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FULL-LENGTH ORIGINAL RESEARCH

Aphasic or amnesic status epilepticus detected on PET but not EEG

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Summary

Purpose: To describe five patients with ictal aphasia and one patient with ictal amnesia, who had focal positron emission tomography (PET) hypermetabolism but no clear ictal activity on electroencephalography (EEG).

Methods: ^{18}F-Fluorodeoxyglucose (FDG)–PET scans with concomitant EEG were obtained in five patients with suspected ictal aphasia or ictal amnesia without ictal activity on EEG. We reviewed medical history, EEG, imaging data, and treatment outcome.

Results: Brain magnetic resonance imaging (MRI) showed no structural abnormalities in any of the patients. EEG showed left temporal irregular delta activity in three patients, with aphasia and nonspecific abnormalities in two other patients, all without clear ictal pattern. All patients demonstrated focal hypermetabolism on PET scan. The hypermetabolism was in the left frontotemporal region in patients with ictal aphasia and in the bilateral hippocampal region in the patient with amnesia. Three patients who received intravenous benzodiazepines during their episodes had transient clinical improvement. With antiepileptic drug (AED) treatment, symptoms gradually resolved in all patients. Concomitant resolution of PET hypermetabolism was documented in three patients who had follow up scans. One patient with ictal aphasia later developed recurrent episodes, each with recurrent PET hypermetabolism. This patient and one other patient required immune-modulating therapy in addition to AEDs.

Discussion: FDG-PET imaging should be considered as a diagnostic tool in patients with suspected ictal aphasia or amnesia, who fail to show clear evidence of ictal activity on EEG.

KEY WORDS: Positron emission tomography, Status epilepticus, Aphasic status epilepticus, Aphasia, Amnesia.

Positron emission tomography (PET) imaging with ^{18}F-fluorodeoxyglucose (FDG) has been useful in the presurgical evaluation of patients with epilepsy (Engel et al., 1982; Uijl et al., 2007). The presence of regional interictal hypometabolism consistent with the location of the epileptic zone by other tests is reassuring and predicts favorable outcome in temporal lobe epilepsy surgery (Manno et al., 1994). If seizures occur during uptake of FDG, PET scans show hypermetabolism in regions that were previously hypometabolic (Engel et al., 1983; Meltzer et al., 2000). Because ictal events are rare and cannot usually be planned during FDG uptake, ictal PET is not typically used clinically. EEG is currently the only test used to determine if mental status changes are ictal in nature. However, there are instances in which the EEG may not show a clear ictal pattern, and some ictal patterns are controversial with respect to their significance. We present a series of patients who presented with subacute persistent aphasia or amnesia in whom FDG-PET was more sensitive than EEG for detecting an underlying ictal origin.

Methods

We collected five patients, four with ictal aphasia and one with ictal amnesia, all with hypermetabolism demonstrated by PET in the absence of clear ictal activity on EEG or structural abnormalities on

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magnetic resonance imaging (MRI). We reviewed all medical records including initial presentation and subsequent follow-up evaluations, PET images, and EEG tracings. PET scanning included EEG monitoring during FDG uptake in all patients. Arterialized blood sampling was obtained in only one patient (Patient 5), allowing calculation of metabolic rate for glucose. In the other patients, FDG uptake was measured by average radioactivity. Brain MRI scans were reviewed, confirming that all were normal.

Results

Case reports

Patient 1

A 29-year-old woman initially presented at age 17 with progressive aphasia for 10 days. This developed gradually, starting the night after she was involved in a car accident as a passenger. She did not have loss of consciousness or serious bodily injury and was able to attend her prom that evening. She was noted to be unusually quiet that evening, and the next day her family noted a progressive difficulty in her ability to express herself. The admission neurologic examination revealed global aphasia and mild right facial weakness. MRI of the brain was normal. Cerebral spinal fluid (CSF) analysis showed normal protein and glucose, and no pleocytosis. EEG showed continuous left hemisphere 1–2.5 Hz polymorphic delta activity with left temporal predominance, but no clear ictal discharge. After receiving intravenous midazolam for sedation before the MRI scan, her speech normalized briefly. FDG-PET showed marked left temporal hypermetabolism. The asymmetry index [AI = 200 × (left − right)/(left + right)] was 36.8%. After treatment with valproate and felbamate, there was gradual normalization of language, with return to baseline after 4–5 months. Follow-up FDG PET images showed normal and symmetrical uptake 5 weeks post admission. She discontinued antiepileptic drugs (AEDs) after 9 months of therapy. At age 25 she had a recurrence of aphasia and was admitted after two generalized tonic–clonic seizures. FDG-PET imaging again showed left temporal hypermetabolism (Fig. 1A). Her EEG showed left temporal irregular delta activity. She improved with intravenous lorazepam and fosphenytoin, and was maintained on oral levetiracetam. Because of persistent dysnomia, oxcarbazepine was added, and her language difficulties resolved. Repeat FDG-PET imaging10 weeks after symptoms restarted was normal (Fig. 1B). She subsequently developed two sequential attacks of left optic neuritis. Two years later, she had one episode of left body tingling, with corresponding FDG-PET hypermetabolism in the right frontoparietal and left cerebellar regions. The EEG showed right frontocentrotemporal irregular delta activity with this episode. Her brain MRI was normal, as were CSF and blood studies for systemic vasculitis and paraneoplastic syndromes. However, an immunologic basis for the optic neuritis was considered as a clinical possibility, and she was placed on low dose prednisone (20 mg daily) and methotrexate (15 mg once a week). Following institution of immunosuppressive therapy her episodes of language difficulties resolved, and she was maintained on lamotrigine for seizure control.

