Characteristics and Surgical Outcomes of Patients With Refractory Magnetic Resonance Imaging–Negative Epilepsies

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Objective: To explore several characteristics of patients with pharmacoresistant epilepsy without distinct lesions on magnetic resonance images (MRI$^-$), who account for a relevant proportion of presurgical patient cohorts.

Design: Retrospective case series.

Setting: University epilepsy center.

Patients: A cohort of 1200 patients who had comprehensive presurgical assessment from January 1, 2000, through December 31, 2006.

Main Outcome Measures: Frequency of MRI$^-$ patients in the total presurgical cohort, seizure-free outcome rates in patients who had surgery and those who did not, outcome predictors, and spatial properties of epileptogenic areas in MRI$^-$ patients with epilepsy. All MRI$^-$ patients were retrospectively analyzed. Presurgical MRIs were reevaluated for subtle cortical dysplasias by postprocessing and visual reassessment.

Results: One-hundred ninety MRI$^-$ patients were identified (16% of all presurgical candidates); 29 (15%) had surgery. Eleven (38%) became seizure free (including those with auras only; 45%). Surgical therapy was more frequently offered to MRI$^+$ patients (76%; $P<.001$), and their outcome was also superior (66% seizure-free; $P=.001$). The seizure-free rate of 16% in MRI$^-$ patients who did not have surgery was, however, inferior to that of the MRI$^-$ patients who did ($P=.008$). Nine MRI$^-$ patients who had surgery had distinct histopathological lesions, 8 of which turned out to be retrospectively detectable on presurgical MRI. Seven of the MRI$^-$ but histopathologically lesional patients became seizure free compared with only 4 of 20 patients without histopathological lesions ($P=.003$). Three-fifths of the histopathologically nonlesional patients had multifocal or extensive epileptogenic areas.

Conclusions: Patients with epilepsy who are MRI$^-$ can be successfully treated with surgery. Improved sensitivity of MRI will improve the outcomes of presurgically studied patients. Surgical failures in patients without histopathological lesions mostly result from extensive epileptogenic areas.

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THE RATE OF SUCCESSFUL resective surgery in patients with intractable focal epilepsy has been increasing during the last decades.[1,2] This is particularly owing to improved brain magnetic resonance imaging (MRI) acquisition and interpretation during presurgical assessment.[3] Resectable epileptogenic brain abnormalities have not only become detectable (like Ammon's horn sclerosis [AHS]); in addition, their extension can be more precisely estimated when the resection is planned (as with cortical dysplasias).[4-6] There are, however, still a proportion of patients seeking presurgical evaluation whose MRIs are not considered to show a lesion potentially causative of chronic epilepsy (referred to hereafter as MRI$^-$). These patients have impaired treatment options. Compared with patients with typically epileptogenic structural abnormalities visible on MRI (MRI$^+$ patients), MRI$^-$ patients are less often offered epilepsy surgery,[7] and if operations are done, they have an inferior seizure-free outcome.[7-16] Despite improving MRI technique, MRI$^-$ patients account for 18% to 43% of presurgically studied patients with epilepsy.[7,14,16,17] They can be subdivided into those with distinct epileptogenic lesions on histopathological investigation (histo$^+$ patients) and those without such lesions (histo$^-$ patients).[8-11,13-17] Little is known as to why epileptogenic lesions are not always detected by preoperative MRI and what the epileptological characteristics of the histo$^-$ patients are. To elucidate these 2 points, we analyzed our presurgically studied cohort of MRI$^-$ pharmacoresistant patients with epilepsy. The ultimate goal was to explain surgical successes and failures, identify outcome predictors, and draw conclusions about the spatial properties of epileptogenic areas in MRI$^-$ patients.

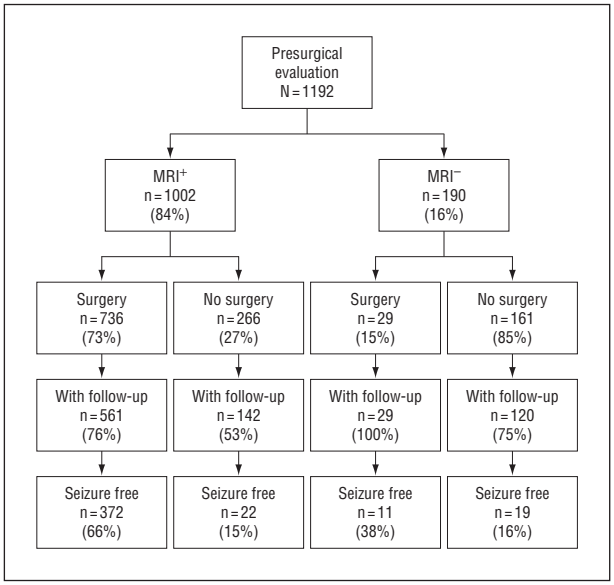

Figure 1. Overview of all presurgically evaluated patients and their outcomes (excluding 8 patients who had callosotomy or pure multiple subpial transections). Percentages are related to the respective total patient numbers. MRI$^+$ indicates magnetic resonance imaging positive (ie, MRI shows a typically epileptogenic lesion); MRI$^-$, MRI negative. Of the 18 MRI$^-$ patients who had surgery and were not totally seizure free, 2 had only auras. Thus, 13 of 29 patients (45%) were seizure free or had auras only.

