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The pathology of magnetic-resonance-imaging-negative epilepsy

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Patients with magnetic-resonance-imaging (MRI)-negative (or 'nonlesional') pharmacoresistant focal epilepsy are the most challenging group undergoing presurgical evaluation. Few large-scale studies have systematically reviewed the pathological substrates underlying MRI-negative epilepsies. In the current study, histopathological specimens were retrospectively reviewed from MRI-negative epilepsy patients ($n=95$, mean age = 30 years, 50% female subjects). Focal cortical dysplasia cases were classified according to the International League Against Epilepsy (ILAE) and Palmini *et al* classifications. The most common pathologies found in this MRI-negative cohort included: focal cortical dysplasia ($n=43$, 45%), gliosis ($n=21$, 22%), hamartia + gliosis ($n=12$, 13%), and hippocampal sclerosis ($n=9$, 9%). The majority of focal cortical dysplasia were ILAE type I ($n=37$) or Palmini type I ($n=39$). Seven patients had no identifiable pathological abnormalities. The existence of positive pathology was not significantly associated with age or temporal/extratemporal resection. Follow-up data post surgery was available in 90 patients; 63 (70%) and 57 (63%) attained seizure freedom at 6 and 12 months, respectively. The finding of positive pathology was significantly associated with seizure-free outcome at 6 months ($P=0.035$), but not at 12 months. In subgroup analysis, the focal cortical dysplasia group was not significantly correlated with seizure-free outcome, as compared with the negative-pathology groups at either 6 or 12 months. Of note, the finding of hippocampal sclerosis had a significant positive correlation with seizure-free outcome when compared with the negative-pathology group ($P=0.009$ and 0.004 for 6- and 12-month outcome, respectively). Absence of a significant histopathology in the resected surgical specimen did not preclude seizure freedom. In conclusion, our study highlights the heterogeneity of epileptic pathologies in MRI-negative epilepsies, with focal cortical dysplasia being the most common finding. The existence of positive pathology in surgical specimen may be a good indication for short-term good seizure outcome. There is a small subset of cases in which no pathological abnormalities are identified.
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Patients with magnetic-resonance-imaging (MRI)-negative (or 'nonlesional') pharmacoresistant focal epilepsy constitute the most challenging group undergoing presurgical evaluation.[1–3] The overall prevalence of nonlesional epilepsy in all surgical studies is ~26%.[4] At present, surgical management of MRI-negative pharmacoresistant focal epilepsy patients relies heavily on invasive intracranial electroencephalography, which is based on complimentary review of other noninvasive modalities including positron emission tomography, ictal single-photon emission computed tomography, and magnetoencephalography when available.[5–8] Despite substantial efforts, the lack of a lesion on MRI has consistently been shown to be one of the predictors for surgical failure.[9,10] Therefore, MRI-negative patients are usually considered unfavorable surgical candidates[4] and are often denied epilepsy surgery. Yet, surgical resection can be effective in well-selected patients with no visible MRI abnormality. In order to improve surgical outcome of MRI-negative patients, it is important to understand the pathologies that these patients may demonstrate on examining their surgically resected tissues.

The pathologic substrates underlying pharmacoresistant focal epilepsy are well established and most

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commonly include hippocampal sclerosis, focal cortical dysplasia, tumors, and remote ischemic events/infarcts.[11,12] Studies specifically on the surgical pathology of MRI-negative patients, however, are limited to small-scale experiences of individual centers,[13–16] or cases buried in larger series containing both MRI-positive and -negative patients.[17,18] Moreover, with the advance in MRI technology over the last decade and the establishment of more uniform epilepsy MRI protocols, the definition of 'MRI-negative' cases in recent studies may not be equivalent to earlier ones. The purpose of this study is to systematically review one institution's recent experience with the pathological substrates underlying strictly defined MRI-negative epilepsies.