Patient 2

A 45-year-old woman, with a history of discoid lupus, presented with a 3-month history of progressive aphasia. Her examination was prominent for global aphasia without any other focal neurologic deficits. Brain MRI at admission was normal. Lumbar puncture showed normal protein and glucose, and no cells. EEG showed left temporal irregular slow activity and attenuation of normal rhythms. FDG-PET imaging revealed left temporal and frontal increased FDG uptake (Fig. 1C). A few minutes after receiving 2 mg of lorazepam intravenously, she began to speak. However, the improvement in her language was transient. The addition of AEDs produced only modest improvement in her language. Because of our experience with Patient 1, prednisone and azathioprine were added along with valproate and oxcarbazepine to this patient's medication regimen. This drug combination resulted in the return of her language function to baseline.

Patient 3

A 44-year-old woman with no prior neurologic history presented with Wernicke's aphasia that developed over one week. The physical examination showed no other neurologic deficits. Brain MRI was normal. Spinal fluid showed normal glucose and protein, and 11 nucleated white blood cells. Routine EEG showed only left temporal irregular slow activity. A 24-h ambulatory EEG recording was requested for the possibility of recurrent seizures, but no ictal discharges were noted. FDG-PET imaging demonstrated left temporal hypermetabolism (Fig. 1D), whereas the concomitant EEG showed left temporal irregular delta activity with no ictal activity (Fig. 2). She responded to lorazepam intravenously and then was maintained on oral oxcarbazepine. She was near baseline at discharge 2 days later, but was lost to follow-up.

Patient 4

A 75-year-old man developed progressive Wernicke's aphasia over 2 days. The physical examination was normal except for low grade fever. There were no other neurologic deficits. Brain MRI was normal. Spinal fluid evaluation showed normal protein, slightly elevated glucose, and no pleocytosis. EEG showed left hemisphere irregular delta activity. FDG-PET imaging demonstrated left posterior temporal increased uptake (Fig. 1E). There was also increased right cerebellar FDG uptake. Language

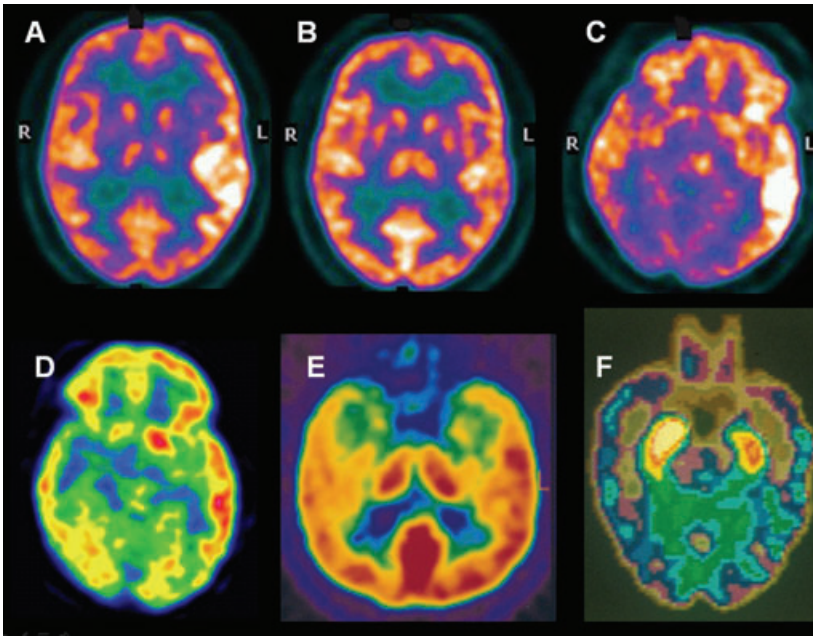

Figure 1.
FDG-PET images on all patients. (**A**) Patient 1 during aphasia; (**B**) Patient 1 after recovery; (**C**) Patient 2 during aphasia; (**D**) Patient 3 during aphasia; (**E**) Patient 4 during aphasia; (**F**) Patient 5 during amnesia.

function and the FDG-PET images normalized with gabapentin therapy. He had two more recurrences with similar presentation and similar FDG-PET findings. He responded to the addition of carbamazepine and is now free of attacks for 4 years.