METHODS

PATIENT SELECTION AND MRI PROTOCOL

From the prospective database of patients having comprehensive presurgical evaluation for intractable focal epilepsy at Bonn epilepsy center, we identified 1200 patients studied between January 1, 2000, and December 31, 2006.[18] We selected all patients who were diagnosed as MRI$^-$. During presurgical evaluation, their MRIs were visually interpreted by experienced neuroradiologists and their findings had been described either as normal or exhibiting abnormalities that are not considered epileptogenic. Patients with the MRI signs of AHS, tumor, malformation of cortical development, vascular malformation, posttraumatic lesions, infarction or bleeding residua, or encephalitis were regarded as MRI$^+$. Magnetic resonance imaging was performed on 1.5-T or, since 2005, 3-T systems (Gyroscan ACS-NT, Gyroscan NT-Intera, Gyroscan Intera, Gyroscan 3 T Intera, or Gyroscan 3T Achieva; Philips Medical Systems, Best, the Netherlands) according to an epilepsy protocol that has been described previously.[6] The MRI$^-$ patients who ultimately had epilepsy surgery formed the core group of this study. The following procedures were performed: standard anteromedial temporal lobe resections, tailored temporal lobe resections (taking into consideration individual results from intracranial electroencephalographic [EEG] recordings), selective amygdalohippocampectomies, and extratemporal focal resections, multilobar resections, or functional hemispherectomies. As outcome comparators, we used all MRI$^-$ patients who did not have resective surgery and all MRI$^+$ patients (subdivided into surgical and nonsurgical patients). All controls came from the same study period. Nonresective surgery, in terms of callosotomy or pure multiple subpial transections, was done in 5 MRI$^-$ and 3 MRI$^+$ cases. They were excluded from analysis, leaving a total of 1192 patients as the basic study population.

ASSESSMENT OF PRESURGICAL AND OUTCOME DATA

Patients' history, seizure semiology, and EEG data were obtained from hospital files and from original recordings if there were uncertainties. Fluorodeoxyglucose-positron emission tomographies as well as interictal and ictal single-photon emission computed tomographies (SPECT) were recorded and visually interpreted as part of the regular presurgical evaluation at the Department of Nuclear Medicine of the University of Bonn. In some cases, SPECT and MRI data were postprocessed during preoperative assessment using subtraction ictal SPECT coregistered with MRI (SISCOM).[19] Seizure outcome data were obtained from outpatient records of the Department of Epileptology. Patients who were MRI$^-$ and did not have follow-up studies were contacted by telephone. The follow-up period was defined as 1 week after surgery or presurgical assessment (in the patients who did not have surgery) until the last available follow-up. Seizure freedom was noted if the patient was free of all seizures including auras during the last year. Only patients with follow-ups more than 6 months later were considered. Whereas "not seizure free" was noted for all patients with ongoing seizures and follow-up of at least half a year, follow-up had to be more than 1 year to be considered seizure free; in patients with a seizure-free follow-up of less than 1 year, "no follow-up" was noted. This was done to avoid overestimation of transient postoperative seizure-free periods.

For the purposes of this study, presurgical MRI data obtained using Avanto 1.5 Tesla or Trio 3.0 Tesla systems (Siemens, Erlangen, Germany; if data from these systems were not available, 3-dimensional T1 data sets from one of the aforementioned Philips systems were used) were postprocessed for detection of subtle signs of focal cortical dysplasia (FCD) using a voxel-based, 3-dimensional, morphometric MRI analysis described elsewhere.[20,21] In short, this method is based on algorithms of the freely available software for statistical parametric mapping and on additional simple calculations and filters. From a high-resolution T1-weighted 3-dimensional MRI data set, 3 new feature maps were derived that characterize, compared with a normal database, 3 potential features of FCD: the abnormal extension of gray matter into white matter, blurring of the gray matter–white matter junction, and abnormal thickness of the cortical ribbon. Postprocessing was performed by J.W., who at this time was blinded to patients' data. Magnetic resonance images found to be suspicious for presence of FCD were visually reanalyzed by H.U. Postprocessing-negative MRIs were also reread by H.U. for abnormalities potentially overlooked at presurgical assessment. H.U. was not blinded to the patients' clinical and neuropathological data because he participated in the original clinical evaluation and follow-up of most patients.

