

Making the Case for Brain ^{18}F -FDG PET Subtraction in Medically Refractory Epilepsy: A Novel, Useful Tool—Practical Points?

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^{18}F -FDG PET plays a major role in the presurgical evaluation of medically refractory epilepsy patients. The current standard of care is performing interictal evaluations of glucose metabolism. Use of this method is related mostly to the tracer kinetics of ^{18}F -FDG because of a long uptake phase that would translate into ictal injections that have low sensitivity and low specificity and demonstrate not only ictal but postictal changes. This limitation can be overcome in some status epilepticus scenarios in which prolonged seizures can then correlate better with ^{18}F -FDG uptake kinetics. In these cases, focal visual qualitative hot spots are suggestive of the seizure-onset zone. However, by using advanced subtraction techniques, the prolonged ^{18}F -FDG uptake phase can be overcome in a variety of other cases as well, opening the door to a slightly larger set of patients who may benefit from this higher-resolution PET method. This article presents 4 cases in which a novel subtraction ^{18}F -FDG PET technique was used and elucidates its impact in these specific cases.

Key Words: brain PET; FDG; epilepsy; subtraction PET

J Nucl Med Technol 2022; 50:353–356

DOI: 10.2967/jnmt.122.264218

In about one third of epilepsy patients, the disease is resistant or not well controlled on multiple medications (1–5). This subset of medically refractory patients may have improved outcomes with surgery (1,4–6). Surgical success requires accurate delineation of the seizure-onset zone (SOZ). Imaging plays a major role, with MRI, SPECT, and PET being essential elements of the work-up (1,7). The current nuclear medicine standard of care for PET (1,2,5–8) is to image patients interictally since the long uptake phase of ^{18}F -FDG in contrast to the short duration of seizures limits evaluation of the ictal phase (8–11). On the other hand, ictal PET has been reported in status epilepticus scenarios, in which prolonged seizures can correlate better with slow ^{18}F -FDG uptake kinetics (12). In these cases, focal visual qualitative hot spots are suggestive of the SOZ (12). Additionally, subtraction ictal–interictal $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime or $^{99\text{m}}\text{Tc}$ -ethyl

cysteinate dimer SPECT, not PET, is used successfully in select cases because of the very short uptake phase—a few seconds—of the cerebral blood flow SPECT radiopharmaceuticals (9–11,13). This article outlines the benefit of using advanced imaging subtraction techniques with ^{18}F -FDG PET. Subtraction is defined as the difference between 2 time points or 2 different conditions/states, and these can be represented by the ictal–interictal time points or 2 different ictal or interictal phases along the continuum of the patient’s disease, including during the pre- and postoperative periods as well as during and after a brain insult such as encephalitis. Advanced semiquantitative or processing techniques are essential tools in the nuclear medicine epilepsy practice.

Use of advanced techniques allows one not only to understand the SOZ but also to uncover propagation pathways and the severity of the seizures (1,14–16). Subtraction ^{18}F -FDG PET is novel and can localize the SOZ for intracranial recording or for surgical resection in lesional and nonlesional epilepsy. It may also directly guide management or lesionectomy if multiple lesions are present.

Subtraction ictal–interictal ^{18}F -FDG PET was performed in the current study. ^{18}F -FDG PET scans were obtained in the ictal and interictal phases after injection of radiopharmaceutical activities according to the guidelines of the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine. Subtraction was performed using MIMneuro software (MIM Software Inc.). Both PET volumes and the patient’s most recent MRI were coregistered. Subtraction of both PET scans was followed by a cluster statistical analysis to define the area of highest significance. The results were coregistered and displayed on the patient’s MRI scan. The patient’s clinical and imaging results were further evaluated at a multidisciplinary epilepsy team meeting. MR images and ^{18}F -FDG PET ictal and interictal scans were reviewed qualitatively. ^{18}F -FDG PET scans were also reviewed semiquantitatively using a reference database control, with *z* score results displayed on stereotactic surface projections (SSPs) of the patient’s MR images. Subtraction ^{18}F -FDG PET/MRI results were also discussed.

