RESEARCH ARTICLE OPEN ACCESS

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

Maurits W. Sanders, MD, Iskander Van der Wolf, MD, Floor E. Jansen, MD, PhD, Eleonora Aronica, MD, PhD, Christoph Helmstaedter, MD, PhD, Attila Racz, MD, PhD, Rainer Surges, MD, PhD, Alexander Grote, MD, PhD, Albert J. Becker, MD, PhD, Sylvain Rheims, MD, PhD, Hélène Catenoix, MD, John S. Duncan, MD, PhD, Jane De Tisi, Thomas S. Jacques, MD, PhD, J. Helen Cross, MD, PhD, Reetta Kalviainen, MD, PhD, Tuomas Rauramaa, MD, PhD, Francine Chassoux, MD, Bertrand C. Devaux, MD, PhD, Giancarlo Di Gennaro, MD, PhD, Vincenzo Esposito, MD, PhD, Istvan Bodi, MD, PhD, Mrinalini Honavar, MD, Christian G. Bien, MD, PhD, Thomas Cloppenborg, MD, Roland Coras, MD, Hajo M. Hamer, MD, PhD, Petr Marusic, MD, PhD, Adam Kalina, MD, Tom Pieper, MD, Manfred Kudernatsch, MD, Till S. Hartlieb, MD, Tim J. Von Oertzen, MD, PhD, Martin Aichholzer, MD, Georg Dorfmuller, MD, Mathilde Chipaux, MD, PhD, Soheyl Noachtar, MD, PhD, Elisabeth Kaufmann, MD, Andreas Schulze-Bonhage, MD, PhD, Christian F. Scheiwe, MD, Cigdem Özkara, MD, PhD, Thomas Grunwald, MD, PhD, Kristina Koenig, MD, Renzo Guerrini, MD, PhD, Carmen Barba, MD, PhD, Anna Maria Buccoliero, MD, PhD, Flavio Giordano, MD, Felix Rosenow, MD, PhD, Katja Menzler, MD, Rita Garbelli, PhD, Francesco Deleo, MD, Pavel Krsek, MD, PhD, Barbora Straka, MD, PhD, Alexis A. Arzimanoglou, MD, PhD, Joseph Toulouse, MD, Wim Van Paesschen, MD, PhD, Tom Theys, MD, PhD, José Pimentel, MD, PhD, Isabel M. Loução De Amorim, MD, Nicola Specchio, MD, PhD, Luca De Palma, MD, Martha Feucht, MD, PhD, Theresa Scholl, MD, PhD, Karl Roessler, MD, PhD, Rafael Toledano Delgado, MD, Antonio Gil-Nagel, MD, PhD, Savo Raicevic, MD, PhD, Aleksandar J. Ristic, MD, PhD, Olaf Schijns, MD, PhD, Jan Beckervordersandforth, MD, PhD, Victoria San Antonio-Arce, MD, PhD, Jordi Rumia, MD, PhD, Ingmar Blumcke, MD, PhD,* and Kees P. Braun, MD, PhD,* as the European Epilepsy Brain Bank Consortium (EEBB)

Correspondence
Dr. Sanders
m.w.c.b.sanders-5@umcutrecht.nl

Neurology® 2024;102:e208007. doi:10.1212/WNL.0000000000208007

*These authors contributed equally to this work.

From the Department of Child Neurology (M.W.S, I.V.d.W., F.E.J, K.P.B.), Member of EpiCARE ERN, University Medical Center Utrecht, Utrecht; Department of (Neuro)Pathology (E.A.), Amsterdam Neuroscience, Amsterdam UMC, University of Amsterdam; Stichting Epilepsie Instellingen Nederland (SEIN) (E.A.), Heemstede, The Netherlands; Department of Epileptology (C.H., A.R., R.S.); Department of Neurosurgery (A.G.), University of Bonn Medical Center, Germany; Department of Neurosurgery (A.G.), Epilepsy Center Hessen, Philipps University, Marburgy; Department of Neuropathology (A.J.B.), University of Bonn Medical Center, Germany; Department of Functional Neurology and Epileptology (Sylvain Rheims, H.C.), Hospices Civils de Lyon and University of Lyon; Lyon's Neurosciences Research Center (INSERM U1028 / CNRS UMR5292) (Sylvain Rheims, Catenoix Hélène), France; UCL Queen Square Institute of Neurology, Department of Clinical and Experimental Epilepsy and National Hospital for Neurology and Neurosurgery (J.S.D., J.D.T.); Developmental Biology and Cancer Programme (T.S.J.), UCL Great Ormond Street Institute of Child Health and the Department of Histopathology, Great Ormond Street Hospital for Children, London; UCL- NIHR BRC Great Ormond Street Institute of Child Health (J.H.C.), Great Ormond Street Hospital for Children, Lingfield, United Kingdom; Kuopio Epilepsy Center (R.K., T.R.), Kuopio University Hospital and University of Eastern Finland; Department of Pathology (R.K., T.R.), Kuopio University Hospital and University of Eastern Finland, Member of EpiCARE ERN, Kuopio, Finland; Hospital Sainte-Anne (F.C., B.C.D.), GHU-Paris, France; IRCCS NEUROMED (G.D.G., V.E.), Pozzilli (IS), Italy; Department of Neurosurgery (V.E.), Sapienza University of Rome, Italy; Department of Clinical Neuropathology (Istvan Bodi, M.H.), King's College Hospital NHS Foundation Trust, Academic Neuroscience Center, Denmark Hill, King's College Hospital, London, United Kingdom; Department of Epileptology (Krankenhaus Mara) (C.G.B., T.C.), Medical School, Campus Bielefeld-Bethel, Bielefeld University; Department of Neuropathology (R.C.); Epilepsy Center (H.M.H.), University Hospital Erlangen, Germany; Department of Neurology (P.M., A.K.), Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic; Center for Pediatric Neurology, Neurorehabilitation, and Epileptology (T.P., M.K.), Schoen-Clinic, Vogtareuth, Germany; Research Institute "Rehabilitation, Transition, Palliation" (M.K.), PMU Salzburg, Austria; Department of Neurology I (T.J.V.O.), Neuromed Campus, Kepler Universitätsklinikum; Faculty of Medicine (T.J.V.O., M.A.), Johannes Kepler University; Department of Neurosurgery (M.A.), Neuromed Campus, Kepler Universitätsklinikum, Linz, Austria; Pediatric Neurosurgery Department (M.C.), Foundation Rothschild Hospital, Paris, France; Epilepsy Center (S.N., E.K.), Department of Neurology, Ludwig-Maximilians University, Munich, Germany; Epilepsy Centre (A.S.-B.); Department of Neurosurgery (C.F.S.), University Hospital, Freiburg, Germany; Department of Neurology (C.O.), Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Turkey; Swiss Epilepsy Center and Department of Neurology (K.K.), University Hospital, Zurich, Switzerland; Neuroscience Department (Renzo Guerrini, C.B.), Pathology Unit (A.M.B.), and Neurosurgery Department (F.G.), Meyer Children's Hospital IRCCS, Florence, Italy; University of Florence (Renzo Guerrini, C.B., F.G.), Florence, Italy; Epilepsy Center Frankfurt Rhine-Main (F.R.), Department of Neurology, and LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe University Frankfurt, Frankfurt am Main; Department of Neurology (F.R., K.M.), Epilepsy Center Hessen, Philipps University, Marburg, Germany; Epilepsy Unit (Rita Garbelli, F.D.), Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy; Department of Pediatric Neurology (P.K., B.S.), Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic; Department of Pediatric Clinical Epileptology (A.A.A., J.T.), Sleep Disorders and Functional Neurology University Hospitals of Lyon (HCL), Lyon, France; Paediatric Epilepsy Unit (A.A.A., V.S.A.-A., J.R.), Child Neurology Department and Neurosurgery Department, Hospital Sant Joan de Déu, Barcelona, Spain; Department of Neurology (W.V.P.); Department of Neurosurgery (T.T.), University Hospital Leuven, Belgium; Laboratory of Neuropathology (J.P., I.M.L.D.A.), Department of Neurosciences and Mental Health, Department of Neurology, Hospital de Santa Maria (CHULN)Lisbon, Portugal; Clinical and Experimental Neurology (N.S., L.D.P.), Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy; Center for Rare and Complex Epilepsies (M.F., T.S.), Department of Pediatrics and Adolescent Medicine; Department of Neurosurgery (K.R.), Medical University of Vienna, Austria; Epilepsy Program (R.T.D., A.G.-N.), Hospital Ruber Internacional, Madrid, Spain; Laboratory for Neuropathology (Savo Raicevic), Department of Pathology; Department for Epilepsy (A.J.R.), Clinic of Neurology, Clinical Center of Serbia, Belgrade; Medical Faculty (A.J.R.), University of Belgrade, Serbia; Department of Neurosurgery (O.S.), Academic Center for Epileptology; Department of Pathology (J.B.), Maastricht University Medical Center, The Netherlands; and University Hospital Erlangen (Ingmar Blumcke), Neuropathology, Erlangen, Germany.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