Presurgical data, MRI postprocessing results and outcome details of the MRI$^-$ histo$^-$ patients were reviewed in detail to retrospectively provide a hypothesis regarding the spatial extent of their epileptogenic areas.[22]

STATISTICS

Two-sided Pearson χ^2 tests and t tests were applied as appropriate. $P < .05$ was considered significant.

RESULTS

Figure 1 shows the numbers of MRI$^+$ and MRI$^-$ patients, with the proportions of patients who had surgery and those who were ultimately seizure free. Demographic data, information on presurgical investigations, types of surgery, and follow-up of the groups are given

Table 1. Patient Data at Presurgical Assessment and Follow-up

	Patients, No. (%)						
	MRI⁻			MRI⁺			
	Resective Surgery (n=29)	No Surgery (n=161)	*P* Value[a]	Resective Surgery (n=736)	*P* Value[a]	No Surgery (n=266)	*P* Value[b]
Female patients	16 (55)	77 (48)	.64[c]	341 (46)	.35[c]	120 (45)	.63[c]
Mean (SD) age at onset of epilepsy, y	12 (9)	13 (10)	.53[d]	17 (15)	.002	16 (13)	<.001[d]
Range	2-31	0-48		0-69		0-61	
Mean (SD) age at operation/presurgical assessment, y	31 (12)	32 (11)	.49[d]	32 (16)	.04	35 (14)	<.001[d]
Range	9-60	12-70		0.5-74		4-68	
Temporal lobe surgery	22 (76)			516 (70)	.51[c]		
Small, selective amygdalohippocampectomy	4			310			
Large, temporal lobe resection (standard 2/3 or tailored)	18			206	<.001		
Extratemporal surgery	7 (24)			220 (30)	.51[c]		
Small, extratemporal focal resection	7			167			
Large, multilobar resection/ hemispherectomy	0/0			7/46			
Patients with follow-up	29 (100)	120 (75)	.006[c]	561 (76)	.003[c]	142 (53)	<.001[c]
Follow-up data							
Outpatient visit	24	85		561		142	
Telephone interview	5	41					
No follow-up data							
No meaningful information through telephone available	0	4					
Suicide of patient	0	1					
No contact made	0	30		176		124	
Mean (SD) follow-up period since latest surgery, y[e]	2.2 (1.8)	2.7 (1.5)	.26[d]	2.7 (1.6)	.11[d]	4.1 (2.3)	<.001
Range	0.6-8.3	0.5-8.0		0.5-8.8		0.5-9.1	
Seizure free[f]	11 (38)[g]	19 (16)	.008[c]	372 (66)	.003[c]	22 (16)	.94[c]

Abbreviations: MRI–/+, magnetic resonance image does/does not show a typically epileptogenic lesion.
[a] Compared with MRI⁻ patients who had surgery.
[b] Compared with MRI⁻ patients who did not have surgery.
[c] Pearson χ^2 test, 2-sided.
[d] *t* Test, 2-sided.
[e] For patients who did not have surgery, period since presurgical assessment.
[f] Percentage is of patients who had follow-up.
[g] Another 2 patients had auras only; together with the completely seizure-free patients, this adds to a seizure-free rate of 45%.

in **Table 1**. The MRI⁻ patients who had surgery had taken at least 4 antiepileptic drugs without achieving seizure control with tolerable adverse effects; those who did not have surgery were resistant to at least 3 antiepileptic drugs. The number of patients who had surgery was smaller in the MRI⁻ than in the MRI⁺ cohorts (15% vs 73%; $P<.001$). Reasons for not performing surgery on MRI⁻ patients were lack of clear-cut focus hypothesis after noninvasive monitoring (n=65; 40%); multiple foci revealed by noninvasive monitoring (n=10; 6%); multifocal seizure onset documented by invasive monitoring (n=19; 12%); expected neurological or neuropsychological risks (n=2; 1%); patient finally decided against surgical approach, in particular, denial of electrode implantation (n=28; 18%); other reason (n=29; 18%); and more than 1 reason (n=8; 5%). The proportion of seizure-free MRI⁻ patients who had surgery was lower than in the MRI⁺ group who had surgery (38% vs 66%; $P=.003$) but higher than in the MRI⁻ patients who did not have surgery (38% vs 16%; $P=.008$).

PREDICTIVE VALUE OF NONINVASIVE PRESURGICAL STUDIES

The predictive value was estimated for all 29 MRI⁻ patients. The results are given in **Table 2**. Localizing information was classified as correct positive, correct negative, false positive, false negative, or inconclusive; positive and negative predictive values were calculated (Table 2).

Postprocessing of MRI and seizure semiology both have a relatively low chance of providing localizing information, but if they do, the positive and negative predictive values are high. Other good outcome predictors are surface EEG and SISCOM.

