MRI-NEGATIVE TEMPORAL LOBE EPILEPSY: IS THERE A ROLE FOR PET?

MRI-negative PET-positive Temporal Lobe Epilepsy: A Distinct Surgically Remediable Syndrome

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Most patients with nonlesional temporal lobe epilepsy (NLTLE) will have the findings of hippocampal sclerosis (HS) on a high-resolution MRI. However, a significant minority of patients with NLTLE and electroclinically well-lateralized temporal lobe seizures have no evidence of HS on MRI. Many of these patients have concordant hypometabolism on fluorodeoxyglucose-PET ([^{18}F]FDG-PET). The pathophysiologic basis of this latter group remains uncertain. We aimed to determine whether NLTLE without HS on MRI represents a variant of or a different clinicopathologic syndrome from that of NLTLE with HS on MRI. The clinical, EEG, [^{18}F]FDG-PET, histopathologic, and surgical outcomes of 30 consecutive NLTLE patients with well-lateralized EEG but without HS on MRI (HS–ve TLE) were compared with 30 consecutive age- and sex-matched NLTLE patients with well-lateralized EEG with HS on MRI (HS+ve TLE). Both the HS+ve TLE group and the HS–ve TLE patients had a high degree of [^{18}F]FDG-PET concordant lateralization (26 of 30 HS–ve TLE vs. 27 of 27 HS+ve TLE). HS–ve TLE patients had more widespread hypometabolism on [^{18}F]FDG-PET by blinded visual analysis [odds ratio (OR, $+\infty$(2.51, –); $P = 0.001$]. The HS–ve TLE group less frequently had a history of febrile convulsions [OR, 0.077 (0.002 to 0.512), $P = 0.002$], more commonly had a delta rhythm at ictal onset [OR, 3.67 (0.97 to 20.47); $P = 0.057$], and less frequently had histopathologic evidence of HS [OR, 0 (0 to 0.85); $P = 0.031$]. No significant difference in surgical outcome despite half of those without HS having a hippocampal-sparing procedure. Based on the findings outlined, HS–ve PET-positive TLE may be a surgically remediable syndrome distinct from HS+ve TLE, with a pathophysiologic basis that primarily involves lateral temporal neocortical rather than mesial temporal structures.

COMMENTARY

Noninvasive imaging modalities are playing an increasingly important role in the evaluation of patients for epilepsy surgery. A classic example is the visualization of mesial temporal sclerosis (MTS) on MRI, which has simplified the identification of patients who might benefit from anteromesial temporal lobectomy. Nevertheless, roughly 30% of patients with electrographic evidence of temporal lobe epilepsy have normal MRI scans (1). The location of the seizure focus is unclear in this patient population. Possibilities include (a) a subtle form of MTS that is not apparent on MRI; (b) other pathology of the medial temporal lobe not visible on MRI, such as microdysgenesis or alterations in synaptic or receptor physiology; or (c) temporal neocortical pathology not detected by MRI, such as certain forms of cortical dysplasia. Distinguishing between these potential etiologies is critical to selecting the appropriate surgical target to ensure optimal seizure control and to minimize the potential neuropsychological sequellae of removing nonepileptic, functional tissue.

One possible solution would be to implant invasive electrodes in patients with temporal lobe epilepsy and a normal MRI scan. In fact, this treatment plan is the standard of care in some centers (2). However, the implantation of subdural grid and depth electrodes is not without morbidity, and avoiding this increased risk, as well as cost and length of stay for the patient, would be preferable if outcome were not compromised (3,4). Another approach would be to eliminate these patients from consideration for surgery altogether, because their seizure-free rate is less than that of patients who have clear evidence of hippocampal atrophy or high signal on preoperative MRI (5). This practice would deprive a large number of patients, who potentially could be cured of their epilepsy, from surgical therapy. Another option is to use additional information, such as history or video-EEG monitoring, to determine who might benefit from surgery without requiring the use of invasive electrodes (6,7).