CASE PRESENTATION 1

A 6-y-old right-handed boy had intractable seizures, which began at the age of 4 y. The seizure semiology was

Received Mar. 31, 2022; revision accepted Jul. 29, 2022.
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Published online Aug. 30, 2022.

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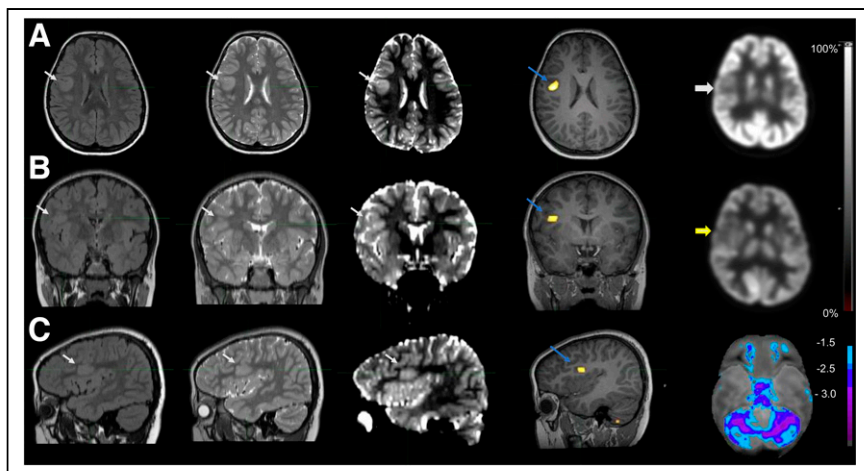


FIGURE 1. Axial (A), coronal (B), and sagittal (C) views of, from left to right, fluid-attenuated inversion recovery MRI, T2-weighted MRI, diffusion-weighted MRI, subtraction ^{18}F -FDG PET fused with T1-weighted MRI, and interictal ^{18}F -FDG PET (in A); ictal ^{18}F -FDG PET (in B); or z score SSP of ^{18}F -FDG PET hypometabolism (in C). Thin white arrows show lesion missed on initial MRI. Thick white arrow shows mild hypometabolism. Yellow arrow shows improved metabolism ictally. Blue arrows show cluster of significance in right Rolandic operculum, corresponding to SOZ.

represented by tonic seizures of the upper limbs lasting 25–30 s and occurring about 30–40 times a day. Generalized seizures also occurred twice a week. Historically, he had a trial of 9 different antiepileptic drugs, and he was currently receiving triple-antiepileptic-drug treatment. His stay in the epilepsy monitoring unit revealed evidence of focal epileptic seizures arising from the right frontal region.

Subtraction ^{18}F -FDG PET was of value in uncovering the SOZ in the right Rolandic operculum (Fig. 1). A small lesion was initially missed on the MRI because of poor technique and the subtle nature of the lesion and was reported only on follow-up MRI (Fig. 1) and only after the subtraction PET revealed the lesion and SOZ. The interictal ^{18}F -FDG PET scan (Fig. 1A) showed a somewhat large area of mild hypometabolism in the right frontal lobe (Fig. 1A). This area had slightly improved metabolism ictally (pseudonormalization of glucose metabolism) (Fig. 1B). Because there were no areas of increased glucose metabolism on the ictal PET, there was no obvious ictal focus to report. However, the subtraction ictal–interictal technique revealed the cluster of significance to be in the right Rolandic operculum, corresponding to the SOZ (Fig. 1). The subtraction technique accurately detected the SOZ and showed its extent, which was much larger on the raw PET data.