Materials and methods

After approval from Institutional Review Board, the Cleveland Clinic Epilepsy Center's surgical database was searched for patients with chronic epilepsy who underwent a surgical resection from 2002 to 2011. During this period, all patients underwent high-resolution 1.5- or 3-Tesla preoperative MRI studies using a standard epilepsy protocol. From this group, we selected patients with strictly defined negative MRI based on two criteria: (1) all MRI scans were evaluated prospectively by dedicated epilepsy neuroradiologists for possible epileptogenic abnormalities during the presurgical evaluation process and showed no lesions and (2) MRI scans were evaluated again by epileptologists, neurosurgeons, and dedicated epilepsy neuroradiologists after re-review of images during the patient management conference, taking into account the results of comprehensive noninvasive testing, and were still judged to be negative. Patients with MRIs that were initially interpreted as normal were excluded if a probable or questionable lesion was identified during re-review of the study in the patient management conference. Patients were excluded if they had poor MRI image quality, for example, motion artifacts hampering image interpretation. Patients with prior surgeries were excluded.

Available microscopic slides from surgical resections were reviewed in all cases (mean = 7, range = 1–20). In 40 cases, all the resected tissues were submitted and reviewed microscopically; a subtotal sampling of resected tissue was done in the remaining 55 cases. Focal cortical dysplasia was classified according to both the International League Against Epilepsy (ILAE) classification[19] as well as Palmini *et al*[20] classification; classification criteria are described in Table 1. Hippocampal sclerosis was defined by a characteristic loss of neurons and gliosis in the hippocampus, preferentially involving the dentate, CA4, CA3, and CA1 regions.[21] Hamartias were defined as collections of small neurons marked by scant cytoplasm and pericellular clearing.[22] Nodular heterotopia is marked by the presence of disordered gray matter tissue in the white matter. Positive pathology is defined by the finding of focal cortical dysplasia, heterotopia, hippocampal sclerosis, other hippocampal abnormalities, and dual osseous metaplasia. Negative pathology is defined by the finding of gliosis only, gliosis with hamartia, or no microscopic abnormality identified.

Based on location of surgical site, resections were classified as frontal, parieto-occipital, neocortical temporal, standard temporal lobectomies with removal of mesial temporal structures, and multilobar resections. We analyzed the outcome at 6 and 12 months. Outcome was classified into two groups: completely seizure-free (Engel's class Ia) and not seizure-free (Engel's class Ib–IV).[23] Statistical significance was assessed using the Fisher's exact test, with significance defined as a probability (P) value of ≤ 0.05.

Table 1 Classification of focal cortical dysplasia for the current study using ILAE classification[19] and a variation of Palmini *et al*[20] classification

FCD type	*Criteria*
ILAE Ia	Isolated lesions presenting as radial dyslamination of neocortex
ILAE Ib	Isolated lesions presenting as tangential dyslamination of neocortex
ILAE Ic	Isolated lesions presenting as both radial and tangential dyslamination
ILAE IIa	Isolated lesion characterized by cortical dyslamination and dysmorphic neurons without balloon cells
ILAE IIb	Isolated lesion characterized by cortical dyslamination and dysmorphic neurons with balloon cells
ILAE IIIa	Occurs in combination with hippocampal sclerosis
ILAE IIIb	Occurs with epilepsy-associated tumors
ILAE IIIc	Adjacent to vascular malformations
ILAE IIId	In association with epileptogenic lesions acquired in early life (ie, traumatic injury, ischemic injury, or encephalitis)
Palmini IA	Isolated architectural abnormalities (dyslamination, accompanied or not by other abnormalities of mild malformation of cortical development, or malformation of cortical development)
Palmini IB	Architectural abnormalities, plus giant or immature, but not dysmorphic, neurons
Palmini IIA	Architectural abnormalities with dysmorphic neurons but without balloon cells
Palmini IIB	Architectural abnormalities with dysmorphic neurons and balloon cells

Abbreviation: ILAE, International League Against Epilepsy.

