Epilepsy Currents
2024, Vol. 24(4) 251-253

DOI: 10.1177/15357597241253413
journals.sagepub.com/home/epi
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Out of Sight, Not Yet Out of Reach: Surgical Outcomes in MRI-Negative and Pathology-Negative Epilepsy Patients

Outcome of Epilepsy Surgery in MRI-Negative Patients Without Histopathologic Abnormalities in the Resected Tissue

Sanders MW, Van der Wolf I, Jansen FE, Aronica E, Helmstaedter C, Racz A, Surges R, Grote A, Becker AJ, Rheims S, Catenoix H, Duncan JS, De Tisi J, Jacques TS, Cross JH, Kalviainen R, Rauramaa T, Chassoux F, Devaux BC, Di Gennaro G, Esposito V, Bodi I, Honavar M, Bien CG, Cloppenborg T, Coras R, Hamer HM, Marusic P, Kalina A, Pieper T, Kudernatsch M, Hartlieb TS, Von Oertzen TJ, Aichholzer M, Dorfmuller G, Chipaux M, Noachtar S, Kaufmann E, Schulze-Bonhage A, Scheiwe CF, Özkara C, Grunwald T, Koenig K, Guerrini R, Barba C, Buccoliero AM, Giordano F, Rosenow F, Menzler K, Garbelli R, Deleo F, Krsek P, Straka B, Arzimanoglou AA, Toulouse J, Van Paesschen W, Theys T, Pimentel J, Loução De Amorim IM, Specchio N, De Palma L, Feucht M, Scholl T, Roessler K, Toledano Delgado R, Gil-Nagel A, Raicevic S, Ristic AJ, Schijns O, Beckervordersandforth J, San Antonio-Arce V, Rumia J, Blumcke I, Braun KP; as the European Epilepsy Brain Bank Consortium (EEBB). *Neurology*. 2024;102(4): e208007. doi:10.1212/WNL.0000000000208007. PMID: 38290094

Background and Objectives: Patients with presumed nonlesional focal epilepsy—based on either MRI or histopathologic findings—have a lower success rate of epilepsy surgery compared with lesional patients. In this study, we aimed to characterize a large group of patients with focal epilepsy who underwent epilepsy surgery despite a normal MRI and had no lesion on histopathology. Determinants of their postoperative seizure outcomes were further studied. Methods: We designed an observational multicenter cohort study of MRI-negative and histopathology-negative patients who were derived from the European Epilepsy Brain Bank and underwent epilepsy surgery between 2000 and 2012 in 34 epilepsy surgery centers within Europe. We collected data on clinical characteristics, presurgical assessment, including genetic testing, surgery characteristics, postoperative outcome, and treatment regimen. Results: Of the 217 included patients, 40% were seizure-free (Engel I) 2 years after surgery and one-third of patients remained seizure-free after 5 years. Temporal lobe surgery (adjusted odds ratio [AOR]: 2.62; 95% CI 1.19-5.76), shorter epilepsy duration (AOR for duration: 0.94; 95% CI 0.89-0.99), and completely normal histopathologic findings—versus nonspecific reactive gliosis—(AOR: 4.69; 95% CI 1.79-11.27) were significantly associated with favorable seizure outcome at 2 years after surgery. Of patients who underwent invasive monitoring, only 35% reached seizure freedom at 2 years. Patients with parietal lobe resections had lowest seizure freedom rates (12.5%). Among temporal lobe surgery patients, there was a trend toward favorable outcome if hippocampectomy was part of the resection strategy (OR: 2.94; 95% CI 0.98-8.80). Genetic testing was only sporadically performed. Discussion: This study shows that seizure freedom can be reached in 40% of nonlesional patients with both normal MRI and histopathology findings. In particular, nonlesional temporal lobe epilepsy should be regarded as a relatively favorable group, with almost half of patients achieving seizure freedom at 2 years after surgery-even more if the hippocampus is resected-compared with only 1 in 5 nonlesional patients who underwent extratemporal surgery. Patients with an electroclinically identified focus, who are nonlesional, will be a promising group for advanced molecular-genetic analysis of brain tissue specimens to identify new brain somatic epilepsy genes or epilepsy-associated molecular pathways.

Commentary

The presence of a structural brain lesion in patients with drug-resistant epilepsy significantly increases the likelihood of identifying the seizure onset zone (SOZ) and achieving seizure freedom following resective epilepsy surgery. The absence of such detectable MRI lesions poses challenges for clinical decision-making, a scenario encountered not infrequently in clinical practice. Previous literature reports nonlesional MRI rates ranging from 35% to 43% in drug-resistant epilepsy patients,[1,2] and surgical outcomes for these patients are less optimal compared to cases where epileptogenic lesions are present on MRI.

Sanders et al[3] recently reported on surgical outcomes for patients with MRI-negative and pathology-negative epilepsy from the European Epilepsy Brain Bank Consortium. They identified 217 patients for final analysis, with 69% (150/217) undergoing temporal lobe surgery. The study revealed that surgical outcomes achieving Engel class I overall were 47.4% at 1 year, gradually decreasing to 40% at 2 years, and 36.3% at 5 years post-surgery. This is lower compared to lesional cases in the same cohort, which had seizure freedom rates of 70%, 62%, and 60% at 1-, 2-, and 5-years post-surgery. Temporal lobe epilepsy showed higher rates of seizure freedom with Engel class I outcomes at 1, 2, and 5 years (58.1% vs 22.4%, 47.3% vs 20.9%, 41% vs 16.4%) compared to extratemporal cases. Additionally, they performed multivariate regression analysis to help identify risk factors for predicting Engel class I surgical outcomes at 2-year follow-up. It revealed that temporal surgical location, normal histopathological findings versus nonspecific gliosis, and shorter epilepsy duration were significantly associated with favorable surgical outcomes for MRI-negative and pathology-negative epilepsy patients.