POTENTIAL ROLE OF TYPE OF SURGERY ON OUTCOME

Different types of operative interventions in the MRI⁻ and MRI⁺ groups may account for their different seizure-free outcome rates. Large, less focused standard interventions may offer a higher chance of seizure freedom than small, selective operations. However, in the temporal lobe surgery group, large operations were more common in the MRI⁻ patients than small interventions (eg, selective amygdalohippocampectomy). There was no significant difference between small (focused) and large extratemporal operations (multilobar resections and hemispherectomies) (Table 1). Taken together, there is no indication that the surgical approaches caused the inferior outcome of the MRI⁻ group.

Table 2. Predictive Value of Noninvasive Diagnostic Tools in Presurgical Assessment of MRI⁻ and Histo⁻ Patients[a]

	No.			No.			
	Correct Positive	False Positive	Positive Predictive Value[b]	Correct Negative	False Negative	Negative Predictive Value[b]	Inconclusive, No. (%)
Semiology (n=29)	10	6	0.6	5	1	0.8	7 (24)
Interictal surface EEG (n=29)	4	6	0.4	7	1	0.9	1 (38)
Ictal surface EEG (n=29)	8	6	0.6	8	2	0.8	5 (17)
PET (n=17)	5	5	0.5	4	1	0.8	2 (7)
SPECT (n=17)	3	6	0.3	5	2	0.7	1 (3)
SISCOM (n=13)	2	2	0.5	5	1	0.8	3 (10)
MRI postprocessing (n=28)	3	0	1.0	3	0	1.0	22 (76)

Abbreviations: EEG, electroencephalogram; histo⁻, histopathology-negative; MRI, magnetic resonance image; MRI⁻, MRI did not show a typically epileptogenic lesion; PET, positron emission tomography; SISCOM, subtraction ictal SPECT coregistered with MRI; SPECT, single-photon emission tomography.

[a] Localizing information was considered to be correct positive if it pointed exclusively to the resected area of a patient who was ultimately seizure free; correct negative, the test did not or did not exclusively indicate the resected area in a patient who did not become seizure free; false positive, the test indicated the resected area of a patient who was not ultimately seizure free; false negative, the test did not or did not exclusively point to the resected area in a patient who was ultimately seizure free; inconclusive, the result did not point to 1 brain area.

[b] Positive predictive value was determined by dividing the correct positives by all positives; negative predictive value, correct negatives by all negatives.

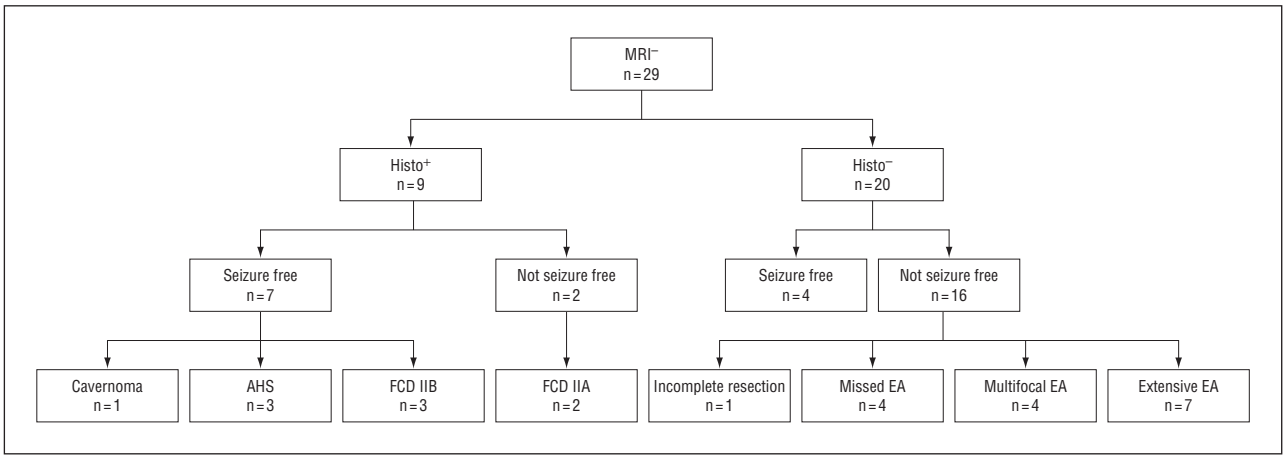

Figure 2. Histopathology-related outcome of all magnetic resonance imaging (MRI)–negative patients. AHS indicates Ammon horn sclerosis; EA, epileptogenic area; FCD, focal cortical dysplasia; histo⁻/⁺, histopathologically negative/positive; MRI⁺, MRI positive (ie, MRI shows a typically epileptogenic lesion); MRI⁻, MRI negative (ie, MRI does not show a typically epilogenetic lesion).