Patient 5

A 55-year-old man presented with fluctuating progressive memory loss for several months, preceded by recurrent episodes of left-sided numbness, then recurrent feelings that he described as ''body surges.'' The neurologic examination demonstrated anterograde amnesia, without any other deficits. Brain MRI was normal. CSF examination showed no abnormalities. Multiple EEG studies were interpreted as normal. The EEG done at our institution showed nonspecific generalized intermingled slow activity. FDG-PET imaging showed hypermetabolism in both mesial temporal regions, right more then left (Fig. 1F). The mesial temporal metabolic rate for glucose was 180% that of the lateral temporal cortex. He normalized clinically with carbamazepine. On follow-up FDG-PET scan, bilateral mesial temporal hypermetabolism resolved: mesial temporal metabolic rate for glucose had decreased by 33% and lateral temporal rate increased by 40%, such that the mesial to lateral temporal ratio had decreased to 86%.

Discussion

We reported five patients with clinical presentation of aphasic or amnestic nonconvulsive status epilepticus that was detected on FDG-PET imaging but not on EEG. Awareness of this phenomenon is important. This report provides evidence that a ''nonictal'' EEG does not rule out status epilepticus, and it highlights the importance of functional imaging in making a timely diagnosis in this group of patients. It is well-known that simple partial seizure activity may be missed on EEG. Simple partial seizures have no associated clear ictal activity on scalp EEG in approximately 80% of occurrences (Devinsky et al., 1988). The same holds true for simple partial status epilepticus, including epilepsia partialis continua (Niedermeyer, 1999). The clinical diagnosis of epilepsia partialis continua is facilitated by the clonic motor activity, which has limited differential diagnosis. However, other forms of simple partial status epilepticus, such as sensory, autonomic, or aphasic status epilepticus can be extremely difficult to identify on the basis of clinical manifestations alone.

Functional imaging may help identify ictal activity. FDG-PET demonstrates ictal hypermetabolism in the epileptogenic zone (Engel et al., 1983; Chugani et al., 1994). However, ictal PET is extremely difficult to arrange for brief seizures. In addition, the typical uptake phase for FDG to accumulate to a steady state is approximately 60 min, so that the PET images reflect both ictal and postictal activity. Ictal SPECT is commonly used to localize the epileptogenic zone for single brief seizures. Ictal SPECT has also been used to identify focal hyperperfusion in patients with epilepsia partialis continua with facial and extremity twitching and no associated EEG ictal activity (Katz et al., 1990). However, FDG-PET has advantages over ictal SPECT in suspected nonconvulsive status epilepticus. FDG-PET evaluates