CASE PRESENTATION 2

The second case was a 13-y-old boy with intractable seizures. The onset of seizures was at 1 y old in the form of a febrile seizure. The first unprovoked seizure was at 2 y old. The seizure semiology was in the form of loss of consciousness and loss of muscle tone for about 10 s and occurring about 20–25 times a day. Historically, the patient had a trial of 4 different antiepileptic drugs, and he was receiving 2 antiepileptic drugs during the current work-up. His autoimmune and inflammatory workup findings were negative. Interictal electroencephalography showed left frontal slow disturbance and abundant epileptic discharges arising from the left anterior frontal region. Ictal electroencephalography showed multiple seizures, which began in the left frontal region and spread to the right

frontal region. No generalized seizures were noted. The patient was injected with ^{18}F -FDG in the nuclear medicine department approximately 1 min after having a seizure. Then, 2 min after the injection, he had another seizure, and he had an additional 3 seizures during the remainder of the uptake phase before his scan. MRI showed subtle loss of differentiation between the gray matter and white matter in the entire left frontal lobe;

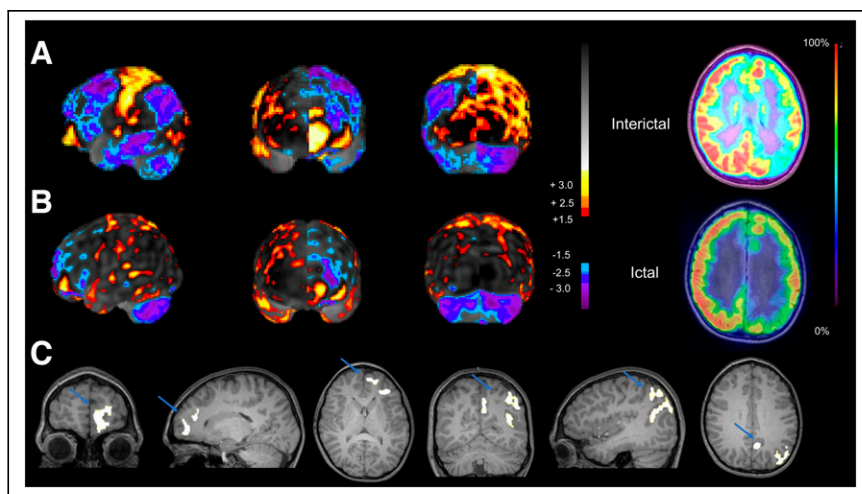


FIGURE 2. (A) From left to right: 2 basal and left lateral z score SSP views for each of, respectively, preoperative cerebral blood flow $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime SPECT image, postoperative cerebral blood flow $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime SPECT image, and postoperative ^{18}F -FDG PET image. Arrows show ^{18}F -FDG PET hypometabolism, which improved postoperatively. (B) Subtraction preoperative and postoperative ^{18}F -FDG PET/MR images displayed in coronal, sagittal, and 3 axial slices. (C) Subtraction ^{18}F -FDG PET/MR images in all 3 planes showing 2 sites of clusters of significance in left frontal and left parietooccipital lobes. Arrows show 2 potential areas for SOZ. On color scale, yellow-red indicates hypermetabolism and blue-purple indicates hypometabolism.