HISTOPATHOLOGY OF MRI⁻ PATIENTS AND RELATED OUTCOME

Nine MRI⁻ patients were histo⁺; 3 had FCD type IIB, 2 FCD type IIA,[23] 3 AHS, and 1 cavernoma (**Figure 2**). The remaining 20 patients had normal or nonspecifically altered histopathological findings. The outcomes of the histo⁺ patients were better than those of the histo⁻ patients (7 of 9 vs 4 of 20 patients seizure free; $P=.003$). The seizure freedom rate in the MRI⁻ histo⁺ group (78%) is similar to that of MRI⁺ patients (67%; $P=.47$). Only the 2 patients with FCD IIA did not achieve seizure freedom. There was no significant correlation between the seizure-freedom rate and site of surgery (7 of 22 patients were seizure free after temporal lobe surgery vs 4 of 7 after extratemporal surgery).

MRI REASSESSMENT OF MRI⁻ HISTO⁺ PATIENTS

Seven of 16 MRI⁻ patients who had 1.5-T scans and 2 of 13 who had 3-T scans were diagnosed with typically epileptogenic lesions on histopathological examination ($P=.1$). Eight of the 9 histopathological abnormalities could be identified on reassessment of pre–surgically-acquired MRI data. Using voxel-based morphometric MRI postprocessing combined with subsequent visual reinspection of MRIs, all 3 patients with FCD IIB and 1 of the 2 with FCD IIA could be unequivocally detected. Two of the 3 histopathologically diagnosed AHS were still difficult to detect on visual reassessment because of the poor signal to noise ratio of the MRIs; the third AHS was clearly visible and had simply been overlooked during presurgical assessment. Also, the temporolateral cavernoma was readily detectable on reinspection of the presurgical images on which it had been missed. One temporolateral FCD IIA remained undetectable on presurgical MRI data, even with use of MRI postprocessing and visual reassessment, knowing the lesion site and histopathological diagnosis.

DETAILED ASSESSMENT OF MRI⁻ HISTO⁻ PATIENTS

Twenty MRI⁻ patients had normal findings or nonspecific alterations on histopathological evaluation. Indi-

Table 3. Patients Without Definite Histopathological Diagnosis: Demographical Data and Results of Presurgical Evaluation (Part 1)

Patient/Sex	Resection	Age at Epilepsy Onset, y/ Duration, y	IPI, Age	Semiology	Preoperative MRI	EEG: Interictal Epileptiform Potentials	Ictal Surface EEG
Temporal Lobe Surgery (n=17)							
Seizure free: epileptogenic area resected (n=3)							
1/F	Tailored AMTL-L	28/10	None	(1) L temporal, (2) R temporal	Negative	L temporal	(1) L temporal, (2) R temporal
2/F	Standard AMTL-L	31/8	None	L temporal	ATC-L	Temporal-bilateral	L temporal
3/F	Standard AMTL-R	30/30	None	R temporal	Negative	R temporal	R temporal
Not seizure free: incomplete resection (n=1)							
4/F	Tailored AMTL-L	7/19	None	L temporal or L frontal	ATC-L	R, L temporal	R, L temporal
Not seizure free: epileptogenic area missed (n=4)							
5/M	Standard AMTL-L	10/20	None	Nonspecific	ATC-L	L temporal-occipital	L temporal-occipital
6/F	Standard AMTL-L	13/17	None	L temporal or L frontal	Negative	L temporal-central	L frontal
7/M	Standard AMTL-R	2/10	None	Frontal	Negative	None	R frontal
8/F	Tailored AMTL-L	19/29	None	Frontal	Negative	(1) L temporal, (2) R temporal, (3) R temporal-posterior	L temporolateral-posterior, >20 s after clinical seizure onset
Not seizure free: multifocal epileptogenic area (n=4)							
9/M	SAH-L	7/15	None	L temporal	Negative	L temporal	L temporal
10/F	Standard AMTL-R	18/27	None	R temporal	Negative	None	R temporal-parietal
11/M	Tailored AMTL-L	4/7	Brain trauma, 2 y	(1) R frontal, (2) L temporal	ATC-L	None	L temporal
12/M	Standard AMTL-R	13/24	None	R temporal	Negative	R temporal	R temporal-central
Not seizure free: epileptogenic area extending beyond resection borders (n=5)							
13/M	SAH-L	19/9	None	L temporal	Negative	None	L temporal
14/M	Tailored AMTL-R	13/6	Encephalitis, 8 y	R insula	Negative	R temporal	R temporal
15/F	Standard AMTL-R	4/29	Encephalitis, 4 mo	Frontal or temporal	ATC-R	R temporal	Not localizing
16/M	Standard AMTL-L	7/3	Encephalitis, 6 y	(1) Frontal, (2) nonlocalizing	ATC-L	L temporal	(1) L temporal, (2) L hemisphere, (3) R, L frontal
17/M	Standard AMTL-L	10/19	None	Nonspecific	ATC-L	L temporal-parietal	L temporal
Extratemporal Surgery (n=3)							
Seizure free: epileptogenic area resected (n=1)							
18/F	Frontal-medial L	14/40	None	Frontal-medial	Negative	None	R central-temporal
Not seizure free: epileptogenic area extending beyond resection borders (n=2)							
19/M	Frontal medial R	10/14	None	Frontal-medial	Negative	R frontal	Not localizing
20/M	Parietal-occipital L	6/29	None	Occipital or frontal-medial	Negative	R, L frontal-central	R, L frontal, almost generalized

