comparable to those reported in several research studies, evaluating both copy number assessment and exome sequencing (3–10). One can only assume that, informed with these results, a systematic approach to testing would produce even higher yields. Based on their findings, we can begin to target populations with highest demonstrated yield (e.g., neonates with epileptic encephalopathies without cause identified from history, examination, and basic screening laboratory evaluation), where we will see benefit for those who might otherwise have gone undiagnosed. However, for counseling and medical decision-making, we should not overlook the value of genetic testing for those with known etiology. These studies help hone the list of genes that need to be examined based on age of presentation and symptoms, informing future development of higher yield gene panels, including those with rapid turnaround time. Both of these studies included all types of genetic testing, though yields were higher using methods with broad coverage. While these results suggest that an approach utilizing chromosomal microarray followed by sequencing methods (either via gene panel or whole exome sequencing) provide the highest yield, it may be judicious to simultaneously pursue such modalities or prioritize rapid sequencing and deletion/duplication testing of panels of genes likely to yield actionable results. As our understanding of genetic epilepsies evolves and our treatments become more precise, genetic testing will expedite diagnoses so we can deliver the most appropriate treatment in hopes of improving long-term outcomes.

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