AOR = adjusted odds ratio; **EEBB** = European Epilepsy Brain Bank; **FCD** = focal cortical dysplasia; **iEEG** = invasive electroencephalography monitoring; **MEG** = magnetoencephalography; **mMCD** = mild malformation of cortical development; **MOGHE** = malformation of cortical development with oligodendroglial hyperplasia and epilepsy; **TLE** = temporal lobe epilepsy; **V-EEG** = video-electroencephalography.

Abstract

Background and Objective

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.

Introduction

Epilepsy surgery is a successful treatment option for patients with medically refractory focal epilepsy with an average 2-year postoperative seizure freedom rate of 67.5%.[1,2] Patients are preferably considered for surgery when the epileptogenic zone is focal, of presumed structural origin, well-delineated, and outside eloquent areas. Palliative procedures excluded, epilepsy surgery aims to completely remove or disconnect the epileptogenic zone.[3] Although the absence of an MRI-detected lesion is associated with a less favorable surgical outcome,[1,4] presurgical evaluation in MRI-negative patients with focal epilepsy is justified, acknowledging that a considerable proportion of those patients have a structural etiology, particularly a subtype of focal cortical dysplasia (FCD) or mild malformation of cortical development (mMCD). A prerequisite for surgical candidacy is a consistent hypothesis about the seizure onset zone, based on multimodal diagnostic noninvasive functional imaging and source localization techniques, often followed by invasive monitoring (subdural grid implantation or stereo-EEG).[5] In addition, genetic testing could improve the selection of eligible surgery candidates[6] because it is increasingly acknowledged that many patients with focal epilepsy have an underlying genetic etiology that may render them less or more suitable surgical candidates, depending on the gene involved.[6,7]

Outcomes of epilepsy surgery in all possible categories of histopathologic diagnoses in a large cohort of patients in Europe

(the European Epilepsy Brain Bank) were recently reported.[1,8] In almost 8% of the reviewed brain tissues, no specific pathologic diagnosis could be identified. The absence of a specific histopathologic diagnosis can theoretically be the consequence of a surgical strategy in which the lesion itself is not—or insufficiently—sampled for pathologic evaluation (i.e., a sample error)—which would include the consequences of certain surgical (e.g., aspiration) techniques that do not allow tissue specimens to be taken—or the lesion is disconnected rather than resected. In these scenarios, the epilepsy can still be lesional, as evidenced by an abnormal MRI. Alternatively, especially in the absence of an MRI-visible lesion, histopathology may be normal because the epilepsy is truly nonlesional and caused by mechanisms that cannot be detected with microscopic testing, such as genetic etiologies causing focal epilepsy.[9,10]

Similar to the relatively poor outcome of surgery in patients with normal MRI findings, normal or nonspecific histopathologic evaluation was also related to less favorable surgical outcomes; the proportion of seizure-free patients in the subgroup of patients in whom histopathologic testing of resected brain tissue revealed no or no specific lesion was 60%, 54%, and 51% after 1, 2, and 5 years, respectively, vs 73%, 69%, and 68%, respectively, in the lesional group.[1]

Although some studies pointed out the potential benefits of surgery even in nonlesional forms of focal epilepsy,[9] a substantial part of these patients is unnecessarily exposed to the risks of invasive presurgical assessment and surgery because they experience recurrent seizures after surgery. Whereas several studies have reported and reviewed the outcomes of patients with MRI-negative epilepsy,[10-12] little is known about the presurgical assessment strategies and postsurgical outcomes of patients with epilepsy who are considered to be "truly" nonlesional, based on both imaging and histopathologic findings.

