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Lesional Epilepsy in Children: Removing Doubt to Cut It Out

Prevalence and Risk Factors for Pharmacoresistance in Children With Focal Cortical Dysplasia-Related Epilepsy

Cohen NT, Chang P, You X, Zhang A, Havens KA, Oluigbo CO, Whitehead MT, Gholipour T, Gaillard WD. *Neurology*. 2022;99(18):e2006-e2013. doi:10.1212/WNL.0000000000201033

Background and objectives: Focal cortical dysplasia is the most common cause of surgically-remediable epilepsy in children. Little is known about the risk factors for the timing and development of pharmacoresistance in this population. This study sought to evaluate the prevalence and risk factors for pharmacoresistance in pediatric FCD-related epilepsy. Methods: In this retrospective single-center cohort design, patients were identified from search of centralized radiology report database and a central epilepsy surgical database. Inclusion criteria consisted of: 3T MRI-confirmed FCD from January, 2011 to January, 2020; ages 0 days to 22 years at MRI; at least 18 months of documented follow-up after MRI, unless had single seizure or incidentally discovered FCD. Records were excluded if there was dual pathology (except for mesial temporal sclerosis), hemimegalencephaly, or tuberous sclerosis complex present in imaging or history. Results: One hundred forty-three patients with confirmed FCD met inclusion criteria. One hundred twenty-four children had epilepsy (87% of FCD patients) with median age of seizure onset 2.7 years (IQR 0.75-6 years, range 0 to 17 years). Twelve children (8.5%) had a single lifetime seizure (provoked or unprovoked) or recurrent provoked seizures. Seven children (4.9%) had incidental FCD. Ninety-two patients (74%) of those with epilepsy met criteria for pharmacoresistance. Of children with epilepsy of all types, 93 children (75%) were seizure-free at the last visit. Eighty-two patients underwent epilepsy surgery, of whom 59 (72%) achieved seizure freedom. 7% (9/124) achieved seizure freedom with a second ASM, and 5.6% (7/124) with a third or more ASMs. Failure of only one antiseizure medication is associated with enormous increased incidence and earlier development of pharmacoresistance (OR 346, 95% CI 19.6-6100). Cox regression showed FCD lobar location, pathologic subtype, and age of seizure onset are not. Conclusions: Failure of one antiseizure medication is associated with substantial risk of pharmacoresistance. These data support an operational re-definition of pharmacoresistance, for surgical planning, in FCD-related epilepsy to the failure of one antiseizure medication, and support early, potentially curative surgery to improve outcomes in this patient population.

Commentary

How do we define pharmacoresistance in epilepsy, and who is a surgical candidate? The International League Against Epilepsy (ILAE) defines pharmacoresistant epilepsy (PRE) as the failure to control seizures after 2 adequate trials of well-tolerated, appropriately chosen anti-seizure medication (ASM) regimens.[1] For 20 years, consensus guidelines of several medical societies have recommended referral of patients with PRE to a surgical center, as seizure freedom with medications alone is unlikely after failing 2 ASMs.[2] Despite these guidelines and substantial evidence that surgery reduces morbidity and mortality in PRE, surgery remains underutilized. Many patients are not referred until they have suffered from 10 or more years of disabling seizures and have failed 5 or more ASMs,[3] and children with epilepsy have diminished access to epilepsy surgery due to inequities in care.[4,5] This is a big problem, because a longer duration of PRE prior to surgery is associated with less favorable seizure outcomes, worsened cognition and quality of life, and progressive perturbations in widespread brain networks.[6] In select patients who have the "most to gain" from surgery, such as children with lesional epilepsy, should we be considering surgery even earlier?

In the presently highlighted study, Cohen and colleagues sought to understand the natural history of epilepsy in children with focal cortical dysplasia (FCD)—one of the most common causes of lesional epilepsy.[7] The authors retrospectively queried a radiology database at their center to identify children with 3T MRI-confirmed FCD, which uncovered 143 patients (41% female) with a median age of 2.7 years (range 0-17) and median follow-up of 51 months. All imaging was interpreted by a