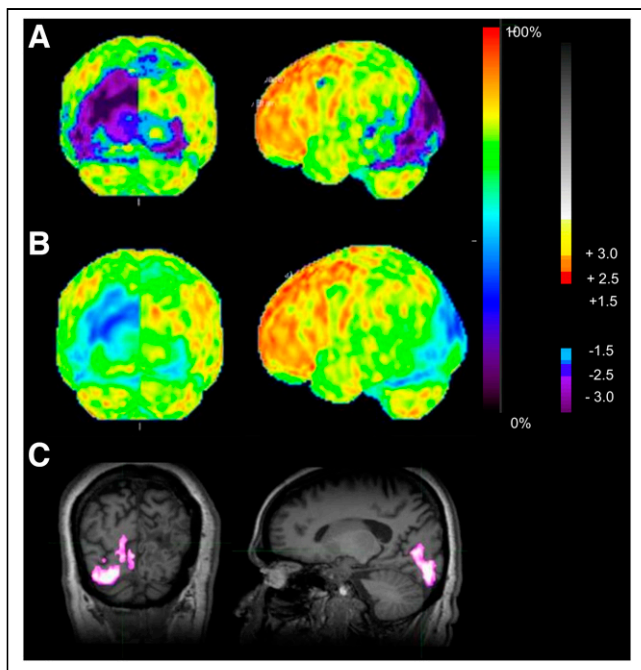


FIGURE 3. (A) Three-dimensional SSPs showing significant areas of hypometabolism in left occipital lobe interictally. (B) Three-dimensional SSPs showing no areas of hypermetabolism in left occipital lobe ictally or elsewhere; however, severity of hypometabolism in left occipital region has diminished (pseudonormalization of glucose metabolism). (C) Subtraction ictal-interictal ^{18}F -FDG PET/MR image showing cluster of significance in left occipital lobe (SOZ).

this finding was most apparent after review of the ^{18}F -FDG PET scan, but the scan findings were initially reported as unremarkable. However, no anatomic or morphologic changes were discernable in the left parietal or parietooccipital regions. Additionally, no obvious ictal region with increased glucose metabolism was noted.

In this case, the raw interictal and ictal ^{18}F -FDG PET data showed a much higher sensitivity at detecting left-hemisphere abnormalities, which were very subtle on the MRI. Additionally, SSPs showed changes in metabolism across the entire brain and how they changed during the ictal phase. The subtraction technique allowed identification of 2 potential areas for the SOZ in the left frontal and left parietooccipital lobes (Fig. 2). This identification guided patient management significantly by defining the SOZ better than was possible on the MRI and raising the possibility of multifocal seizures, as well as allowing for improved selection of the proper

surgical approach (lesionectomy, disconnection, or other), including contemplation of intracranial mapping that would cover both seizure clusters.

CASE PRESENTATION 3

The third case was a 40-y-old man with medically refractory epilepsy due to prior encephalitis. The seizure semiology consisted of simple partial visual seizures, which started when the patient was in his 30s. There were no generalized seizures. ^{18}F -FDG PET scans were performed ictally and interictally. Ictal ^{18}F -FDG PET (Fig. 3B) did not show any areas suggestive of increased glucose metabolism when reviewed as a single study or even when compared with a reference database. Persistent hypometabolism was seen, but when compared with the interictal exam (Fig. 3A), hypometabolism showed improvement in the left occipital region ictally. Therefore, there was a so-called relative increased glucose metabolism ictally that was uncovered only when compared with the interictal study. The subtraction technique clearly uncovered and defined a cluster of significance in the left occipital lobe (Fig. 3C), as looking at the ictal ^{18}F -FDG PET alone showed changes in the SOZ and along the propagation pathway (network effect). Pseudonormalization can also occur in other areas of the brain, hence the value of the subtraction technique. In essence, the ictal ^{18}F -FDG PET scan as an independent examination is limited. However, this limitation can be overcome through comparison to the interictal scan and especially with advanced techniques such as statistical mapping and subtraction using healthy controls as demonstrated here (Fig. 3).