Table 2 Summary of pathological findings

Pathology	n *(%)*
Focal cortical dysplasia	
ILAE Ib	9 (9)
ILAE Ic	28 (30)
ILAE IIb	4 (4)
ILAE IIIa	2 (2)
Palmini IA	26 (27)
Palmini IA + hippocampal sclerosis	2 (2)
Palmini IA + Nodular heterotopia	2 (2)
Palmini IB	9 (9)
Palmini IIB	4 (4)
Total	43 (45)
Gliosis only	21 (22)
Hamartia + gliosis	12 (13)
Hippocampal sclerosis only	9 (9)
No pathology identified	7 (7)
Dual osseous metaplasia	1 (1)
Hippocampal neuronal loss	1 (1)
Granular cell dispersion in hippocampus	1 (1)
Total	*95*

Abbreviation: ILAE, International League Against Epilepsy.

Results

Patient Demographics

A total of 95 patients (median/mean age = 29/30 years, range 4–64 years; 50% female subjects) fulfilled the selection criteria. Histological slides were available in all patients. Surgery included 21 frontal resections, 6 parieto-occipital resections, 34 neocortical temporal resections, 32 standard temporal lobectomies with removal of mesial structures, and 2 multilobar resections. Left-sided resections were performed in 49 (52%) patients.

Pathological Findings

Table 2 summarizes the pathological findings observed in this MRI-negative cohort. The most commonly identified pathology was focal cortical dysplasia ($n = 43$, including 2 coexisting with hippocampal sclerosis and 2 with nodular heterotopia). A majority of cortical dysplasias were ILAE type I ($n = 37$), with the majority being Ic ($n = 28$); using Palmini classification, the majority were type I as well ($n = 39$), with type IA being most common ($n = 30$). Examples of ILAE type Ic (Palmini type IA) and Ib (Palmini type IB) are shown in Figures 1 and 2, respectively. Two patients had nodular heterotopia in addition to focal cortical dysplasia (Figure 3). Nine patients had hippocampal sclerosis alone (Figure 4). Twenty-one patients only had gliosis, and an additional 12 patients showed gliosis accompanied by hamartia (Figure 5). In seven patients, no microscopic abnormality was identified.

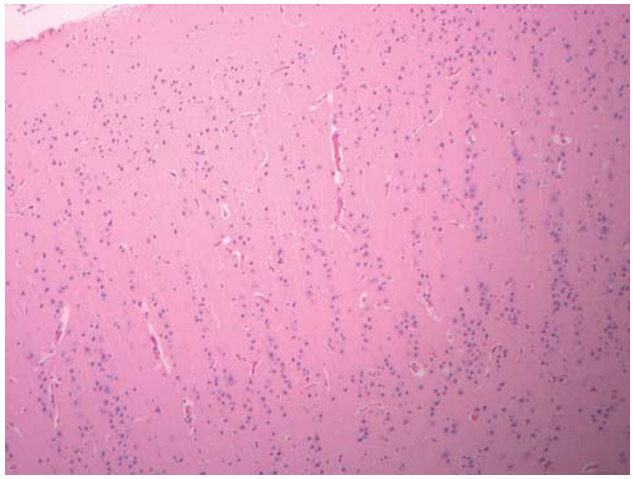

Figure 1 Low-magnification view of the cortex showing a linear arrangement of neurons in central layers 2 and 3, consistent with ILAE type Ic focal cortical dysplasia (Palmini *et al*[20] type IA). (Hematoxylin and eosin staining; original magnification × 100.)

Overall, 12/19 (63%) children (17 years or younger) had positive pathology, compared with 43/76 (57%) adults. No difference in positive pathology was noted between these two age groups ($P = 0.8$). Twenty-one of the 29 (72%) extratemporal lobe epilepsy patients had positive pathology compared with 34/66 (52%) of patients with temporal lobe epilepsy. The finding of positive pathology was not significantly associated with temporal/extratemporal lobe epilepsy groups ($P = 0.07$). Seventeen of the 55 (31%) subtotally submitted specimens had negative pathology; 23/40 (58%) of totally submitted specimens had negative pathology.