Abbreviations: AMTL, anteromedial temporal lobe resection; ATC, anterior temporal changes; EEG, electroencephalogram; IPI, initial precipitating injury; L, left; R, right; SAH, selective amygdalohippocampectomy.

vidual data of these patients and retrospective hypotheses about their epileptogenic areas are given in **Table 3** and **Table 4**. Seventeen had temporal lobe resections. In the remaining 3, extratemporal topectomies were performed (2 in the anterior parts of the medial frontal cortex, 1 in the posterior cortex). One frontal and 3 temporal resections resulted in seizure-free outcomes (Table 3 and Table 4; patients 1-3 and 18). All seizure-free patients were female ($P=.02$) and had a higher age at onset than the non–seizure-free patients (median age, 29; range 14-31 years vs median, 8; range, 2-19 years; $P=.006$); epilepsy duration was, however, not different between seizure-free and non–seizure-free patients (median, 20; range, 8-40 years vs median, 18; range, 3-29 years). No seizure-free and 4 non–seizure-free patients had a history that was potentially related to subsequent epilepsy, ie, initial precipitating injuries (3 cases of encephalitides and 1 brain trauma; $P=.45$).

A case-by-case review of the 20 MRI$^-$ histo$^-$ patients led to the following hypotheses regarding the spatial extent of their epileptogenic areas according to 5 possible scenarios[24]:

1. Adequate determination of a circumscribed epileptogenic area and sufficient resection, as evidenced by

Table 4. Patients Without Definite Histopathological Diagnosis: Results of Presurgical Evaluation (Part 2), Surgical Outcome, and Final Hypothesis on Epileptogenic Area

Patient/Sex	PET	SPECT	SISCOM	Intracranial Ictal EEG (Implanted Electrodes)[a]	MRI Postprocessing	Outcome	Hypothesized Postop Epileptogenic Area
Temporal Lobe Surgery (n=17)							
Seizure free: epileptogenic area resected (n=3)							
1/F	L temporal	L temporal	L temporal	L temporal-medial (temporal-standard)	Negative	Seizure free	None
2/F	L temporal	ND	ND	L temporal-medial-basal (temporal-standard)	Negative	Seizure free	None
3/F	R temporal	ND	ND	R temporal-medial (R, L temporal-medial)	Negative	Seizure free	None
Not seizure free: incomplete resection (n=1)							
4/F	R temporal	L temporal	R, L multifocal	L temporolateral (temporal-standard)	Negative	Reduction, semiology unchanged	Postop MRI revealed incomplete resection of electrode positions showing seizure onset
Not seizure free: epileptogenic area missed (n=4)							
5/M	ND	L temporal-parietal-occipital	L temporal-parietal-occipital	L temporal-parietal (L temporal-parietal-occipital)	Negative	Unchanged	L temporal-parietal-occipital (all data)
6/F	ND	ND	ND	ND	Insula-L	Unchanged	L frontal-insula (surface EEG, MRI postprocessing)
7/M	ND	ND	ND	ND	Frontal-IH-R	Unchanged	R frontal-IH (ictal surface EEG, MRI postprocessing, postop intracranial recordings)
8/F	L temporal	(1) L temporal, (2) R occipital	(1) R, L temporal-lateral, (2) R occipital	(1) L temporal -lateral; (2) L frontal-lateral; clinical seizure signs partly precede EEG onset (R, L frontal-lateral, temporal-standard)	Negative	Reduction	R temporal-posterior-occipital, anterior seizure spread (interictal surface, intracranial EEG, SPECT, SISCOM)
Not seizure free: multifocal epileptogenic area (n=4)							
9/M	R, L temporal	ND	ND	(1) L temporal-medial, (2) R temporal-medial (temporal-standard)	Negative	8 mo seizure-free, then relapse	R temporal (PET, intracranial EEG)
10/F	R, L temporal	ND	ND	No seizure in 33 d (temporal-standard)	Negative	Reduction, postop L temporal seizure recorded	L temporal (PET, postop seizure recording)
11/M	ND	ND	ND	ND	Negative	1 y seizure free, then relapse, new semiology	R frontal (semiology)
12/M	R temporal	ND	ND	R temporal-medial-basal (temporal-standard)	Negative	1 y seizure free, then relapse, postop temporal-posterior-L seizures recorded	L temporal-posterior (postop seizure recording)
Not seizure free: epileptogenic area extending beyond resection borders (n=5)							
13/M	ND	L temporal	L temporal-insula	L temporal-medial (temporal-standard)	Negative	2.5 y seizure free, then relapse	L insula (SISCOM)
14/M	ND	R insula	ND	R temporal (temporal-standard)	NA	Reduction, semiology unchanged	Toward R insula (SPECT, semiology)
15/F	R temporal	R temporal	ND	R temporal-basal (temporal-standard, R, L frontal-medial-lateral)	Negative	Reduction, postop only auras	Toward R temporal-posterior
16/M	L temporal-parietal, R temporal	L temporal	ND	All contacts (temporal-medial-basal-lateral-L)	Negative	Unchanged	Diffuse
17/M	L temporal	ND	ND	All contacts (L temporal-medial-basal-lateral)	Negative	Unchanged	Diffuse