Interictal positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG-PET) hypometabolism is known to lateralize the side of seizure onset in patients with mesial temporal lobe epilepsy and correlates well with seizure control after surgery (8). In this study, Carne et al. attempted to use PET scans to try to identify a subgroup of patients with normal MRI scans who might benefit from temporal lobectomy. They found that 87% of patients with normal MRI scans had PET hypometabolism that was lateralized concordant with their EEG (compared with 100% of patients with

MTS on MRI). In addition, 66% of these scans had more widespread hypometabolism in the temporal lobe than in a control group of patients with MTS, for whom the hypometabolism was more focal in the mesial structures. Unfortunately, the surgical approach was not uniform, and half of the 20 MRI-normal patients had a standard anterior temporal lobectomy and amygdalohippocampectomy (the authors do not define the extent of neocortical resection), whereas the other half had a hippocampal-sparing neocortical resection guided by the extent of PET hypometabolism. The surgical results were extremely good, with an 80% rate of Engel Ia or Ib after a minimum follow-up of 2 years, regardless of the type of surgery performed.

The authors conclude that patients with MRI-negative temporal lobe epilepsy and concordantly lateralized PET scans, with widespread temporal lobe hypometabolism, are a unique group that likely has neocortical onsets and can benefit from neocortical resections. However, in spite of their good results, this conclusion is questionable because some of the data are inconsistent. The authors propose using PET scans to differentiate a subtype of patients with MRI-negative temporal lobe epilepsy, but they do not describe a comparison group of patients in whom the PET is either nonlateralized or more focally mesial that are in any way different from the rest of the study group. The authors point out that two patients with nonlateralized and one with a contralaterally lateralized PET scan were all rendered seizure free after surgery. Hence, the value of the PET scan in their decision making is unclear, and the predictive value of the PET scan results is not discussed. In addition, the authors never address the possibility that patients with normal MRI scans can actually have strictly mesial temporal lobe onsets. This omission is clearly misleading, because a subgroup of these patients can be cured after selective mesial temporal surgery. Finally, the value of removing the neocortical tissue to the extent of the PET abnormality seems unjustified, because even patients with MTS and strictly mesial onsets often have regions of PET hypometabolism that extend far beyond the margins of the epileptic focus (9).

The idea of identifying a subgroup of patients with temporal lobe epilepsy and normal MRI scans that might be able to avoid invasive monitoring and undergo potentially curative surgery is attractive. Although the authors only describe the role of PET in this algorithm, it is likely that a combination of video-EEG, PET, neuropsychology, Wada test, and potentially ictal SPECT or interictal MEG results may be more successful in determining which of these patients have mesial temporal onsets and which have temporal neocortical onsets. For example, a patient with more mesiobasal interictal and ictal electrophysiology and mesiobasal PET hypometabolism, poor ipsilateral memory on the Wada test, and neuropsychological testing and ictal SPECT demonstrating mesial temporal hyperperfusion may have an extremely high rate of cure after a selective amygdalohippocampectomy, in spite of a normal MRI scan. In contrast, a patient with more posterior temporal electrophysiology, neocortical PET hypometabolism, good ipsilateral memory, and a temporal neocortical ictal SPECT result might benefit from a neocortical resection with sparing of the mesial structures. Although the authors hint at this type of result, their data are not quite adequate for a definitive conclusion. In addition, the safe and most effective extent of neocortical resection would be unknown in the absence of surface recordings and language mapping.

Given the lack of convincing results, one is left thinking that perhaps all of these MRI-normal patients should be implanted with intracranial electrodes as the "gold standard." However, no publications are available in the literature, even from centers that routinely implant patients who have temporal lobe epilepsy and normal MRI scans, showing better than an 80% rate of Engel Ia or Ib outcome after 2 years. Hence, as in most of the literature on the *best* surgical treatment for temporal lobe epilepsy, the clinician is left with the realization that still many aspects of this disease are not well understood.

by Theodore H. Schwartz, M.D.

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