board-certified pediatric neuroradiologist over a 9-year period. Overall, epilepsy was diagnosed in 124 (87%) patients, which did not include individuals with a single lifetime seizure, and pharmacoresistance was identified in 92 (74%) children with epilepsy. Of note, the authors defined PRE as beginning a third ASM trial due to persistent seizures after prior agents or having epilepsy surgery after the failure of 2 ASMs. Overall, only 8% of the entire cohort with PRE (7/92) achieved seizure freedom with medications alone, while 89% of PRE patients (82/92) elected to undergo epilepsy surgery. Of those who had surgery, 72% achieved seizure freedom with 44 months median post-operative follow-up. The vast majority (96%) of PRE patients who had surgery underwent resection, and FCD pathology was type II in most (64%) of these children, while others harbored type I (28%) or type III (8%) pathology. The authors then used Kaplan-Meier survival curves and a Cox proportional hazards model to evaluate predictors of pharmacoresistance. While neuroanatomical, pathological, or demographic variables were not predictive of PRE, the failure of only one ASM was associated with the development of pharmacoresistance with an astounding odds ratio of 346 (95% CI 19.6-6100). Of note, only 15% of patients who failed to achieve seizure freedom with one ASM across the entire cohort (pharmacoresistant and pharmacosensitive patients) ultimately attained seizure freedom with ASMs alone. The authors argue that the likelihood of pharmacoresistance is high after failing one ASM in FCD-related pediatric epilepsy, and that earlier surgery should be considered.

The study by Cohen et al is one of the largest single-center cohorts of pediatric FCD. While the likelihood of FCDs causing seizures will be inflated with this analysis, as children who suffer from a seizure are much more likely to receive an MRI scan, the data demonstrate that individuals with FCD who do present with seizures are at very high risk of developing PRE. As the study is retrospective, it does not allow direct comparison of long-term seizure freedom rates with surgery versus ASMs alone in FCD. Most children in the cohort who developed epilepsy eventually "crossed over" from ASM treatment alone to having surgery. And while the duration of epilepsy at surgery is not explicitly reported, the median age at surgery (9.5 years) is nearly 7 years greater than the median age of seizure onset in the entire cohort (2.7 years), suggesting that surgical patients likely suffered from several years of seizures before resection. What is most notable, however, is that a large majority of epilepsy patients who continued to have seizures after failing one ASM then went on to meet the traditional definition of PRE (failure of $\geq$2 ASMs). This prompts an obvious question: Should surgical candidacy in epilepsy be defined sooner than failure of $\geq$2 ASMs, at least in individuals where the likelihood of safe surgical cure is high?

Recently, the ILAE Surgical Therapies Commission provided updated recommendations on the timing of epilepsy surgical referral, based on both an Expert Consensus Recommendations Writing Group and a Delphi Working Group.[8] It was recommended that nearly *all* patients with PRE who have failed $\geq$2 ASMs should be offered referral to a surgical center, regardless of epilepsy duration and type, demographics, and comorbidities, thus reiterating and strengthening prior ILAE guidelines. However, the new consensus also went further, and recommended that surgical referral should be considered for children and adults who are seizure free on 1 to 2 ASMs but have a brain lesion in non-eloquent cortex. This consensus recognized the high likelihood of seizure freedom in lesional epilepsy surgery, the low risk of complications in non-eloquent neocortical resection, and more favorable surgical outcomes with shorter duration of epilepsy. Thus, many of the children with FCD-related epilepsy in the present study would have met the criteria for surgical referral prior to meeting the standard definition of PRE.

Bottom line: Should we refer lesional epilepsy patients who have failed only one ASM, or who are seizure free on 1 to 2 ASMs, for surgical evaluation? It should be noted that formal guidelines do not yet explicitly recommend surgical referral for these individuals, and it has been nearly 20 years since the last pediatric-specific criteria for referral were proposed by ILAE, where consensus was not yet present.[9] However, these recommendations were published prior to the first randomized controlled trial demonstrating improved seizure outcomes with surgery in childhood PRE,[10] and the ILAE Pediatric Epilepsy Surgery Task Force is currently reexamining these criteria. Clearly, studies by Cohen et al and others demonstrate that the likelihood of developing PRE is very high in lesional epilepsy, and surgical risks are relatively low in non-eloquent cortex. So, yes, we should consider early referral of lesional epilepsy patients to a comprehensive epilepsy center even before pharmacoresistance. A team-based evaluation can help determine whether the patient is a surgical candidate, and whether the lesion is in a region that is safe to resect. The more we learn about non-eloquent lesional epilepsy, the less doubt there is to cut it out.

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Declaration of Conflicting Interests

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