(continued)

Table 4. Patients Without Definite Histopathological Diagnosis: Results of Presurgical Evaluation (Part 2), Surgical Outcome, and Final Hypothesis on Epileptogenic Area (continued)

Patient/Sex	PET	SPECT	SISCOM	Intracranial Ictal EEG (Implanted Electrodes)[a]	MRI Postprocessing	Outcome	Hypothesized Postop Epileptogenic Area
Extratemporal Surgery (n=3)							
Seizure free: epileptogenic area resected (n=1)							
18/F	L hemisphere	(1) R insula, (2) L hemisphere	(1) R parietal, (2) not localizing	L frontal-medial (R, L frontal-lateral-medial, L occipital	Negative	Seizure free	None
Not seizure free: epileptogenic area extending beyond resection borders (n=2)							
19/M	ND	L frontal	Not localizing	R frontal-medial	Negative	Reduction, semiology unchanged	R frontal-medial (semiology)
20/M	ND	L occipital	L occipital	All contacts (R, L frontal-parietal-occipital)	Negative	Unchanged	Diffuse

Abbreviations: EEG, electroencephalogram; IH, interhemispheric; L, left; MRI, magnetic resonance imaging; NA, not available; ND, not done; PET, positron emission tomography; postop, postoperative; R, right; SISCOM, subtraction ictal SPECT coregistered with magnetic resonance imaging; SPECT, single-photon emission tomography.

[a] Temporal standard implantation includes bihippocampal depth electrodes and bitemporolateral and bitemporobasal subdural strip electrodes.

postsurgical seizure freedom (n=4). The 3 patients who became seizure free after temporal resections had highly concordant presurgical results (patients 1-3). Surprisingly, this strong concordance was not present in the 1 seizure-free patient who had frontomedial resection (patient 18).

2. Insufficient resection owing to neurosurgical failure (n=1). The temporolateral seizure-onset zone of patient 4, as determined by invasive EEG monitoring, had been incompletely resected, as evidenced by coregistration of MRI with intracranial electrodes and postoperative MRI. No structural abnormality was suggested by postprocessing of preoperative MRI data. This patient was offered a repeated operation but she did not give consent.

3. Epileptogenic area missed during presurgical assessment (n=4). In patients who had temporal lobe operations (patients 5-8) without subsequent seizure freedom, postoperative review suggested an epileptogenic area outside of the presurgically designated region and, therefore, not approached by the surgical procedure. In 2 of these 4 patients, MRI postprocessing with subsequent visual reassessment of MRIs suggested dysplastic tissue outside of the resected areas at sites emerging as probably epileptogenic on review of the other presurgically obtained data. In 1 patient with daily seizures (patient 7), this postoperative discovery on the preoperative MRI data led to exploration of the suspected area plus adjacent parts of the same lobe by intracranial depth and subdural electrodes. The depth electrode inserted at the site indicated by MRI postprocessing showed focal low amplitude fast activity at seizure onset. Subsequently, this area was resected. On histopathological examination, no abnormal neurons were found. The fragmented state of the material, however, did not permit assessment of potential architectural abnormalities. At the most recent follow-up, 6 months after this second surgical procedure, the patient was still continuously seizure free.

4. Multifocal epileptogenic areas (n=4). This was hypothesized retrospectively in patients 9 through 12, who had temporal lobe resections: 1 had an additional frontal and 4 had additional contralateral temporal epileptogenic areas. None of these patients had an additional MRI abnormality on postprocessing and visual MRI reassessment.

5. Extensive epileptogenic area insufficiently determined (epileptological failure, n=8). In these patients (patients 13-17, 19, and 20), the epileptogenic areas were, in part, removed but obviously extended broadly beyond the designated resection borders, as evident on reanalysis of the presurgical data. None of these patients had an additional MRI abnormality on postprocessing and visual MRI reassessment.