We conducted this observational cohort study to evaluate the presurgical trajectory, surgery characteristics, and postoperative outcomes in patients with MRI-negative focal epilepsy in whom histopathologic examination of resected brain tissue as well showed no specific abnormalities. We hypothesized that outcomes of these patients are worse compared with those with normal pathology but a likely epileptogenic MRI lesion. Last, we assessed determinants of postoperative outcome in this challenging group of nonlesional patients.

Methods

Patient Selection

We retrospectively evaluated data from the presurgical and postsurgical trajectories in a cohort of 836 pathology-negative patients derived from the European Epilepsy Brain Bank (EEBB) cohort that included a total of 9,147 operated patients from 34 epilepsy surgery centers across 14 countries.[1] All patients underwent epilepsy surgery between 2000 and 2012. We included patients of any age in whom histopathologic examination of the resected brain tissue revealed no abnormalities or only mild nonspecific reactive gliosis, therefore not demonstrating a specific structural etiology (thus not in the context of, e.g., a vascular lesion).

First, we contacted collaborators from the EEBB consortium to retrospectively collect additional data from the patients who were categorized in this pathology-negative cohort.[1] Second, from the patients whose complete datasets were acquired, we identified a subgroup of patients in whom MRI strongly suggested a structural epileptogenic lesion—notwithstanding the absence of histopathologic abnormalities. In these individuals, histopathologic results were considered to be nonrepresentative and falsely negative. In the remaining group, both MRI and histopathology revealed no epileptogenic lesion, and the epilepsy was considered to be nonlesional.

Data Collection

Our collaborators retrieved information on the clinical course of the patients' epilepsies, presurgical diagnostic trajectories, surgeries, and their postsurgical outcomes retrospectively from the patients' health records. Clinical variables included age at epilepsy onset, disease duration until epilepsy surgery, age at surgery, family history of epilepsy, comorbidities, and the presurgical presumed etiologic diagnosis. Information on the presurgical diagnostic evaluation included the following: duration of the presurgical trajectory as defined by the duration from start of the evaluation program until surgery, results of MRI as reported by a dedicated neuroradiologist in the participating center, highest magnetic field strength used, use of video-electroencephalography monitoring (V-EEG), invasive intracranial electroencephalography (iEEG), PET, SPECT, and magnetoencephalography (MEG). Furthermore, types and results of genetic testing, if performed—either before or after surgery—were collected.

Surgical procedures were categorized as (1) hemispherotomy, (2) (multi)lobar resection, (3) focal resection, and (4) disconnection (other than hemispherotomy). Moreover, we collected side and location of surgery and (expected) completeness of the resection, as documented with perioperative electrocorticography or based on preresection iEEG findings. Outcome reports of histopathologic examination were reviewed by a dedicated pathologist, and results were characterized as (1) completely normal or (2) only nonspecific reactive changes, such as mild gliosis, not indicative of a structural epilepsy etiology. In our previous study, detailed information on seizure freedom (defined as Engel I) and postoperative pharmacologic treatment regimen (freedom of antiseizure medication) at 3 different time points (1, 2, and 5 years after surgery) had already been collected.[13]

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the University of Erlangen ethical review board (193_18b for EEBB of the European Reference Network "EpiCare"). Deidentified datasets were submitted from local epilepsy centers to the EEBB database in Erlangen,

Table 1 Baseline Characteristics of Patients With Complete Data (N = 571)

Characteristics	Cohort		
	Nonlesional (n = 217)	MRI-lesional (n = 354)	*p* Value of difference
Epilepsy trajectory			
Age at onset, y, mean (SD)	15.0 (±10)	12.7 (±11)	0.02
Male sex, n (%)	105 (48)	213 (60)	0.02
Age at surgery, y, mean (SD)	32.8 (±12)	28.2 (±15)	0.00
MRI field strength ≥1.5T, n (%)	175 (81)	297 (84)	0.62
Presurgical trajectory			
Duration of presurgical trajectory, mo, median (IQR)	18 (9–36)	14 (6–40)	0.04
PET, n (%)	157 (71)	109 (31)	0.00
SPECT, n (%)	50 (23)	50 (14)	0.01
MEG, n (%)	25 (12)	22 (6)	0.02
HD-EEG, n (%)	14 (6)	45 (13)	0.02
iEEG, n (%)	158 (73)	57 (16)	0.00
Genetic testing, n (%)	15 (7)	16 (5)	0.20
Surgery			
Surgery location			
Temporal, n (%)	150 (69)	199 (56)	0.01
Frontal, n (%)	40 (18)	59 (17)	0.59
Parietal, n (%)	11 (5)	10 (3)	0.31
Occipital, n (%)	3 (2)	8 (2)	0.26
Multilobar, n (%)	13 (6)	78 (22)	0.00
Surgery type			
Resective, n (%)	213 (98)	293 (83)	0.00
Disconnective/hemispherotomy, n (%)	4 (2)	61 (13)	0.00

Germany, using electronic Excel data sheets. Informed consent was obtained from all patients at the submitting center, and all procedures were performed in accordance with the ethics requirements of the contributing center.

Data Availability

Sharing of pseudonymized data will be considered on request.

Analysis

Differences in baseline characteristics between the likely nonlesional vs the MRI lesional group were examined by the use of χ^2 tests for categorical variables and Mann-Whitney or independent-sample *t* tests for continuous variables. Categorical data are presented as percentages and continuous variables as median and mean values. As a primary analysis, we performed univariable and multivariable regression analyses in the nonlesional cohort to calculate (adjusted) odds ratios in patients who were rendered seizure-free compared with those with recurrent seizures after surgery, associated with the following available and possibly relevant determinants of seizure outcome: age at surgery and duration of epilepsy, surgery location (temporal vs extratemporal), use of invasive diagnostics, and histopathologic diagnosis (normal findings vs nonspecific reactive gliosis). Due to high collinearities, completeness of resection was not included in the multivariable model. Data analysis was performed with IBM SPSS 23.

