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Genetic Testing in the Presurgical Evaluation of Drug-Resistant Epilepsy: Bells and Whistles or Nuts and Bolts?

Genetic Testing in Children Enrolled in Epilepsy Surgery Program. A Real-Life Study

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Objective: Although genetic causes of drug-resistant focal epilepsy and selected focal malformations of cortical development (MCD) have been described, a limited number of studies comprehensively analysed genetic diagnoses in patients undergoing pre-surgical evaluation, their outcomes and the effect of genetic diagnosis on surgical strategy. Methods: We analysed a prospective cohort of children enrolled in epilepsy surgery program over January 2018-July 2022. The majority of patients underwent germline and/or somatic genetic testing. We searched for predictors of surgical outcome and positive result of germline genetic testing. Results: Ninety-five patients were enrolled in epilepsy surgery program and 64 underwent resective epilepsy surgery. We ascertained germline genetic diagnosis in 13/74 patients having underwent germline gene testing (pathogenic or likely pathogenic variants in CHRNA4, NPRL3, DEPDC5, FGF12, GRIA2, SZT2, STXBP1) and identified three copy number variants. Thirty-five patients underwent somatic gene testing; we detected 10 pathogenic or likely pathogenic variants in genes SLC35A2, PTEN, MTOR, DEPDC5, NPRL3. Germline genetic diagnosis was significantly associated with the diagnosis of focal epilepsy with unknown seizure onset. Significance: Germline and somatic gene testing can ascertain a definite genetic diagnosis in a significant subgroup of patients in epilepsy surgery programs. Diagnosis of focal genetic epilepsy may tip the scales against the decision to proceed with invasive EEG study or surgical resection; however, selected patients with genetic focal epilepsies associated with MCD may benefit from resective epilepsy surgery and therefore, a genetic diagnosis does not disqualify patients from presurgical evaluation and epilepsy surgery.

Utility of Genetic Testing in the Pre-Surgical Evaluation of Children With Drug-Resistant Epilepsy

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We evaluated the utility of genetic testing in the pre-surgical evaluation of pediatric patients with drug-resistant focal epilepsy. This single-center retrospective study reviewed the charts of all pediatric patients referred for epilepsy surgery evaluation over a 5-year period. We extracted and analyzed results of genetic testing as well as clinical, EEG, and neuroimaging data. Of 125 patients referred for epilepsy surgical evaluation, 86 (69%) had some form of genetic testing. Of these, 18 (21%) had a pathogenic or likely pathogenic variant identified. Genes affected included NPRL3 (3 patients, all related), TSC2 (3 patients), KCNH1, CHRNA4, SPTAN1, DEPDC5, SCN2A, ARX, SCN1A, DLG4, and ST5. One patient had ring chromosome 20, one a 7.17p12 duplication, and one a 15q13 deletion. In six patients, suspected epileptogenic lesions were identified on brain MRI that were thought to be unrelated to the genetic finding. A specific medical therapy choice was allowed due to genetic diagnosis in three patients who did not undergo surgery. Obtaining a molecular diagnosis may dramatically alter management in pediatric patients with drug-resistant focal epilepsy. Genetic testing should be incorporated as part of standard investigations in the pre-surgical work-up of pediatric patients with drug-resistant focal epilepsy.

Commentary

The molecular genetic revolution that we witnessed over the past decades has enhanced our understanding of epilepsy and significantly improved its non-surgical management. For example, we now know to avoid sodium channel blockers in patients with SCN1A gene mutations, to favor them in patients

with SCN2A and SCN8A gene mutations, to recommend oxcarbazepine/carbamazepine for PRRT2 gene mutations, pyridoxine for ALDH7A1 and pyridoxal phosphate for PNPO gene mutations, to consider everolimus for patients with TSC gene mutations, and to introduce ketogenic diet for patients with SLC2A1 gene mutations.[1] Yet, the contribution of genetic testing to the surgical management of drug-resistant epilepsy (DRE) is more controversial. These 2 studies[2,3] attempt to elucidate that controversy.

In the first study,[2] the authors analyzed a pediatric cohort of patients with focal DRE due to radiologically identified and/or electroclinically suspected focal cortical dysplasia (FCD) undergoing presurgical evaluation in Czech Republic over a 4-year period. Of the 95 patients enrolled, 74 underwent germline testing and 13 (17.5%) of them were identified with a genetic diagnosis. Out of the 64 patients who underwent resective surgery, somatic gene testing was performed in 35, and 10 of them (28.5%) had pathogenic or likely pathogenic variants detected. As suspected preoperatively, most histopathological specimens confirmed FCD. Surgical outcome did not depend on the presence or absence of a germline mutation.[2]