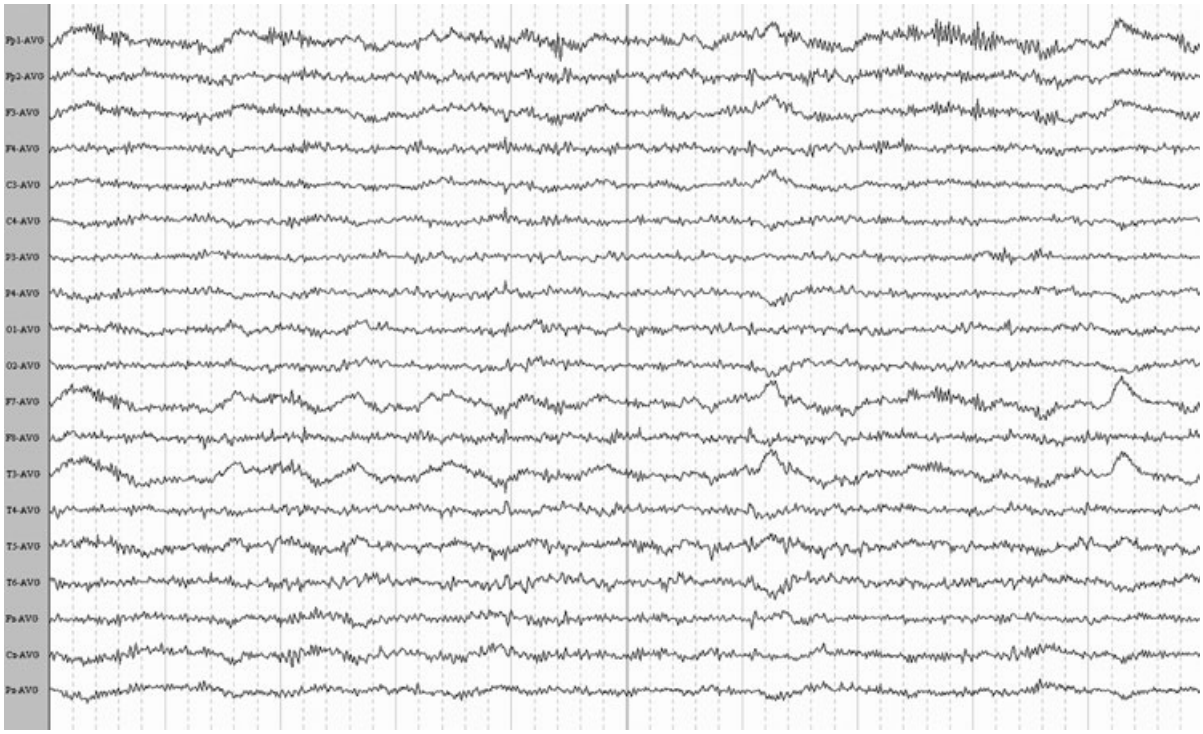

Figure 2.
EEG from Patient 3 during aphasia, obtained in conjunction with PET scan. Left hemisphere irregular delta activity was noted predominantly in the left anterior and mid-temporal regions (electrodes F7 and T3).
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glucose metabolism, whereas SPECT evaluates perfusion, which is usually but not consistently coupled to metabolism. Hence PET provides a more direct measure of cerebral activation. The SPECT tracer uptake levels off with high flow rate so that it is no longer linear with blood flow (Yonekura et al., 1988). Ictal PET is well-suited for suspected nonconvulsive partial status epilepticus, as seen in our patients. Single case reports support that ictal FDG-PET imaging is highly sensitive for detection of ictal hypermetabolism in this setting (Handforth et al., 1994; Kirshner et al., 1995; Yoshida et al., 1995; Van Paesschen et al., 2007). In addition, PET has higher resolution than SPECT.

Our report demonstrated that FDG-PET imaging can be more sensitive in detecting ictal activity than EEG, and should be considered as a diagnostic tool in patients with suspected ictal aphasia or amnesia who fail to show clear ictal activity on EEG. Our case series was notable for absence of MRI abnormality, which prompted more intensive search for a functional disorder underlying the neurologic manifestations.

One might argue that the hypermetabolism could have reflected a nonepileptic process related to inflammation. However, this possibility is not supported by the dramatic response to benzodiazepines and the response to AEDs. In addition, patients with serial FDG-PET imaging showed resolution of hypermetabolism in conjunction with resolution of symptoms, without intervening therapy other than AEDs. Focal hypermetabolism has been reported in cases of suspected encephalitis (Lee et al., 2004), limbic encephalitis (Provenzale et al., 1998; Fakhoury et al., 1999; Kassubek et al., 2001; Na et al., 2001; Fauser et al., 2005), Landau-Kleffner syndrome (Luat et al., 2006), and the syndrome of continuous spike-and-wave activity during slow-wave sleep (Luat et al., 2005). The reports noted previously could not exclude the possibility that hypermetabolism was ictal. For example, the case report of suspected Landau-Kleffner syndrome was of a 4-year-old child with episodic receptive aphasia. FDG-PET imaging showed intensive hypermetabolism in the left temporal neocortex during the aphasic episodes, whereas concurrent EEG showed frequent sharp-wave activity in the left and right temporal regions but no electrographic seizures. However, the episodic nature of the aphasia argues for an ictal origin that the EEG failed to identify. For some cases of limbic encephalitis, there were no EEG findings reported, and the authors did not indicate if an EEG study was performed.

The etiology of aphasic or amnesic status epilepticus in our patients remains unclear. No patient had clinically

significant CSF abnormalities. In Patient 1 there was evidence of inflammatory disease of the central nervous system because of recurrent optic neuritis. Patients 1 and 2 required immunosuppressive medications in addition to AEDs for optimal control of seizure activity. However, follow-up studies have failed to show evolution of the initial symptom complex into recognized neuroinflammatory or auto-immune disorders. In the absence of structural abnormalities, as evidenced by normal brain MRI, the possibility that these disorders may reflect an as yet undefined channelopathy (or other distinct immune disorder) is an intriguing possibility that remains unproven.

In summary, FDG-PET imaging should be considered as a diagnostic tool in patients with suspected ictal aphasia or amnesia who fail to show clear evidence of ictal activity on EEG and have normal brain MRI scan.

Acknowledgments

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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