Results

After contacting the treating physicians from the 34 epilepsy surgery centers of the original EEBB cohort,[1] we were able to retrieve additional data of 706 of 836 (84%) pathology-negative patients from 31 centers (eTable 1, links.lww.com/WNL/D359). In 571 of 706 patients (83%), the data were sufficient to draw conclusions on the presence or absence of a structural cause. Disease characteristics—other than age at epilepsy onset and surgery—and surgical outcomes did not

Table 2 Surgery Outcome in Nonlesional Temporal vs Extratemporal Cases: Noninvasive vs Invasive Monitoring; Normal Histopathologic Findings vs Nonspecific Reactive Gliosis

	Seizure outcome			
Nonlesional cohort	**N**	**Engel I 1 y (%)**	**Engel I 2 y (%)**	**Engel I 5 y (%)**
All	217	47.4	40.0	36.3
Temporal	150	58.1	47.3	41.0
No iEEG	50	71.4	60.9	50.0
iEEG	100	51.5	41.1	36.4
Normal histopathologic findings	38	57.9	55.6	44.1
Nonspecific reactive gliosis	112	58.1	44.2	38.8
Hippocampectomy	60[a]	63.3	54.0	52.0
No hippocampectomy	23[a]	39.1	28.5	25.0
Extratemporal	67	22.4	20.9	16.4
No iEEG	10	30.0	20.0	20.0
iEEG	57	21.1	21.1	15.7
Normal histopathologic findings	28	35.7	32.0	25.0
Nonspecific reactive gliosis	39	12.8	12.8	12.8

[a] No definitive data on type of surgery (hippocampectomy yes or no) could be retrieved in 67 patients.

differ between the 571 included patients and the remaining 265 of whom data were incomplete or could not be retrieved (eTable 2).

Of these 571 patients, 354 (62%) had evidence of a causative MRI lesion. Their MRI findings, and thus imaging-based presumed structural etiologies, are summarized in eTable 3 (links.lww.com/WNL/D359). The remaining 217 MRI-negative patients (38%) with normal histopathologic examination were considered to be nonlesional.

Patient Characteristics and Presurgical Trajectory

Clinical characteristics of the 571 histopathology-negative patients with complete data are summarized in Table 1. Most of the variables significantly differed between the 217 nonlesional and 354 lesional patients, except for highest MRI field strength used, frequency of genetic testing, and location of surgery. The mean age at epilepsy onset was significantly higher in the nonlesional group (14.98 years) when compared with the MRI lesional cases (12.73 years), as was age at surgery (32.8 years vs 28.2 years) and mean duration of the presurgical trajectory (18 vs 15 months). At the time of surgery, 24 (11%) of nonlesional patients were children (younger than 18 years), compared with 104 (29%) of the lesional cases. One hundred sixty-four nonlesional patients (76%) underwent additional imaging modalities (PET, SPECT) or source localization techniques (MEG, high density electroencephalography). Nonlesional patients significantly more often underwent invasive monitoring (73% vs 16%).

Any form of genetic testing—on blood or tissue and either before or after surgery—during data collection was performed in only 15 (7%) of nonlesional patients and 16 (5%) of patients with a structural cause of epilepsy. None of the 16 genetic tests performed in the 15 nonlesional patients yielded a causative variant. In the 26 tests performed in the 16 lesional patients, 1 likely pathogenic germline variant (*CCM2*) and 3 germline variants of unknown significance were identified (eTable 4, links.lww.com/WNL/D359).

Surgery Characteristics and Postoperative Seizure Outcomes

Fifty-four of the 217 nonlesional patients (25%) underwent surgery in either the frontal, parietal, or occipital lobe. Most of the patients underwent temporal lobe surgery, comprising 150 (69%) patients with nonlesional epilepsy, and in 13 patients (6%), the location was considered multilobar. Two percent of nonlesional surgical cases underwent (hemispheric) disconnective surgery.

Postoperative seizure outcome data were not available in 1% of nonlesional cases at 1 year, 12% of cases at 2 years, and 43% of patients at 5 years. Engel I seizure freedom rates at 1, 2, and 5 years after surgery in patients with nonlesional epilepsy are listed in Table 2. All other seizure outcome rates (Engel I–IV) are listed in eTable 5 (links.lww.com/WNL/D359). On average, 40% was seizure-free after 2 years, ranging from 20.9%

Table 3 Uni- and Multivariate Regression Analysis in Nonlesional Patients With Favorable vs Unfavorable Outcome

Characteristics	Seizure outcome				
	Engel I[a] (n = 76)	Engel II–IV[a] (n = 114)	*p* Value of difference	Univariable odds ratio (95% CI)	Multivariable odds ratio (95% CI)[b]
Age at surgery, y, mean (SD)	32.1 (±12.0)	32.1 (±12.5)	0.98	1.00 (0.98–1.02)[c]	1.04 (0.99–1.09)
Duration of epilepsy, y, median (IQR)	14.5 (8.1–21.5)	19 (9.0–26.8)	0.05	0.97 (0.94–0.99)[c]	0.94 (0.89–0.99)
Temporal surgery location, n (%)	62 (82)	69 (60)	0.00	2.89 (1.45–5.76)	2.62 (1.19–5.76)
iEEG, n (%)	49 (64)	93 (82)	0.01	0.41 (0.21–0.80)	0.45 (0.17–1.22)
Complete resection, n (%)	39/46 (85)[d]	47/81 (58)[e]	0.00	4.03 (1.61–10.09)	—[e]
Normal histopathologic findings, n (%, vs nonspecific gliosis)	28 (37)	33 (29)	0.25	1.43 (0.77–2.65)	4.49 (1.79–11.27)

[a] Engel classification at 2 y follow-up, 27 missing cases (12%).
[b] Adjusted for all other covariates.
[c] Odds ratio per year.
[d] No exact information on completeness of resection (n = 28), no resective surgery (n = 2).
[e] No exact information on completeness of resection (n = 32), no resective surgery (n = 1).
[f] Not included because of high collinearities.

in extratemporal to 47.3% in temporal lobe surgery. Seizure freedom in combination with complete tapering of antiseizure medication was achieved in 17.2% of patients at 2 years of follow-up. Univariably, longer duration of epilepsy, extratemporal surgery, long-term invasive monitoring, incomplete resection, and nonspecific reactive gliosis (vs completely normal histopathologic findings) were significantly associated with a lower chance of reaching seizure freedom at 2 years (Table 3). Among patients who underwent temporal lobe surgery, there was a trend toward favorable outcome in patients of whom resection included hippocampectomy (OR: 2.94; 95% CI 0.98–8.80). Multivariable analysis (Table 3) showed a significant association between seizure freedom at 2 years and temporal 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 (AOR: 4.49; 95% CI 1.79–11.27). Of the nonlesional patients who were seizure-free at 1 year after surgery, 23.4% lost seizure freedom at later follow-up.

