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EDITORIAL

The Role of SPECT Brain Imaging in Epilepsy

Seizure disorders are prevalent and serious neurological conditions (*1*). Long-term prognosis for patients who respond to antiepileptic drug therapy is good, with total remission expected in up to 90% of all medical responders. Unfortunately, 30%–60% of patients with complex partial seizures become medically refractory. Epilepsy surgery is considered the treatment of choice for such patients (*2*), and EEG monitoring is the gold standard for seizure focus localization. However, scalp EEG often fails to adequately localize the focus (*3,4*); depth EEG is more successful (*5*). Both intraoperative corticography and depth EEG are extremely invasive, expensive and present a surgical risk.

The principal motivation for functional neuroimaging in patients with refractory complex partial seizures is therefore to localize the epileptic focus. However, in this issue of *The Journal of Nuclear Medicine*, Tatum et al. (*6*) demonstrate a potential role for regional cerebral blood flow (rCBF) imaging by SPECT in the diagnosis of partial status epilepticus. This report provides two important reminders: First, SPECT should be used as part of a complement of diagnostic tools. Second, there can be substantial diagnostic value in a negative (normal) study. In this editorial, we examine the effectiveness of SPECT in localizing seizure foci, and highlight the areas of opportunity for SPECT imaging in epilepsy beyond focus localization.

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For correspondence or reprints contact: Dr. Michael D. Devous Sr., Nuclear Medicine Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9061.

Focus Localization in Temporal Lobe Seizures

Interictal imaging with PET and ^{18}F-fluorodeoxyglucose (FDG) demonstrates temporal lobe hypometabolism in 60%–80% of patients with complex partial seizures (*7–9*), but clinical utility is limited by availability and cost (*9*). Interictal rCBF SPECT is more accessible, but demonstrates hypoperfusion at the seizure focus with a sensitivity of only about 50% (*10,11*). In a recent review of SPECT in epilepsy (*11*), the combination of all EEG data was localizing in 71% of patients. By contrast, interictal imaging (SPECT or PET) was localizing in 59% of patients, increasing to about 90% for ictal or postictal studies (*12,13*).

There are three promising areas for future work regarding the role of SPECT in focus localization in partial seizures: (1) the role in postictal or ictal studies involving secondarily generalized seizures (*13,14*); (2) the meaning of disagreement between SPECT and EEG (some patients demonstrate focal rCBF abnormalities without EEG localization (*11*). Since such patients are not currently operated on, it is unknown whether the SPECT localization was correct. Other patients have normal SPECT findings in the face of localizing EEG. Devous and Leroy (*15*) have shown that such patients are at higher risk for poor surgical outcome than patients with localizing SPECT results); and (3) the relationship between SPECT localization and surgical outcome. (The data described above for sensitivity of localization are relative to classical diagnostic criteria, primarily EEG. Since such criteria can be false localizing, the sensitivity of SPECT relative to surgical outcome is of greater interest.)

Extratemporal Seizures

The literature on patients with pure but extratemporal foci is sparse (*16,17*). Frontal lobe seizures may represent an area for concentration since they have been difficult to localize using standard EEG techniques, and depth EEG has not proven to be as beneficial for localizing the site of seizure origin as in temporal lobe seizures (*18*).

Primary Generalized Seizures

Little is known about abnormalities in cerebral perfusion or metabolism in generalized seizures (*19–21*). Using PET, Theodore et al. (*19*) found that interictal glucose metabolism was normal in 8/9 patients. Using SPECT, Devous et al. (*20*) found interictal hypoperfusion in only 3/15 patients, while Leroy et al. (*21*) found mild frontal rCBF abnormalities in 11/24 patients. These results are consistent with the failure of surface or depth EEG or CT and MRI to define a specific anatomic region of seizure origin in patients with absence (*22*).

Surgical Outcome

Most SPECT findings are compared to EEG as the gold standard in presurgical lesion localization. Since EEG is not infallible, SPECT should be validated against outcome following surgery. Of course, poor surgical outcome can result from poor surgical technique or incomplete removal of the focus rather than inaccurate localization. However, if SPECT is to complement or replace EEG procedures, there must be significant correlation between SPECT findings and surgical outcome. In this regard, it is surprising how few papers report the surgical outcome of their patients. In fact, there is only one report comparing surgical outcome to interictal, postictal and ictal scans (*23*).