Correlation With Outcome

Follow-up data were available in 90 patients. Outcome data grouped by pathology are shown in Table 3. At 6 months' follow-up, 63 (ie, 70% of the entire cohort) attained seizure freedom (Engel class Ia). Overall, 42 of the 53 (79%) patients with positive pathology, and 21 of the 37 (57%) patients with negative pathology were seizure-free. The finding of positive pathology was significantly associated with seizure-free outcome ($P = 0.035$). We further performed subgroup analysis. Although focal cortical dysplasia constituted the largest group of seizure-free patients (30/63, 48%), there was no significant correlation between the existence of focal cortical dysplasia in surgical specimen and seizure-free outcome, as compared with the negative-pathology group ($P = 0.16$) or gliosis alone ($P = 0.09$). Of note, the finding of hippocampal sclerosis (including nine hippocampal sclerosis only, and two hippocampal sclerosis + focal cortical dysplasia) had a significant positive correlation with seizure-free outcome when compared with the negative-pathology group ($P = 0.009$). The ILAE Ib group trended towards being positively associated

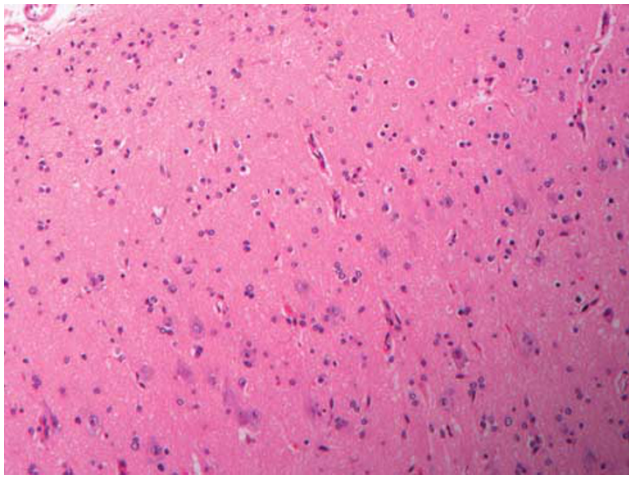

Figure 2 Intermediate magnification view of the cortex showing an absence of a well-formed cortical layer 2 and neuronal cytomegaly, consistent with ILAE type Ib focal cortical dysplasia (Palmini *et al*[20] type IB). (Hematoxylin and eosin staining; original magnification × 200.)

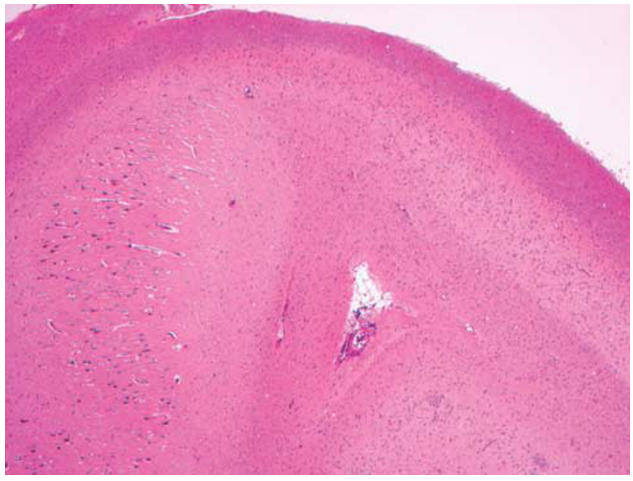

Figure 4 Low magnification appearance of hippocampal sclerosis marked by permanent neuronal loss and gliosis (upper right) in the CA1 region. (Hematoxylin and eosin staining; original magnification × 50.)

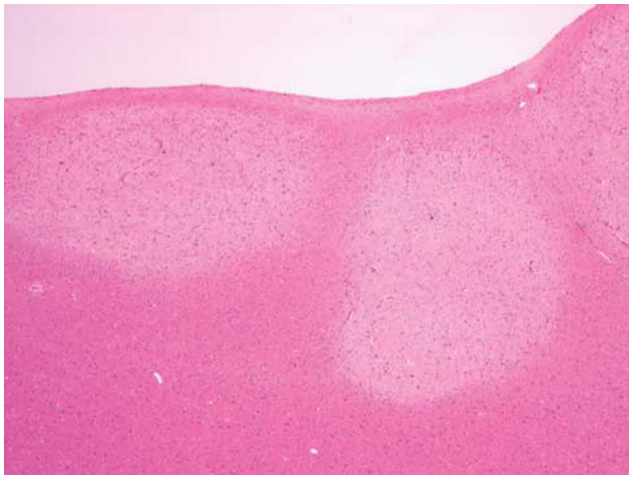

Figure 3 Low magnification view of multiple periventricular nodular heterotopia, which were associated with an overlying focal cortical dysplasia. (Hematoxylin and eosin staining; original magnification × 50.)