In patients with MRI lesional epilepsy, seizure outcomes were better than in nonlesional cases, with an inversed odds ratio of 0.39 of being seizure-free 1 year following surgery in patients with nonlesional epilepsy compared with MRI lesional cases, who had seizure freedom rates of 70%, 62%, and 60% at 1, 2, and 5 years following surgery, respectively (eTable 6, links.lww.com/WNL/D359).

Discussion

This study presents a cohort of 217 European patients with epilepsy who were considered truly nonlesional, having neither imaging nor histopathologic abnormalities pointing toward a structural epilepsy cause. Their seizure outcome was remarkably poor, with little more than one-third of nonlesional patients being seizure-free 5 years following surgery and one-fifth of patients achieving seizure freedom when considering extratemporal surgery only. However, nonlesional patients who underwent temporal lobe surgery had a—statistically significant—more favorable outcome, with almost half of patients achieving seizure freedom 2 years postoperatively. Patients in whom surgery also involved resection of the hippocampus experienced even better postoperative results: more than half of patients in this subcategory were rendered seizure-free at 2 and 5 years following surgery. Longer duration of epilepsy and nonspecific histopathologic abnormalities each were independently related to poorer outcome.

Most previous studies on surgical outcomes in the so-called nonlesional epilepsy referred to the absence of either an MR-visible epileptogenic lesion or abnormal histopathologic findings not combined with imaging findings. A systematic review on surgical outcomes in such MRI-nonlesional epilepsy reported seizure freedom in 46% of 398 patients, without specifying duration of seizure freedom, and in 39% of 302 nonlesional patients when considering only histopathology.[14] In a substantial part of the MRI-negative surgical patients, however, histopathologic examination reveals a structural cause of epilepsy, particularly subtypes of FCD.[15,16] One retrospective review addressed outcomes of surgical patients who were nonlesional from a histopathologic perspective and showed a seizure freedom rate of 42.9% of 21 patients, after a mean follow-up duration of 6.5 years.[9] We are aware of only one other relatively small study that evaluated seizure outcome specifically in patients who underwent temporal lobe epilepsy (TLE) surgery and had both normal MRI and microscopic examination that reported seizure freedom in 61.5% of 26 patients 2 years following surgery.[17]

Although for the entire group of MRI-negative and pathology-negative patients, long-term seizure freedom rates were disappointing, this study underlines that in a specific group of patients without a structural cause of epilepsy, comprising candidates for temporal lobe surgery and mesiotemporal surgery particularly, resective surgery is a viable treatment option with a relatively favorable seizure outcome. These findings suggest that a focal, nonstructural, and possibly genetic subtype of TLE patients has a relatively high chance of complete removal of the epileptogenic zone, therefore representing good surgical candidacy. Part of the nonlesional TLE patients who do not reach seizure freedom after resective surgery may consist of patients with the so-called temporal plus epilepsy, an electroclinical entity known to have a poor surgical outcome.[18]

Previous studies indicated that variants in mTOR pathway genes—associated with a structural cause of epilepsy—are an important predictor of good surgical candidacy, especially in patients with no visible lesion on MRI. On the contrary, variants associated with channel or synaptic transmission function could predict poor surgical candidacy.[6,19]

However, the exact influence of underlying genetic factors on etiologic background and associated surgical outcome in nonlesional patients with heterogenous responses to presurgical assessment and surgical treatment remains largely uncharacterized, and therefore, it is incompletely known in which of these patients epilepsy surgery is indicated or contraindicated. In our cohort with surgical patients included between 2000 and 2012, genetic testing was only rarely performed.

The MRI lesional group in our study had surgical outcomes that were comparable with the lesional group of patients, as based on histopathology results in the full EEBB cohort.[1] This suggests that in a high fraction of patients from the MRI lesional cohort, no representative tissue sample was obtained during surgery.

This study has some limitations, part of which are inherent to its retrospective design. Despite a positive response rate from most participating centers across Europe, we had to exclude 265 patients with lacking or inconclusive MRI data from our analysis (32%). Thus, it is possible that nonresponse in combination with incomplete data may have introduced a selection bias. It may be the case that patients in whom insufficient data could be retrieved more often were lost to follow-up because of a favorable outcome. Seizure outcome rates in the centers with the highest response rates, however, were similar to those in the overall group. In addition, because MRI-negative patients with positive histopathologic findings could not be systematically included in this cohort, the impact of our findings on presurgical decision-making is limited. Next, the group of nonlesional patients who underwent parietal, occipital, or multilobar surgery was small, which compromises the conclusions drawn from these subgroups. Another limitation of this study includes possible differences in histopathologic characterization of brain tissue samples among the collaborating centers. As a consequence, the presence of mild malformations of cortical development (mMCD, FCD type I, and malformation of cortical development with oligodendroglial hyperplasia and epilepsy [MOGHE]) could have been missed on MRI and on histopathologic examination in some patients. Spatial sampling errors may have played a role as well, with only parts of the resected specimen and not the entire resected brain tissue being examined. This error, however, is inherent to all epilepsy surgery series and bears the small risk of not detecting subtle lesions in the resected brain tissue. In addition, the retrospective design does not allow conclusions on the role of invasive EEG recordings before epilepsy surgery, and the lack of available data on noninvasive EEG recordings hampers conclusions on its role in surgery outcome in this study. Almost three-quarters of the included patients with likely nonlesional epilepsy underwent intracranial EEG. The MD team's reasons to decide for or against iEEG could not be retrospectively assessed but may have differed between centers and influenced patient selection and outcomes. Regarding completeness of resection, information on (expected) completeness of resection as documented by either ACoG or preresection invasive EEG findings was limited to "complete," "incomplete," or "unknown." Exact reasons for incompleteness of resection were not provided, but in line with general practice, we assume that this was either assessed as such when eloquent areas prevented extension of resection, or surgical risks (otherwise) prevented completeness of resection, or the identified area to be epileptogenic—based on preresection invasive EEG monitoring—was found to not be completely resected based on postresection MRI. Last, the application of genetic testing is most likely undervalued because of the inclusion period.