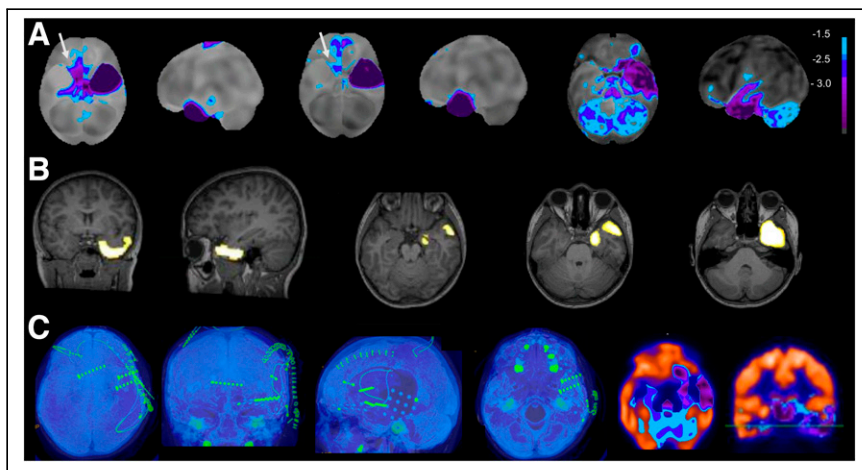


FIGURE 4. (A) From left to right: 2 basal and left lateral z score SSP views for each of, respectively, preoperative cerebral blood flow $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime SPECT image, postoperative cerebral blood flow $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime SPECT image, and postoperative ^{18}F -FDG PET image. Arrows show ^{18}F -FDG PET hypometabolism, which improved postoperatively. (B) Subtraction preoperative and postoperative ^{18}F -FDG PET/MR images displayed in coronal, sagittal, and 3 axial slices. (C) Left: intracranial mapping with grid, strip, and depth electrodes; right: z score hypometabolism on preoperative ^{18}F -FDG PET images.

CASE PRESENTATION 4

The fourth case was a 10-y-old right-handed girl with intractable epilepsy of the left temporal lobe after removal of that lobe and left medial amygdalohippocampectomy. Her seizures started at the age of 5 y. She continued to have seizures after the surgery, with a similar semiology to the preoperative seizures. Scalp electroencephalography recordings after surgery showed a mild, focal, intermittent slow disturbance of cerebral activity in the right frontotemporal region, as well as a multifocal epileptic abnormality seen independently in the left and right anterior head regions. During her stay in the epilepsy monitoring unit, 6 stereotyped seizures were noted, with no definite localizing or lateralizing features. Some seizures were associated with subtle δ -slowing in the bifrontal region, at times with left frontopolar predominance, whereas others were associated with a clear right frontotemporal postictal slowing. These consensus findings from the multidisciplinary epilepsy team suggested a deep left hemispheric epileptogenic focus (orbitofrontal vs. insular), although an independent right-sided focus could not be excluded, considering the electroencephalogram findings. A further evaluation with invasive recordings was performed to further localize the SOZ. Before intracranial mapping, interictal postoperative ^{18}F -FDG PET was performed (Supplemental Fig. 1; supplemental materials are available at <http://jnm.snmjournals.org>). Subtraction images of pre- and postoperative interictal ^{18}F -FDG PET scans (Fig. 4B) excluded any focus in the contralateral right hemisphere, allowing intracranial grids, strips, and depth electrodes to be placed in the left hemisphere only (orbitofrontal, left insular, left cingulate and left posterior temporal regions) (Fig. 4C). Subtraction also suggested that the SOZ extended posteriorly in the left temporal lobe (Fig. 4B). Contralateral right-sided medial temporal lobe hypometabolism seen on the preoperative ^{18}F -FDG PET scan improved postoperatively (Fig. 4A arrows). This change was reported to be associated with better Engel outcomes.

CONCLUSION

^{18}F -FDG PET subtraction techniques offer a significant advantage over traditional interictal ^{18}F -FDG PET evaluations and can be used successfully to delineate the SOZ and guide the management of medically refractory epilepsy patients. It is hoped that the results of the current study will encourage wider use and larger datasets for proper comparison and further expansion of the pool of patients who may benefit.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Can advanced novel PET imaging techniques impact clinical management in medically refractory epilepsy patients?

PERTINENT FINDINGS: Advanced ^{18}F -FDG PET subtraction techniques allow better delineation of the SOZ in medically refractory epilepsy patients.

IMPLICATIONS FOR PATIENT CARE: Advanced ^{18}F -FDG PET subtraction techniques enhance clinical management in medically refractory epilepsy patients.

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