

Characteristics and Surgical Outcomes of Patients with Refractory Magnetic Resonance Imaging-Negative Epilepsies. Bien CG, Szinay M, Wagner J, Clusmann H, Becker AJ, Urbach H. *Arch Neurol* 2009;66(12):1491–1499. **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.

COMMENTARY

MRI is arguably one of the most important developments in the treatment of drug-resistant partial epilepsy. Although epilepsy surgery was a therapeutic modality prior to MRI, the era of widely available, high-resolution structural imaging made noninvasive identification of epileptogenic lesions possible, and ushered in the modern era of epilepsy surgery. For example, an early seminal advance was the noninvasive identification of the pathological changes of mesial temporal lobe sclerosis with MRI—one of the most common causes of medically resistant epilepsy (1,2). Once the clinical, pathological, and imaging correlations of mesial temporal sclerosis were established, the evaluation and potential for surgical cure of patients with decades of intractable seizures became routine—or at least they should have (3). For patients whose scalp-EEG and

MRI lesion assessment are concordant, the complete resection of the MRI lesion is often associated with an excellent outcome. Similarly, other lesional partial epilepsies, such as cavernous angiomas and low-grade gliomas, became surgical targets with excellent outcomes. An important exception is cortical dysplasia, for which the entire pathological lesion may not be apparent on MRI, again suggesting the importance of identifying the entire structural lesion. In multiple retrospective studies, patients with MRI lesions are found to have approximately a 70 to 90 percent chance of excellent outcome from epilepsy surgery (4). In the only prospective, randomized trial of epilepsy surgery, Wiebe et al. found that 64% of patients who had temporal lobectomy were free of consciousness-impairing seizures compared to just 8% of patients randomized to medications (5). Concordant temporal lobe MRI lesions were preoperatively identified in 85% of these patients.

Unfortunately, the MRI is normal in many patients with drug-resistant epilepsy, and these are among the most

challenging patients evaluated in epilepsy centers. In the paper reviewed here, Bien et al. describe the results from 1,192 patients presenting with drug-resistant epilepsy. In this study, 16% (190 patients) of patients had a normal MRI, which is consistent with previous reports indicating that 15 (5) to 25 percent (6) of patients presenting with drug-resistant epilepsy had a normal MRI. The current study again highlights the challenge presented by patients with normal MRI, as is evidenced by the fact that at a comprehensive epilepsy center they evaluated, only 15% (29 patients) of the normal MRI patients they evaluated went on to resective surgery, compared to 73% (763 patients) of the patients with MRI lesions. Unfortunately, this clinically important difference in resection rates significantly limits the ability to draw strong conclusions about the 29 patients with normal MRI, who had epilepsy surgery. Nonetheless, the study found that this group of 29 patients had significantly inferior outcomes compared to patients with lesional MRI, which is also a finding that is consistent with previous reports (7,8). Overall, the investigators found 38% of patients with a normal MRI had a seizure-free outcome compared to 66% of patients with lesional MRI.

Unlike many surgical series, the study by Bien et al. provides interesting information about the 85% (161 patients) of normal MRI patients who did not go to surgery. For example, in 40% (65 patients) the authors could not generate a clear-cut hypothesis to guide an invasive evaluation or surgery. In 12% (19 patients) invasive EEG monitoring was performed, but did not lead to identification of a discrete, resectable focus, while another 18% or 28 patients declined invasive EEG monitoring. These data highlight the inadequacy of the currently available technology, that is, in 40% of patients, lateralization and localization of seizure onset was not adequate. It is interesting to consider that 25% (48/190) of normal MRI patients had highly invasive procedures—29 patients had resective surgery and 19 patients had invasive EEG monitoring but were not resective surgery candidates. The fact that only 23% (11/48) of these patients having highly invasive neurosurgical procedures are rendered seizure free again highlights the challenge.

The authors further stratify patients with normal MRI undergoing resection into those with distinct histopathological abnormalities (9/29 patients) and those with nonspecific or normal histology (20/29 patients). The patients with unremarkable histology had inferior seizure-free outcomes (4/20 patients) compared to patients with distinctly abnormal histopathology (7/9 patients). The nine patients with distinct histopathology had focal cortical dysplasia types IIA and IIB, mesial temporal sclerosis, and even a cavernoma. The authors also report the reassessment of MRI guided by quantitative voxel-based morphometry. Remarkably, using this technology, in eight of nine patients with positive histology, the lesion could be identified on retrospective visual review. This result begs the question of what is and is not nonlesional.

One surprising finding is that the normal MRI, extratemporal lobe epilepsy patients fared better than the temporal lobe epilepsy patients, although this was not statistically significant (32% seizure free after temporal lobectomy vs 57% seizure free after extratemporal resection). The outcome likely reflects the small number of patients (22 temporal lobe and only seven frontal lobe operations) evaluated. Other, larger retrospective studies of temporal lobectomy in nonlesional temporal lobe epilepsy report 60 to 65 percent excellent outcome (4,8). Previous, larger retrospective studies report excellent surgical outcomes for MRI normal, extratemporal epilepsy, ranging from 17 to 41 percent (7,9).

From the Bien et al. study it would appear that . . . to see is a potential to cure. What is thought to be nonlesional today, hopefully, will be illuminated in the future. The development of new imaging modalities and computational methods that can render the so-called nonlesional visible is an important pursuit. One only has to look back three decades, when mesial temporal sclerosis was first noninvasively visualized, to appreciate the impact of MRI on medial temporal lobe epilepsy.

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