With this study, we demonstrate the relatively poor seizure outcomes of patients with MRI-negative focal epilepsy who undergo surgery but in whom no pathologic lesional diagnosis can be made. There is an urgent need for expanding the knowledge of pathologic substrates and molecular mechanisms underlying nonlesional focal epilepsy and for a long time, genetic analysis only found limited application in unraveling its background. To improve patient selection and surgery outcomes, we need new—possibly genetic—biomarkers for poor surgical candidacy. Patients such as those from this cohort will be a promising group for advanced molecular-genetic analysis of brain tissue specimens to identify new brain somatic epilepsy gene variants or epilepsy-associated molecular pathways.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 1, 2023. Accepted in final form December 6, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Barbara Jobst, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Maurits W. Sanders, MD	Child Neurology, University Medical Center Utrecht, The Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Iskander Van der Wolf, MD	Child Neurology, University Medical Center Utrecht, The Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Floor E. Jansen, MD, PhD	Child Neurology, University Medical Center Utrecht, The Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Eleonora Aronica, MD, PhD	Department of (Neuro)Pathology, Amsterdam Neuroscience, Amsterdam UMC, University of Amsterdam; Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Christoph Helmstaedter, MD, PhD	Department of Epileptology, University of Bonn Medical Center, Germany	Drafting/revision of the article for content, including medical writing for content
Attila Racz, MD, PhD	Department of Epileptology, University of Bonn Medical Center, Germany	Drafting/revision of the article for content, including medical writing for content
Rainer Surges, MD, PhD	Department of Epileptology, University of Bonn Medical Center, Germany	Drafting/revision of the article for content, including medical writing for content
Alexander Grote, MD, PhD	Department of Neurosurgery, University of Bonn Medical Center; Department of Neurosurgery, Epilepsy Center Hessen, Philipps University, Marburg, Germany	Drafting/revision of the article for content, including medical writing for content
Albert J. Becker, MD, PhD	Department of Neuropathology, University of Bonn Medical Center, Bonn, Germany	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Sylvain Rheims, MD, PhD	Department of Functional Neurology and Epileptology, Hospices Civils de Lyon and University of Lyon; Lyon's Neurosciences Research Center (INSERM U1028 / CNRS UMR5292), France	Drafting/revision of the article for content, including medical writing for content
Hélène Catenoix, MD	Department of Functional Neurology and Epileptology, Hospices Civils de Lyon and University of Lyon; Lyon's Neurosciences Research Center (INSERM U1028 / CNRS UMR5292), France	Drafting/revision of the article for content, including medical writing for content
John S. Duncan, MD, PhD	UCL Queen Square Institute of Neurology, Department of Clinical and Experimental Epilepsy and National Hospital for Neurology and Neurosurgery, London, United Kingdom	Drafting/revision of the article for content, including medical writing for content
Jane De Tisi	UCL Queen Square Institute of Neurology Department of Clinical and Experimental Epilepsy and National Hospital for Neurology and Neurosurgery, London, United Kingdom	Drafting/revision of the article for content, including medical writing for content
Thomas S. Jacques, MD, PhD	Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health and the Department of Histopathology, Great Ormond Street Hospital for Children, London, United Kingdom;	Drafting/revision of the article for content, including medical writing for content
J. Helen Cross, MD, PhD	UCL- NIHR BRC Great Ormond Street Institute of Child Health, Great Ormond Street Hospital for Children, Lingfield, United Kingdom	Drafting/revision of the article for content, including medical writing for content
Reetta Kalviainen, MD, PhD	Kuopio Epilepsy Center, Kuopio University Hospital and University of Eastern Finland; Department of Pathology, Kuopio University Hospital and University of Eastern Finland, Finland	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Tuomas Rauramaa, MD, PhD	Kuopio Epilepsy Center, Kuopio University Hospital and University of Eastern Finland; Department of Pathology, Kuopio University Hospital and University of Eastern Finland, Finland	Drafting/revision of the article for content, including medical writing for content
Francine Chassoux, MD	Hospital Sainte-Anne, GHU-Paris, France	Drafting/revision of the article for content, including medical writing for content
Bertrand C. Devaux, MD, PhD	Hospital Sainte-Anne, GHU-Paris, France	Drafting/revision of the article for content, including medical writing for content
Giancarlo Di Gennaro, MD, PhD	IRCCS NEUROMED, Pozzilli (IS), Italy	Drafting/revision of the article for content, including medical writing for content
Vincenzo Esposito, MD, PhD	IRCCS NEUROMED, Pozzilli (IS); Department of Neurosurgery, Sapienza University of Rome, Italy	Drafting/revision of the article for content, including medical writing for content
Istvan Bodi, MD, PhD	Department of Clinical Neuropathology, King's College Hospital NHS Foundation Trust, Academic Neuroscience Center, Denmark Hill, King's College Hospital, Londo, United Kingdom	Drafting/revision of the article for content, including medical writing for content
Mrinalini Honavar, MD	Department of Clinical Neuropathology, King's College Hospital NHS Foundation Trust, Academic Neuroscience Center, Denmark Hill, King's College Hospital, Londo, United Kingdom	Drafting/revision of the article for content, including medical writing for content
Christian G. Bien, MD, PhD	Department of Epileptology (Krankenhaus Mara), Medical School, Campus Bielefeld-Bethel, Bielefeld University, Germany	Drafting/revision of the article for content, including medical writing for content
Thomas Cloppenborg, MD	Department of Epileptology (Krankenhaus Mara), Medical School, Campus Bielefeld-Bethel, Bielefeld University, Germany	Drafting/revision of the article for content, including medical writing for content
Roland Coras, MD	Department of Neuropathology, University Hospitals Erlangen, Germany	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Hajo M. Hamer, MD, PhD	Epilepsy Center, University Hospital Erlangen, Germany	Drafting/revision of the article for content, including medical writing for content
Petr Marusic, MD, PhD	Department of Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic	Drafting/revision of the article for content, including medical writing for content
Adam Kalina, MD	Department of Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic	Drafting/revision of the article for content, including medical writing for content
Tom Pieper, MD	Center for Pediatric Neurology, Neurorehabilitation, and Epileptology, Schoen-Clinic, Vogtareuth, Germany	Drafting/revision of the article for content, including medical writing for content
Manfred Kudernatsch, MD	Center for Pediatric Neurology, Neurorehabilitation, and Epileptology, Schoen-Clinic, Vogtareuth, Germany; Research Institute "Rehabilitation, Transition, Palliation", PMU Salzburg, Austria	Drafting/revision of the article for content, including medical writing for content
Till Sebastian Hartlieb, MD	Center for Pediatric Neurology, Neurorehabilitation, and Epileptology, Schoen-Clinic, Vogtareuth, Germany; Research Institute "Rehabilitation, Transition, Palliation", PMU Salzburg, Austria	Drafting/revision of the article for content, including medical writing for content
Tim J. Von Oertzen, MD, PhD	Department of Neurology I, Neuromed Campus, Kepler Universitätsklinikum; Faculty of Medicine, Johannes Kepler University, Linz, Austria	Drafting/revision of the article for content, including medical writing for content
Martin Aichholzer, MD	Faculty of Medicine, Johannes Kepler University; Department of Neurosurgery, Neuromed Campus, Kepler Universitätsklinikum, Linz, Austria	Drafting/revision of the article for content, including medical writing for content
Georg Dorfmuller, MD	Pediatric Neurosurgery Department, Foundation Rothschild Hospital, Paris, France	Drafting/revision of the article for content, including medical writing for content