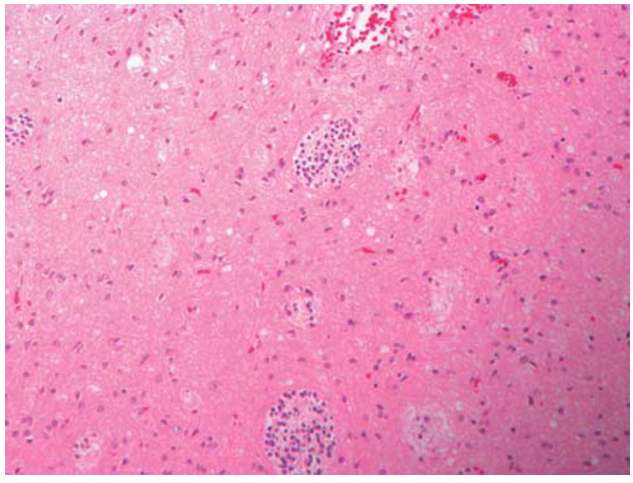

Figure 5 Intermediate magnification view showing clustered collections of small neurons (hamartia) and gliosis. (Hematoxylin and eosin staining; original magnification × 200.)

with seizure-free outcome when compared with the gliosis only plus no-identifiable-pathology group ($P = 0.06$), but did not reach statistical significance. In the group where no pathology was identified, four out of the seven patients were seizure-free.

At 12-month follow-up, 57 (63%) were completely seizure-free (Engel class Ia outcome). Overall, 37 of the 53 (70%) patients with positive pathology, and 20 of the 37 (54%) patients with negative pathology were seizure-free. Different from the 6-month follow-up data, the finding of positive pathology was *not* significantly associated with seizure-free outcome 12 months after surgical resection ($P = 0.18$). Other data trends are similar to the 6-month-outcome data. Patients with focal cortical dysplasia were still more likely to attain seizure-free outcome (27/57, 47%), but there was no significant correlation between the existence of focal cortical dysplasia in surgical specimen and seizure-free outcome, as compared with the negative-pathology group ($P = 0.35$) or gliosis alone ($P = 0.27$). The finding of hippocampal sclerosis still had a significant positive correlation with seizure-free outcome at 12 months when compared with the negative-pathology group ($P = 0.004$). The ILAE Ib group trended toward being positively associated with seizure-free outcome when compared with the Ic group ($P = 0.056$) and the gliosis plus no-identifiable-pathology group ($P = 0.06$), but did not reach statistical significance for either. Four out of the seven patients with no-identifiable pathology remained seizure-free at 12 months.

Table 3 Relationship between pathology findings and surgical outcome in 90 patients at 6- and 12-month follow-up

Pathology	*Outcome at 6 months*		*Outcome at 12 months*	
	Engel's class Ia	*Engel's class Ib–IV*	*Engel's class Ia*	*Engel's class Ib–IV*
Focal cortical dysplasia				
ILAE Ib	8	1	8	1
ILAE Ic	16	10	13	13
ILAE IIb	4	0	4	0
ILAE IIIa	2	0	2	0
Palmini IA	16	9	13	12
Palmini IA + nodular heterotopia	2	0	2	0
Palmini IA + hippocampal sclerosis	2	0	2	0
Palmini IB	6	2	6	2
Palmini IIB	4	0	4	0
Gliosis only	10	10	10	10
Hamartia + gliosis	7	3	6	4
Hippocampal sclerosis only	9	0	8	1
No pathology identified	4	3	4	3
Dual osseous metaplasia	1	0	0	1
Hippocampal neuronal loss	1	0	1	0
Granular cell dispersion in hippocampus	1	0	1	0
Total = 90	*63*	*27*	*57*	*33*

Abbreviation: ILAE, International League Against Epilepsy.

