Application of Ictal Brain SPECT for Differentiating Epileptic From Nonepileptic Seizures

Ovidio A. De León, M.D.
Michael J. Blend, Ph.D., D.O.
Thomas H. Jobe, M.D.
María Pontón, M.D., Moisés Gaviria, M.D.

The authors report 2 clinical cases that illustrate the difficulties with video-monitored EEG and the advantages of brain SPECT in differential diagnosis of true epileptic seizures and nonepileptic seizures. Injection of [^{99m}Tc]HMPAO at the time of the ictal event provides a means to obtain a SPECT image postictally for comparison with interictal examinations so that an epileptic or nonepileptic focus may be localized.

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The differentiation of nonepileptic seizures from true epilepsy is difficult. Symptoms characteristic of real seizures are often present in pseudoseizures. Furthermore, the coexistence of true epilepsy and pseudoseizures has been well documented. The diagnosis of nonepileptic seizures has been attempted by precipitating an attack with suggestion and terminating it by placebo under EEG monitoring.[1] This strategy relies on the surface EEG as the gold standard for diagnosis. It is well known that spiking discharges associated with behavioral changes can be recorded from the inferior frontal region, the hippocampus, and the amygdala, but that the surface recording is not epileptiform. The differential diagnosis between these two conditions has important therapeutic implications. Nonepileptic seizure patients may be unnecessarily treated with anticonvulsant medication, exposing them to potentially dangerous side effects and needless financial costs. Besides, antiepileptic drugs may actually worsen the nonepileptic seizure disorder.[2]

SPECT, as a measure of relative cerebral perfusion and metabolism, is useful in the localization of epileptogenic foci.[3,4] There is some indication that ictal SPECT has greater localizing power for seizure focus than other noninvasive procedures.[5] Podreka et al.[6] reported that in 60% to 86% of cases it is possible to detect regions of impaired metabolism interictally by using PET or SPECT imaging in patients with complex partial seizures, and they also believed that the sensitivity and specificity of seizure focus detection can be increased by comparing ictal with interictal SPECT findings. To our knowledge there are no specific reports in the literature describing regional cerebral blood flow (rCBF)/SPECT patterns that can be used to differentiate epileptic from nonepileptic seizures. The purpose of this article is to report on the usefulness of ictal SPECT to differentiate true epileptic from nonepileptic seizures in 2 clinical cases.

METHODS

At our institution, SPECT studies of the brain are performed by use of a dedicated triple-headed camera system (Picker 3000 XP) with an attached UNIX-based computer workstation. Each camera head is equipped with a low-energy ultra-high-resolution fan beam collimator. The raw projection images are acquired on a 128 × 128 matrix by using a rapid acquisition scan protocol with 40 steps per head at 7 seconds per step. Acquisitions without motion artifact are summed and processed. The summed data are then reconstructed by using a Parsen window, and the resulting transverse slices are postfiltered by using a low-pass filter (order = 8.1, cutoff = 0.31). An attenuation correction map is then applied to the filtered data set. Orthogonal images are zoomed, summed, and displayed. Each individual slice represents approximately 0.84–0.86 cm of thickness.

A software program developed in our laboratory was used to analyze relative cerebral perfusion in interictal and ictal studies in the same patient. Both images are normalized to the same total counts. The entire brain volume is preprocessed by using a thresholding tech-

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From the Department of Psychiatry and the Section of Nuclear Medicine, University of Illinois College of Medicine, Chicago. Address correspondence to Dr. De León, Department of Psychiatry (M/C 913), University of Illinois College of Medicine, 912 S. Wood St., Chicago, IL 60612.

nique to reduce noise and scalp activity. The two image sets are then coregistered by correcting three-dimensional shift and rotation errors. This image registration process minimizes the differences between the corresponding images in the nonactivated regions. Baseline activity is subtracted from the corresponding activated data set to generate differential images representing a net change in regional counts. These differences are then normalized to the mean activity counts of the whole brain volume and displayed in color steps. The changes range from –25% to +25% of the mean activity, with each color step representing a change of 5% in the regional counts. The light colors (shades of white) indicate positive changes in the activation images compared with the baseline study, and the dark colors (grays and black) represent negative changes.

CASE REPORTS

Case 1. Ms. A., a 36-year-old woman, had a history of seizures since age 14. Her seizures were generalized tonic-clonic, but she also described other spells where she turned her eyes upward and to the right, moved her right arm slowly, moved her right foot rhythmically, was unresponsive, and cried. Emotional problems usually provoked these spells. Listening to old folk songs that she used to sing during her childhood and adolescence also triggered these episodes. According to her, these songs stimulated unpleasant memories that reminded her of the abuses she was subjected to during those years. Phenytoin, phenobarbital, carbamazepine, and valproic acid failed to control the seizures. She was hospitalized after she became depressed and acutely suicidal. A baseline surface EEG showed slow wave activity and sharp waves in the right temporal area. A baseline brain SPECT and MRI were normal. After informed consent was obtained, seizure activity was successfully activated by playing folk songs. We obtained a 10-lead surface EEG while she was listening to the songs, and after 20 minutes she presented a partial complex seizure with eyes fixed upward and to the right, right-arm posturing, right-foot pedaling movements, unresponsiveness, and wailing. Seizure rhythms were recorded in the right temporal area. At this moment, 25 mCi of [^{99m}Tc]HMPAO (Ceretec) was injected intravenously, followed 2 minutes later by diazepam 10 mg to stop the seizure. The brain SPECT obtained 30 minutes after her seizure was compared with the baseline study. The ictal SPECT showed increased tracer activity in the right frontobasal and frontolateral regions, in the temporal structures, and in the insula. Also noted were areas of relative hypoperfusion in the frontal lobes bilaterally on the ictal images, visible as a region of negative difference on the differential images.