Continued

Appendix *(continued)*

Name	Location	Contribution
Mathilde Chipaux, MD, PhD	Pediatric Neurosurgery Department, Foundation Rothschild Hospital, Paris, France	Drafting/revision of the article for content, including medical writing for content
Soheyl Noachtar, MD, PhD	Epilepsy Center, Department of Neurology, Ludwig-Maximilians University, Munich, Germany	Drafting/revision of the article for content, including medical writing for content
Elisabeth Kaufmann, MD	Epilepsy Center, Department of Neurology, Ludwig-Maximilians University, Munich, Germany	Drafting/revision of the article for content, including medical writing for content
Andreas Schulze-Bonhage, MD, PhD	Epilepsy Centre, University Hospital, Freiburg, Germany	Drafting/revision of the article for content, including medical writing for content
Christian F. Scheiwe, MD	Department of Neurosurgery, University Hospital, Freiburg, Germany	Drafting/revision of the article for content, including medical writing for content
Cigdem Özkara, MD, PhD	Department of Neurology, Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, Turkey	Drafting/revision of the article for content, including medical writing for content
Thomas Grunwald, MD, PhD	Swiss Epilepsy Center and Department of Neurology, University Hospital, Zurich, Switzerland	Drafting/revision of the article for content, including medical writing for content
Kristina Koenig, MD	Swiss Epilepsy Center and Department of Neurology, University Hospital, Zurich, Switzerland	Drafting/revision of the article for content, including medical writing for content
Renzo Guerrini, MD, PhD	Neuroscience Department, Meyer Children's Hospital, Florence, Italy; University of Florence, Italy	Drafting/revision of the article for content, including medical writing for content
Carmen Barba, MD, PhD	Neuroscience Department, Meyer Children's Hospital, Florence, Italy; University of Florence, Italy	Drafting/revision of the article for content, including medical writing for content
Anna Maria Buccoliero, MD, PhD	Pathology Unit, Meyer Children's Hospital, Florence, Italy	Drafting/revision of the article for content, including medical writing for content
Flavio Giordano, MD	Neurosurgery Department, Meyer Children's Hospital; University of Florence, Italy	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Felix Rosenow, MD, PhD	Epilepsy Center Frankfurt Rhine-Main, Department of Neurology, and LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe University Frankfurt, Frankfurt am Main; Department of Neurology, Epilepsy Center Hessen, Philipps University, Marburg, Germany	Drafting/revision of the article for content, including medical writing for content
Katja Menzler, MD	Department of Neurology, Epilepsy Center Hessen, Philipps University, Marburg, Germany	Drafting/revision of the article for content, including medical writing for content
Rita Garbelli, PhD	Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy;	Drafting/revision of the article for content, including medical writing for content
Francesco Deleo, MD	Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy;	Drafting/revision of the article for content, including medical writing for content
Pavel Krsek, MD, PhD	Department of Pediatric Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic	Drafting/revision of the article for content, including medical writing for content
Barbora Straka, MD, PhD	Department of Pediatric Neurology, Motol Epilepsy Center, Second Medical Faculty, Charles University, Motol University Hospital, Prague, Czech Republic	Drafting/revision of the article for content, including medical writing for content
Alexis A. Arzimanoglou, MD, PhD	Department of Pediatric Clinical Epileptology, Sleep Disorders and Functional Neurology; University Hospitals of Lyon (HCL), Lyon, France; Paediatric Epilepsy Unit, Child Neurology Department and Neurosurgery Department, Hospital Sant Joan de Déu, Barcelona, Spain	Drafting/revision of the article for content, including medical writing for content
Joseph Toulouse, MD	Department of Pediatric Clinical Epileptology, Sleep Disorders and Functional Neurology; University Hospitals of Lyon (HCL), Lyon, France	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Wim Van Paesschen, MD, PhD	Department of Neurology, University Hospital Leuven, Belgium	Drafting/revision of the article for content, including medical writing for content
Tom Theys, MD, PhD	Department of Neurosurgery, University Hospital Leuven, Belgium	Drafting/revision of the article for content, including medical writing for content
José Pimentel, MD, PhD	Laboratory of Neuropathology, Department of Neurosciences and Mental Health, Department of Neurology, Hospital de Santa Maria (CHULN), Lisbon, Portugal	Drafting/revision of the article for content, including medical writing for content
Isabel M. Loução De Amorim, MD	Laboratory of Neuropathology, Department of Neurosciences and Mental Health, Department of Neurology, Hospital de Santa Maria (CHULN), Lisbon, Portugal	Drafting/revision of the article for content, including medical writing for content
Nicola Specchio, MD, PhD	Clinical and Experimental Neurology, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content
Luca De Palma, MD	Clinical and Experimental Neurology, Bambino Gesu' Children's Hospital, IRCCS, Rome, Italy	Drafting/revision of the article for content, including medical writing for content
Martha Feucht, MD, PhD	Center for Rare and Complex Epilepsies, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria	Drafting/revision of the article for content, including medical writing for content
Theresa Scholl, MD, PhD	Center for Rare and Complex Epilepsies, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria	Drafting/revision of the article for content, including medical writing for content
Karl Roessler, MD, PhD	Department of Neurosurgery, Medical University of Vienna, Austria	Drafting/revision of the article for content, including medical writing for content
Rafael Toledano Delgado, MD	Epilepsy Program, Hospital Ruber Internacional, Madrid, Spain	Drafting/revision of the article for content, including medical writing for content