Structural Imaging

CT and MRI identify structural lesions that may or may not be related to the epileptic focus. Thus, one might expect sensitivity of lesion detection to increase with newer MRI techniques, while specificity for focus localization might not. In a recent retrospective study, 78% correct lateralization was achieved using MRI (*24*). Clearly, much is to be learned about the relative relationship between SPECT and MRI.

Neuropathology

Resected temporal lobes in patients with intractable complex partial seizures normally demonstrate only microscopic changes in areas of hypometabolism (*25,26*). Also, functional lesions are generally larger than the depth EEG focus. This is consistent with animal studies demonstrating focal neuropathology by light microscopy and a focal depth electrode measured seizure focus, with wider areas of hypometabolism (*27*). Animal models have also demonstrated abnormal metabolism in structurally normal "mirror" foci and increased glucose utilization in regions distant from a kindled focus (*28*). Unfortunately, these data do not address the question of whether metabolic and pathologic lesions observed in adults with epilepsy are caused by or are the cause of epileptiform activity. Data in new onset adult seizure patients are sorely needed. However, pediatric studies imply that such abnormalities can be present very early in life (see below).

Relationships with Medical Therapy

It is difficult to assess the relationship of medical therapy to interictal hypoperfusion or hypometabolism. It is clear that seizures themselves, at least in animal models of epilepsy, produce such changes (*27–30*). However, anticonvulsants, especially phenytoin and phenobarbital, are also known to reduce cerebral metabolism (*31,32*). Two studies addressing this issue focused on the cerebellum, since it does not participate in ictal electrical activity during seizures or demonstrate interictal epileptiform discharges, but may be affected by anticonvulsants. Theodore et al. (*33*) using PET and Homan et al. (*34*) using SPECT found that in patients with partial seizures, at least cerebellar hypometabolism can be caused by anticonvulsant therapy.

Clinical and Cognitive Correlates

Few studies have examined the relationship between interictal rCBF reductions and either clinical symptomatology or cognitive impairment (*35–37*). Valmier et al. (*35*) found a correlation between the severity of hypoperfusion and disease severity. Homan et al. (*36*) found predictive relationships between deficits on specific neuropsychological tests and visually identified regions of hypoperfusion. Related studies include reports of improved regional cerebral metabolism with improved seizure control (*38*) and increased glucose metabolism with the discontinuation of barbiturates in patients remaining on other anticonvulsants (*8*). These data suggest that functional neuroimaging studies may be useful in assessing impairments of cognitive function, and thus may be of value in the pharmacologic management of epileptic patients.

Pediatric Studies

Given the effectiveness of functional brain imaging in adults with epilepsy, it might be expected to play a substantial role in the pediatric population. Unfortunately, there are only a handful of studies in pediatric epilepsy, most of which involve PET. The Lennox-Gastaut syndrome has been the subject of greatest study (*39–41*), primarily demonstrating bilateral diffuse hypometabolism. Other reports deal with Sturge-Weber syndrome (*42*) or the role of PET in the surgical treatment of intractable neonatal-onset seizures (*43*). The total literature for SPECT includes reports on only 18 children with interictal scans (of whom six had surgical follow-up), four children with postictal scans (of whom two had surgical follow-up) and four patients with ictal SPECT (*44–46*). These limited studies suggest both prognostic and diagnostic roles for functional brain imaging in pediatric patients, but such roles are not yet established.

Receptor Studies

The benzodiazepine (BN) receptor is a marker of the GABA-BN complex, which is believed to be the main mediator of neuronal inhibition. This complex is probably involved in epilepsy since GABA antagonists and BN-receptor inverse agonists induce seizures, while GABA and BN agonists prevent them. Both PET (*47*) and SPECT (*48*) studies have shown reduced BN receptor binding exclusively in the epileptic focus in patients with partial epilepsy, even when rCBF is normal (*48*).

Conclusion

SPECT imaging already plays an important role in the management of patients with epilepsy, offering an accuracy of localization of the focus on the order of 90% in adult patients with complex partial seizures of temporal lobe origin. However, the role of SPECT beyond seizure focus localization is largely unexplored. This represents the proverbial good news/bad news story. The good news is that we have many opportunities for exciting research and clinical effectiveness. Tatum et al. (*6*) and a few other brave souls have inspired our imagination. The bad news is that, in the modern health care world, we will have to quickly (during this formative period) and clearly (in a cost-effectiveness context) establish all of the roles for SPECT in epilepsy.

Michael D. Devous Sr.
The Nuclear Medicine Center
University of Texas Southwestern Medical Center
Dallas, Texas

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