Case 2. Ms. B., a 43-year-old woman, had onset of seizures 3 years prior to admission. Episodes were characterized by syncopal-like attacks with loss of consciousness for about 2 to 5 minutes and no associated muscular activity. She failed to respond to carbamazepine and was admitted after she became severely depressed and had increased frequency of spells in which she would faint for no apparent reason and remain unarousable for several minutes. During these episodes she was apparently unconscious and unaware of her surroundings. She showed no resistance to opening of the eyelids; her eyes were in the midline and pupillary reflexes were normal. Deep tendon reflexes were preserved, and there were no pathologic reflexes. Vasovagal and orthostatic syncope were ruled out. An EEG showed rare sharp waves on the left temporal area. A video monitoring EEG failed to document ictal rhythms during episodes of loss of consciousness. Brain MRI was normal. While being observed on a video-monitored EEG, she presented the behavioral changes associated with her seizures. Video-monitored EEG findings were nondiagnostic. At this moment the patient received an injection of [^{99m}Tc]HMPAO intravenously. The brain SPECT study was performed 30 minutes after the injection. No focal areas of increased uptake were noted; however, the examination showed 15%–20% bifrontal and left temporal hypoperfusion during ictus as compared with the baseline study.

DISCUSSION

Brain SPECT examination was helpful in differentiating true epileptic from nonepileptic seizures in both of the cases presented above. Ms. A. was clinically thought to be suffering from a nonepileptic seizure disorder, and she was responding poorly to antidepressants and mild doses of anticonvulsants. The right temporal area of relative hyperperfusion observed during ictal SPECT, extending to the right frontobasal and frontolateral regions, correlated well with EEG findings and was strongly suggestive of an epileptic seizure disorder. Anticonvulsant medications were maximized, and her seizure episodes significantly decreased. The relative hypoperfusion in the frontal lobes described in this patient has been previously reported[7,8] on ictal images. Its clinical significance has not been fully explained.

Ms. B., conversely, was clinically thought to be suffering from an epileptic seizure disorder and was responding poorly to anticonvulsant medication. Her ictal SPECT showed no areas of hyperperfusion but demonstrated bifrontal and left temporal lobe hypoperfusion. She was taken off her anticonvulsant medication and is undergoing psychotherapy and antidepressant pharmacotherapy, with improvement of her clinical condition. The possibility of postictal hypoperfusion cannot satisfactorily explain the hypoperfusion observed in this patient for two reasons. First, the tracer was injected during the ictal event. Second, the simultaneous video-monitored EEG recorded the behavioral changes but not ictal rhythms. This occurrence of ictal hypoperfu-

sion in nonepileptic seizures requires replication in future studies. More research is needed to tease apart possible confounding variables, such as drug effects, background EEG activity, and level of cognitive functioning, among others. Along these lines, Jibiki et al.[9] described a case of hyperventilation producing hypoperfusion in a neurotic patient and suggested that the cause was cerebral ischemic change, presumably due to cerebral vasoconstriction. Hypoperfusion in that case, however, was widespread and not localized.

The two cases presented above illustrate the differential diagnostic problem in distinguishing a partial complex seizure with an emotional and/or sensory trigger from a pseudoseizure that lacks tonic-clonic movements and presents largely as an alteration in consciousness and postural tone. As is often the case, the patient with the pseudoseizure has a poor response to anticonvulsants.[2,10] On the other hand, patients with partial complex seizures are frequently undermedicated if the diagnosis is in doubt.

The video-monitored EEG has been the mainstay tool in helping with this differential diagnosis. However, two kinds of difficulties that have plagued this technique can be remedied by the use of [^{99m}Tc]HMPAO SPECT. The first difficulty is the false-positive problem due to the difficulty of interpreting muscle and movement artifact in the video-monitoring EEG, especially fasciculatory movement in the temporalis muscle. An ictal event may be falsely imputed to an artifact occurring during a pseudoseizure. Brain SPECT will detect a decrease rather than an increase in rCBF in such a pseudoseizure case. The second difficulty is the false-negative problem, in which a deep-lying ictal focus, often in the frontal lobe, fails to propagate to the surface EEG leads during the video-monitoring procedure. Here again, brain SPECT will show a blush of hyperperfusion at the deep brain region during the episode.

Another advantage of the brain SPECT method is the ability to separate isotope fixation in the brain, which occurs at the time of the event, from the signal collection, which can take place half an hour or longer after the event when the patient is relaxed and able to cooperate in the scanning procedure. This feature is useful in providing flexibility around the induction process. Epilepsy centers use a variety of induction procedures, most of which are unreliable. Luther et al.[11] reported on 30 pseudoseizure patients who did respond, but not reliably, to a variety of induction procedures. They found that 53% of the patients were induced by either suggestion alone, hyperventilation, or photic stimulation; another 27% were induced by saline infusion; and the remaining 20% could not be induced by these methods but did have spontaneous spells. Thus, onset of a seizure after induction is unpredictable. However, with the availability of a stable radioligand preparation, an injection of the [^{99m}Tc]HMPAO bolus can now be achieved at any time during an inpatient admission or at daytime hours during outpatient appointments—whenever the seizure occurs. This flexibility also allows the clinician to study patients whose seizures are noninducible or whose seizures do not become more likely after reduction of anticonvulsants.

The advantage of using SPECT can be negated, however, if a timely tracer injection is not achieved at the onset of a seizure. The strategy used in this study, consisting of keeping the tracer at the bedside during the induction process or during simultaneous video-monitored EEG, allows the prompt injection of radioactive material as soon as a clear EEG or behavioral abnormality is observed.

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