Discussion

We present the pathologic results of a large single-center series of 95 patients with strictly defined MRI-negative focal epilepsy who underwent epilepsy surgery. Consistent with previous studies, our data show that focal cortical dysplasia is the most common pathological substrate of surgically treated nonlesional epilepsy. In addition, our results show that the presence of positive pathology is significantly associated with early seizure-free outcome. There was no significant correlation between the existence of focal cortical dysplasia in surgical specimens and seizure-free outcome, as compared with the negative-pathology groups in either 6- or 12 months' outcome data. Of note, the finding of hippocampal sclerosis had a significant positive correlation with seizure-free outcome, when compared with the negative-pathology group. Absence of a significant histopathology in the resected surgical specimen did not preclude seizure freedom.

Limitations of the previous literature examining pathological substrates of nonlesional epilepsy include: small number of patients, variable definitions of 'nonlesional', and variable approaches to pathological diagnosis. Pathological findings are typically reported in small-scale studies from individual centers,[13–16] or buried in larger series containing a full spectrum of patients among which only a small number was MRI-negative.[17,18] A few attempts at meta-analysis have been performed to better understand surgical outcome and factors such as pathology, surgery type, and seizure semiology in MRI-negative patients. Ansari *et al*[24] reported 95 pediatric extratemporal nonlesional epilepsy patients from 17 studies, and classified surgical pathology into three categories: cortical dysplasia, gliosis, and others (neuronal loss, encephalitis, polymicrogyria, ulegyria, chronic inflammation, and normal). Their analysis demonstrated that a positive histopathological finding has a favorable association with postoperative outcome: a majority of patients in the Engel class I outcome group harbored cortical dysplasia. In a parallel study, Ansari *et al*[25] reported on 131 adult patients with extratemporal nonlesional epilepsy and found that none of the variables, including surgical pathology, had any significant association with outcome in the adult group. This study also found focal cortical dysplasia to be the most common substrate in patients with seizure-free outcome. Both meta-analysis studies defined 'nonlesional' epilepsies based on pathological substrates, whereas only mass-like lesions such as tumors, vascular lesions, multiple sclerosis, and heterotopias were considered 'lesional', and focal cortical dysplasia was considered 'nonlesional'. From a practical, presurgical evaluation point of view, however, MRI findings are generally used to define a case as 'nonlesional'. In our study, we only included patients with negative MRI based on consensus review of high-resolution MRI studies during a multidisciplinary patient management conference, in addition to an independent neuroradiology interpretation. This approach ensured the inclusion of a highly selected group of patients with negative MRI findings who underwent surgical resection of identified epileptic foci, followed by a blinded neuropathological examination of the resected specimens.

The high incidence of various focal cortical dysplasia types in the current study supports that the most common epileptic pathological correlate not visualized by MRI was indeed focal cortical dysplasia. These results are concordant with previous reports that showed that cortical dysplasia was identified in up to one-third of tissue specimens, following resective epilepsy surgery in both MRI-positive and -negative cases.[24–27] Among the focal cortical dysplasia subtypes, our data also show that focal cortical dysplasia type I (by either classification) is the most common substrate of MRI-negative epilepsy. There were only four cases of balloon cell cortical dysplasia. The higher prevalence of type I lesions than type II further illustrates the challenging nature of presurgical identification and mapping of this pathology, and highlights the need for more sensitive and accurate

presurgical studies. Focal cortical dysplasia type I lesions have highly idiosyncratic presentations and are usually more diffuse than type II lesions, making them the most challenging ones to be detected by structural imaging methodology.[28–30] In addition to the accurate definition, delineation of the boundaries of type I focal cortical dysplasia is also difficult, as the microscopically dysplastic lesion may extend well beyond the margins defined by the MRI-visible abnormality (in MRI-positive cases),[30–32] even with the use of high-resolution dedicated epilepsy MRI protocols and review of the images by expert neuroradiologists.[26,32] Our finding of MRI-negative patients with hippocampal sclerosis is also consistent with previous literature that up to 30% of patients with hippocampal sclerosis may have normal findings on conventional MRI.[33]