This study provides an important piece of evidence for evaluating MRI-negative drug-resistant epilepsy in clinical practice. Although the overall favorable outcome of achieving seizure freedom at 1 year is lower compared to cases with detectable MRI lesions, the success rate reaches 63.3% when the mesial temporal structure is considered part of the SOZ and hippocampectomy is performed as part of temporal lobe surgery, even in cases with negative MRI and pathology results. This success rate is on par with the 70% success rate for lesional surgical cases from the same database. In a previous landmark paper, the 1-year seizure-free surgical outcome for temporal lobe epilepsy was approximately 58% in a different cohort, comprising a mix of lesional (85%) and non-lesional cases (15%).[4] Similarly, this study reported a lower rate of Engel class I outcome post-surgery follow-up for extratemporal cases, with the subgroup of normal histopathological findings showing slightly better outcomes at 1 year and 2 years follow-up. This finding is consistent with a previous study of MRI-negative extratemporal epilepsy case series (n = 24), which reported a 38% patient excellent surgical outcome at 1 year and 10-year follow-up.[5] The efficacy of temporal lobe epilepsy surgery is likely related to the fact that temporal lobe epilepsy most commonly originates from the anteriomesial temporal lobe, while in nonlesional extratemporal lobe epilepsy, the networks implicated in epileptogenesis are often less clearly delineated, posing a considerable challenge when devising surgical strategies for these patients.

It is worth pointing out some limitations of this study. Firstly, there is a potential selection bias upon recruitment due to the retrospective nature of the study. A total of 571 (68%) of 836 pathology-negative patients were identified with sufficient information to assess eligibility for the study. Additionally, there is a notable loss of follow-up, with 43% of patients not evaluated for long-term surgical outcomes at 5 years post-surgery. Furthermore, as the authors noted, 15% of extratemporal and 20% of temporal MRI and pathology-negative cases in the cohort did not undergo intracranial electroencephalography (IEEG) prior to epilepsy surgery. The reasons for this could not be retrieved due to the retrospective study design, but it raises doubts about the true SOZ identification and the completeness of resection of the SOZ without intracranial EEG data in these cases. While other modalities of diagnostic testing such as PET scans or MEG may add additional value to identify the SOZ, in our practice, it is not uncommon to encounter these patients ended up with multifocal epilepsy based on IEEG data, and surgical planning would significantly change when compared to cases without this information.

While the focus of this study was on patients with MRI-negative and pathology-negative epilepsy who underwent surgery, the pathology information is often unavailable during the presurgical workup in clinical practice. Therefore, the findings may not be generalized in clinical practice to all cases of MRI-negative drug-resistant epilepsy patients as pathology is not known at the point of clinical decision-making during presurgical evaluation. Previous studies have highlighted the most common pathologies observed in MRI-negative cohorts, including focal cortical dysplasia (45%), gliosis (22%), hamartia and gliosis (13%), and hippocampal sclerosis (9%).[6] With advancements in high-resolution MRI technology, the detection rate of subtle findings including focal cortical dysplasia cases have significantly improved. Over the study period (2000-2017), MRI has shown enhanced sensitivity, uncovering an additional 18% to 23% of lesions in MRI-negative patients previously examined with 1.5 T MRI scans.[7] This brings up another major study limitation as one suspects a heterogeneous cohort of lesional and "truly-nonlesional" cases to be mixed in the cohort evaluated.

In cases of drug-resistant epilepsy with negative MRI and pathology findings, identifying the underlying etiology is critical. According to the International League Against Epilepsy (ILAE) classification, the etiology of epilepsy includes structural, metabolic, immune, genetic, infectious, and unknown factors. While MRI-negative cases exclude the structural category, the etiology of epilepsy can still vary broadly. Genetic diagnostic workup has recently been recommended for all epilepsy cases of unknown etiology, regardless of age.[8] However, this was not routinely evaluated in the current study, as only 7% of patients received genetic workup. A recent international study demonstrated that genetic testing for epilepsy and the resulting delivery of genetic epilepsy diagnoses often led to clinical management changes within 3 months, with 64.7% reporting a reduction or elimination of seizures after tailored treatment.[9] Additionally, it's important to acknowledge the possibility of somatic variation, as mutations may occur solely in the SOZ beyond germline mutations. Current research endeavors are exploring the genetic mutation burden from the samples extracted around IEEG leads or cerebrospinal fluid and their correlation with surgical outcomes.[10] With advancements comparable to those seen in oncology field, the prospects of molecular diagnosis and personalized treatment for epilepsy appear promising for the near future.

This study offers crucial insights into the surgical outcomes of patients with MRI-negative and pathology-negative epilepsy, illuminating a challenging clinical scenario. Despite the absence of detectable lesions on MRI and histopathology, the study reveals that a significant proportion of these patients achieve seizure freedom following surgery, particularly in cases of temporal lobe epilepsy. Furthermore, the findings underscore the value of early surgical intervention for MRI and pathology-negative refractory epilepsy cases, as it emerges as an independent risk factor for favorable surgical outcomes. Further research into the potential role of advanced molecular diagnostics would add further value in guiding personalized treatment approaches.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research and/or authorship of this article: Dr. Yi Li receives research support from the Stanford Maternal and Child Health Research Institute and American Epilepsy Society.

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