COMMENT

In this cohort, patients with MRI$^-$ epilepsies have a lower chance of having surgery than those with lesions demonstrated by presurgical MRI and, if so, less chance of becoming seizure free. This confirms previous data.[7,25] The seizure-free outcome rate of MRI$^-$ patients who had surgery is, on the other hand, better than that of those who did not. This has not been demonstrated before by direct comparison. The MRI$^-$ patients for whom surgery was successful demonstrate that the process of multimodal presurgical evaluation may lead to good outcomes in patients with refractory focal epilepsies, even if they do not have an MRI correlate. When choosing a particular test modality, MRI postprocessing, interictal EEG, and semiology have the highest likelihood of providing inconclusive results. If a certain brain area is contemplated as the to-be-resected area, any conclusive test result may be weighted according to the data given in Table 2. Concordant data from MRI postprocessing, semiology, and ictal surface EEG, in that order, are the best predictors of a seizure-free outcome if the planned resection is done. Discordant results of MRI postprocessing, interictal surface EEG, semiology, and SISCOM are

the strongest predictors of a non–seizure-free outcome if the contemplated operation is performed. These predictive values and suggestions have, however, several limitations. They are the results of decisions of the center's clinicians, and the values of these tests may vary depending on the location of the pathology (positron emission tomography, for example, is probably better in identifying mediotemporal lobe than extratemporal foci). Both potential biases can hardly be controlled for in this type of retrospective analysis and small sample size. Epilepsies that are MRI$^-$ are not necessarily nonlesional. Thirty percent of MRI$^-$ patients in this study and a median proportion of 46% in other series[8-11,13-17] have epileptogenic lesions. In the present cohort, these MRI$^-$ histo$^+$ patients had a postoperative seizure-free outcome as favorable as that of the MRI$^+$ control patients, clearly better than that of the histo$^-$ patients who had surgery. Conversely, the proportions of seizure-free patients in the MRI$^+$ and MRI$^-$ cohorts who did not have surgery are almost identical, suggesting more similarities than dissimilarities regarding the underlying pathology of the epilepsies. It may be expected that previously MRI$^-$ histo$^+$ patients will be found to be MRI$^+$ in the near future, which will increase their chances of proceeding to successful resective epilepsy surgery. Improved MRI acquisition at field strengths of more than 1.5 T and appropriate postprocessing techniques, together with growing experience of MRI evaluators, will likely contribute to this advance.[20,26] This assumption is supported by the results of this series; about three-fourths of the false-negative MRIs (ie, those of MRI$^-$ histo$^+$ patients) were acquired using 1.5 T systems. Reevaluation by postprocessing and visual reinspection of existing MRI data permitted the detection of underlying brain lesions in all but 1 of 9 such patients. Only 1 temporal lobe FCD IIA remained undetected. Furthermore, the renewed MRI assessment indicated nonresected dysplastic lesions in 2 histo$^-$ patients who did not become seizure free after resection of an MRI$^-$ histo$^-$ area. In both, renewed assessment of presurgical data confirmed that their epileptogenic areas were congruent with the retrospectively identified lesions and had been missed during the original preoperative evaluation. One subsequently had resection after intracranial studies unequivocally confirmed seizure onset in the area, found to be dysplastic during MRI postprocessing.

Presurgical detection of focal lesions by MRI not only guides presurgical evaluation along more effective pathways[26]; epilepsies caused by such focal lesions appear different in nature from histopathologically nonlesional ones. Seizures related to FCD or AHS arise mostly from strictly circumscribed, and therefore completely resectable, epileptogenic areas (tightly related to the structural abnormalities). In contrast, the major reasons for frequently unsuccessful focal resections in cases without such lesions were multifocality or large extension of the epileptogenic areas (12 of 20, ie, three-fifths). Initial precipitating injuries that cause extended brain damage such as trauma or encephalitis may contribute to widespread epileptogenic areas in those cases. This study further supports the concept that many MRI$^-$ patients have poorly localized epileptogenic areas; more than two-thirds of MRI$^-$ patients were rejected from surgery after comprehensive evaluation owing to multifocality or poor demarcation of the epileptogenic area. These observations may indicate a more elaborate and extensive presurgical diagnostic procedure (including, for example, more extensive electrode implantations) in this patient group.

Only 3 of 20 histo$^-$ patients (15%) had sufficiently restricted epileptogenic areas to become seizure free after resections of typical extension. In this series, seizure-free histo$^-$ patients had a relatively high age at epilepsy onset (median, 29 years) and were all female; the meaning and predictive relevance of these features, however, are unclear.

In summary, it is worthwhile to perform presurgical epileptological evaluation of patients with features compatible with monofocal epilepsy, even in the absence of a typically epileptogenic MRI lesion. Patients with concordant noninvasively obtained focus signs should have intracranial EEG and proceed to epilepsy surgery if a monofocal, resectable epileptogenic area is found. At the same time, all efforts should be made to improve the yield of MRI because of the higher effectiveness of presurgical evaluation in MRI$^+$ epilepsy patients.

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