Surgical outcome of MRI-negative patients can be hard to determine due to heterogeneity of patient populations, surgical techniques, follow-up time, and outcome definition in the literature. A recent meta-analysis showed only 34–45% long-term seizure-free rate, whereas MRI-positive (or 'lesional') surgical candidates may have a two times higher probability of attaining seizure freedom.[4] Our MRI-negative cohort (comprised of temporal and extratemporal cases) had seizure-free rate of 59% at 12 months, this percentage is consistent with other studies from our center and can be anticipated to drop as follow-up durations increase.[10,34,35] Overall, we found that positive pathology in surgical specimen positively associated with seizure-free outcome at 6 months, but not at 12 months. This finding is consistent with the hypothesis that immediate postoperative seizure recurrence may indicate a mislocalization and/or incomplete resection of the active epileptic focus, whereas long-term recurrence may be attributed to other factors such as the natural history of the disease and the postsurgical development of secondary epileptogenesis.[36] Subgroup analysis revealed that focal cortical dysplasia did not positively correlate with seizure-free outcome, as the cortical dysplasia type I pathology (majority of the group) is generally more widespread, and often involves eloquent cortex in extratemporal cases, making it less amenable to resection. On the other hand, MRI-negative patients with hippocampal sclerosis appeared to have a better chance for seizure-free outcome, as these lesions are relatively more circumscribed, and temporal lobectomy with complete removal of the epileptic and histopathologically abnormal mesial structures is usually an effective approach.

In a subset of patients in the current study, no pathologic substrate was identified. One possible explanation is a presurgical mislocalization. In a recent study from our center,[37] patients with multiple surgeries were examined in terms of their pathology: three of the 13 patients had no pathology on the first surgery, but focal cortical dysplasia was pathologically identified on the second surgery. Similarly, false localization could explain the pathological findings in patients with gliosis or no-identifiable pathology who were not seizure-free in this study. It is even more intriguing to speculate on the four patients who became seizure-free, but had no-identifiable pathology. Notably, with three of these four patients, resected tissue was totally submitted and examined. A number of possible explanations may include: evolving pathology due to neural plasticity and ongoing development of cortex[38,39] (given we could only sample surgically at one point of time), alterations at a neurotransmitter and/or neuromodulator level, mitochondrial level,[40] genetics level,[41,42] or neurogenesis level.[43,44]

One limitation of our study is the subtotal sampling of some specimens, which potentially could result in an underestimation of the epileptic pathologies. Another limitation is that we evaluated the relationship between pathology and outcome without the full consideration of the location and extent of resection. Patients who showed nonspecific gliosis or no-identifiable pathology may have focal cortical dysplasia pathology in an unresected lobe of the brain.

In conclusion, our study highlights the heterogeneity of epileptic pathologies in MRI-negative epilepsies, with focal cortical dysplasia being the most common finding. The existence of positive pathology in surgical specimen may be a good indication for short-term good seizure outcome, but does not necessarily predict long-term seizure freedom.

The subset of patients without any pathological findings is intriguing, and may indicate limitations of microscopic histopathological examination of resected human epileptic tissue, mislocalization/inadequate resection, or incomplete histopathological sampling of the resected specimens. Advanced imaging and neurophysiological modalities, invasive or noninvasive, are called for to adequately delineate the anatomical, functional, and epileptic extent of these lesions.

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Disclosure/conflict of interest

Andreas V Alexopoulos serves on the editorial board of *Epileptic Disorders*, and has received research support from UCB, Pfizer Inc, and from the American Epilepsy Society. Imad M Najm is on the Speakers' Bureau of UCB Inc and receives research funding from the US Department of Defense. The remaining authors declare no conflict of interest.

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