In the second study,[3] the authors analyzed a pediatric cohort of patients with focal DRE undergoing presurgical evaluation in Germany over a 5-year period. Of the 125 patients enrolled, 86 had some form of genetic testing; 18 (21%) of them had a pathogenic/likely pathogenic variant detected. Ten (56%) of these patients, all with lesional epilepsy of variable pathology, underwent open surgery, with the majority resulting in good surgical outcome. One third of the surgically or medically treated patients bearing a genetic mutation had magnetic resonance imaging (MRI) abnormalities that were deemed to be unrelated to the genetic finding. Conversely, half of them had MRI abnormalities attributable to the genetic finding; in a couple of those cases the lesion was detected in hindsight after the genetic testing alerted for the possibility of FCD. Most importantly, three patients were steered toward medical management after genetic testing pointed toward a channelopathy (CHRNA4, SCN2A, and SCN1A).[3]

Both studies[2,3] have the advantages that they explore large cohorts of DRE requiring evaluation for epilepsy surgery. As such, they provide valuable insight into the yield and impact of genetic testing as part of the presurgical diagnostic armamentarium. On the other hand, both are single-center studies focusing on children, and they are inevitably fraught by heterogeneous timing and protocols of the genetic and other presurgical evaluations performed. All patients had focal epilepsy and were investigated for resective/disconnective surgery; hence, the value of genetic testing in the presurgical evaluation for neuromodulation, including for patients with medication refractory symptomatic or primary generalized epilepsy, remains unclear. The postsurgical follow-up time was limited, and non-seizure outcomes (eg, cognitive and psychosocial) were not assessed. Lastly, the design of both studies[2,3] precluded the ability to compare outcomes with control cohorts who had a diagnostic genetic abnormality but no alteration of the surgical plan, or patients without genetic evaluation who were treated based on standard epilepsy surgery practices.

Prior literature looking at the overall yield of genetic testing in epilepsy suggested variable results. For chromosomal microarrays, the diagnostic yield is only 3%, but it rises up to 15% in patients with developmental epileptic encephalopathies (DEEs).[4] These percentages increase to 9% and up to 50% respectively for whole exome sequencing and, even further, for whole genome sequencing.[5,6] For target gene panels, the overall yield is 19%, but in early onset DEEs, it can be up to 39%.[5,6] The yield identified in these 2 surgical cohorts of focal, pediatric DRE in the current studies,[2,3] where diverse genetic protocols were deployed, falls within this literature range. Unsurprisingly, epileptologists seem to favor the use of genetic testing in such presurgical patients, foremost those with early onset, positive family history, non-lesional focal epilepsy, and epilepsy with psychomotor deficits.[7]

With regards to the overall impact of genetic testing in epilepsy, prior investigations reported medical management changes in half of the evaluated patients and improved outcomes in 3 quarters of them.[8] From a surgical management standpoint, the outcomes vary depending on the underlying pathogenesis; structural lesions associated with mTORopathies or genetically determined FCDs, cavernomas or hypothalamic hamartomas with concordant electroclinical picture portend to better prognosis compared to channelopathies, synaptopathies, and mitochondriopathies.[7,9,10] The current 2 studies[2,3] appear overall congruent with this contention.

The proponents of genetic testing in epilepsy highlight the benefits of altering medical management, securing a diagnosis and, hence prognosis, watching for related comorbidities, providing reproductive counseling, facilitating clinical trials design and registries formation to inform future practice, accessing support groups and associated services, and alleviating the diagnostic uncertainty along with the stress and guilt that this often entails for the afflicted families.[5] As shown in these 2 cohorts,[2,3] incorporating genetic testing may also obviate the need for subsequent, costly and invasive interventions or, conversely, assist in presurgical planning by alerting for the presence of certain, surgically remediable pathologies. On the other hand, the sceptics of genetic testing bring up the heightened cost, the limited accessibility, the time delays, the added complexity of epigenetic factors, low penetrance and variable expressivity, the low sensitivity due to noncoding regions, novel transcriptional regulation mechanisms or even yet-to-be discovered mutations, as well as the potential diagnostic and prognostic uncertainty in the case of variants of unknown significance.[11]

In reality, incorporating genetic testing is neither a necessary nor a sufficient reason to perform or deny surgery for an individual patient. As illustrated in these 2 studies,[2,3] it is possible for patient with a genetic defect to develop a clear-cut epileptogenic focus (eg, FCD, cavernoma, tuber, hamartoma) or secondary foci of epileptogenesis complicating intractability (eg, mesial temporal sclerosis) that are surgically treatable. By contrast, when multifocality or a broader epileptic network

due to ion channel function and synaptic transmission gene mutation is implicated, then the odds are against a resective surgery.[7,9,10] Through large-scale registries and multi-center, prospective trials, it remains to be seen how genetic testing could alter the benefit to risk and cost ratio in this blurry landscape of "structural" vs "genetic" epilepsies.[2,7] And whether alternative methods of testing through cerebrospinal fluid analysis, stereo-electroencephalography electrodes sampling, or intraoperatively during resection could be systematically utilized.[12] Like with any other test in our presurgical armamentarium, the therapeutic decision ultimately lies on the thoughtful integration of all clinical, electrophysiological, radiological, and laboratory data.

So, when available, should genetic testing become standard element of presurgical evaluation? Most definitely! And the more we learn from it, the more its role will shift from being luxurious bells and whistles to essential nuts and bolts in the presurgical vehicle navigating toward seizure freedom.

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Declaration of Conflicting Interests

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