Appendix *(continued)*

Name	Location	Contribution
Antonio Gil-Nagel, MD, PhD	;Epilepsy Program, Hospital Ruber Internacional, Madrid, Spain	Drafting/revision of the article for content, including medical writing for content
Savo Raicevic, MD, PhD	Laboratory for neuropathology, Department of pathology, Clinical Centre of Serbia, Belgrade	Drafting/revision of the article for content, including medical writing for content
Aleksandar J. Ristic, MD, PhD	Department for Epilepsy, Clinic of Neurology; Medical Faculty, University of Belgrade, Serbia	Drafting/revision of the article for content, including medical writing for content
Olaf Schijns, MD, PhD	Department of Neurosurgery, Academic Center for Epileptology, Maastricht University Medical Center, The Netherlands	Drafting/revision of the article for content, including medical writing for content
Jan Beckervordersandforth, MD, PhD	Department of Pathology, Maastricht University Medical Center, The Netherlands	Drafting/revision of the article for content, including medical writing for content
Victoria San Antonio-Arce, MD, PhD	Paediatric Epilepsy Unit, Child Neurology Department and Neurosurgery Department, Hospital Sant Joan de Déu, Barcelona, Spain	Drafting/revision of the article for content, including medical writing for content
Jordi Rumia, MD, PhD	Paediatric Epilepsy Unit, Child Neurology Department and Neurosurgery Department, Hospital Sant Joan de Déu, Barcelona, Spain	Drafting/revision of the article for content, including medical writing for content
Ingmar Blumcke, MD, PhD	University Hospital Erlangen, Neuropathology, Germany	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Kees P. Braun, MD, PhD	Child Neurology, University Medical Center Utrecht, The Netherlands	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Lamberink HJ, Otte WM, Blümcke I, et al. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet Neurol.* 2020;19(9):748-757. doi:10.1016/S1474-4422(20)30220-9
2. West S, Nolan SJ, Cotton J, et al. Surgery for epilepsy. *Cochrane Database Syst Rev.* 2015(7):CD010541. doi:10.1002/14651858.CD010541.pub2
3. Cuello Oderiz C, von Ellenrieder N, Dubeau F, et al. Association of cortical stimulation-induced seizure with surgical outcome in patients with focal drug-resistant epilepsy. *JAMA Neurol.* 2019;76(9):1070-1078. doi:10.1001/jamaneurol.2019.1464
4. Wang X, Zhang C, Wang Y, et al. Prognostic factors for seizure outcome in patients with MRI-negative temporal lobe epilepsy: a meta-analysis and systematic review. *Seizure*. 2016;38:54-62. doi:10.1016/j.seizure.2016.04.002
5. So EL, Lee RW. Epilepsy surgery in MRI-negative epilepsies. *Curr Opin Neurol.* 2014;27(2):206-212. doi:10.1097/WCO.0000000000000078
6. Stevelink R, Sanders MW, Tuinman MP, et al. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review. *Epileptic Disord.* 2018;20(2):99-115. doi:10.1684/epd.2018.0959
7. Helbig I, Tayoun AAN. Understanding genotypes and phenotypes in epileptic encephalopathies. *Mol Syndromol.* 2016;7(4):172-181. doi:10.1159/000448530
8. Blumcke I, Spreafico R, Haaker G, et al. Histopathological findings in brain tissue obtained during epilepsy surgery. *N Engl J Med.* 2017;377(17):1648-1656. doi:10.1056/NEJMoa1703784
9. Benedetti-Isaac JC, Torres-Zambrano M, Fandiño-Franky J, et al. Long-term surgical outcomes in patients with drug-resistant temporal lobe epilepsy and no histological abnormalities. *Neurologia*. 2013;28(9):543-549. doi:10.1016/j.nrl.2013.01.011
10. Arya R, Leach JL, Horn PS, et al. Clinical factors predict surgical outcomes in pediatric MRI-negative drug-resistant epilepsy. *Seizure*. 2016;41:56-61. doi:10.1016/j.seizure.2016.07.004
11. Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. *Arch Neurol.* 2009;66(12):1491-1499. doi:10.1001/archneurol.2009.283
12. Siegel AM, Jobst BC, Thadani VM, et al. Medically intractable, localization-related epilepsy with normal MRI: presurgical evaluation and surgical outcome in 43 patients. *Epilepsia*. 2001;42(7):883-888. doi:10.1046/j.1528-1157.2001.042007883.x
13. Engel J Jr, van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies*, 2nd ed. Raven Press; 1993:609-621.
14. Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res.* 2010;89(2-3):310-318. doi:10.1016/j.eplepsyres.2010.02.007
15. Lee SK, Kim DW. Focal cortical dysplasia and epilepsy surgery. *J Epilepsy Res.* 2013;3(2):43-47. doi:10.14581/jer.13009
16. Jayakar P, Dunoyer C, Dean P, et al. Epilepsy surgery in patients with normal or nonfocal MRI scans: integrative strategies offer long-term seizure relief. *Epilepsia*. 2008;49(5):758-764. doi:10.1111/j.1528-1167.2007.01428.x
17. Ivanovic J, Larsson PG, Østby Y, et al. Seizure outcomes of temporal lobe epilepsy surgery in patients with normal MRI and without specific histopathology. *Acta Neurochir (Wien)*. 2017;159(5):757-766. doi:10.1007/s00701-017-3127-y
18. Barba C, Rheims S, Minotti L, et al. Surgical outcome of temporal plus epilepsy is improved by multilobar resection. *Epilepsia*. 2022;63(4):769-776. doi:10.1111/epi.17185
19. Sanders MWCB, Lemmens CMC, Jansen FE, et al. Implications of genetic diagnostics in epilepsy surgery candidates: a single-center cohort study. *Epilepsia Open.* 2019;4(4):609-617. doi:10.1002/epi4.12366