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Imaging inflammation in a patient with epilepsy due to focal cortical dysplasia

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Abstract

Background and Purpose—Evidence from animal models and examination of human epilepsy surgery specimens indicates that inflammation plays an important role in epilepsy. PET using [C11]PK11195, a marker of activated microglia, provides a means to visualize neuroinflammation *in vivo* in humans. We were interested in learning whether [C11]PK11195 PET (PK-PET) can identify areas of focally increased inflammation corresponding to seizure foci of patients with epilepsy.

Methods—A young woman with intractable epilepsy underwent PK-PET as part of an approved research study. PK-PET results were compared with results from other clinical studies.

Results—PK-PET revealed an area of focally increased radiotracer uptake in the right frontal lobe corresponding to this patient's seizure focus as identified by ictal and interictal FDG-PET and a video-EEG. Routine brain MRI was considered normal, though high-resolution studies showed possible subtle dysplasia of the right frontal lobe. The patient underwent a right frontal lobe resection, and pathological evaluation showed focal cortical dysplasia with activated microglia.

Conclusions—PK-PET can identify neuroinflammation associated with subtle focal dysplasia, and may therefore have a clinical role in guiding epilepsy surgery for patients with difficult-to-localize seizure foci.

Case Report

A 31 year old woman had a seven year history of complex partial seizures consisting of behavioral arrest, rarely secondarily generalizing to a convulsion. She had no known risk factors for epilepsy. Brain MRI was initially considered normal, though subsequent high-resolution studies showed possible subtle dysplasia of the right frontal lobe (Figure 1A). She was hospitalized for persistent confusion after a seizure and was found to be in complex partial status epilepticus. After treatment and clinical recovery, frequent right frontal electrographic seizures persisted (Figure 1B). 18-FDG Positron Emission Tomography (FDG-PET) performed at this time, considered to be an ictal study, showed intense right frontal hypermetabolism (Figure 2A). A subsequent FDG-PET performed during a seizure-free period after treatment with lorazepam showed right frontal hypometabolism (Figure 2B). As part of an approved research study, the patient provided informed consent to undergo PET using [C11]PK11195, a radiotracer that identifies brain inflammation by binding to the translocator protein expressed by activated microglia.¹ [C11]PK11195 PET (PK-PET) has identified inflammation associated with multiple sclerosis, Alzheimer's Disease, and stroke,¹ but has not yet been applied to epilepsy, except for rare cases of epilepsy due to known inflammatory causes such as vasculitis or encephalitis.^{2, 3} Using a two-parameter linearized reference tissue model⁴ implemented in PMOD (PMOD Technologies, Zurich, Switzerland), images of tracer uptake (relative to cerebellum) were generated (Figure 2C). Focally increased [C11]PK11195 uptake was apparent in the right frontal lobe in the same region identified as metabolically abnormal by ictal and interictal FDG PET. Because the patient's seizures were difficult to control using medication, she underwent right frontal lobe resection. Surgery was guided by intraoperative electrocorticography, which showed frequent epileptic activity in the right frontal region corresponding to imaging abnormalities. Examination of resected tissue revealed focal cortical dysplasia (FCD) with prominent microglial activation (Figure 3). The patient is seizure free one year after surgery.

Discussion

Inflammation is increasingly recognized to play a critical role in the pathogenesis of epilepsy.⁵ This case illustrates the ability of PK-PET to identify focal inflammation corresponding to a patient's seizure focus as identified by (rarely obtainable) ictal FDG-PET, as well as interictal FDG-PET and video-EEG. PK-PET localization of the seizure focus occurred in the setting of very subtle and easily overlooked MRI abnormality. Histopathological demonstration of activated microglia in tissue obtained at surgery confirms PK-PET findings. This result broadens significantly the potential use of PK-PET in epilepsy beyond patients with a known systemic or CNS inflammatory process^{2, 3} to include patients with focal epilepsy of unknown etiology, or epilepsy due to FCD.

FCD is considered the most common etiology of medically intractable epilepsy in children, and the second most common etiology in adults.⁶ It is a common pathological diagnosis in patients with normal brain MRI's who undergo epilepsy surgery, indicating that it is often not visible in routine neuroimaging studies.⁷ Neuropathologically, FCD is a class of disorders involving abnormal neuronal morphology (e.g balloon cells), organization (e.g.

disrupted lamination) and/or location (e.g. ectopic neurons within white matter.)⁸ Prior studies of FCD surgical specimens have demonstrated that neuronal abnormalities are accompanied by neuroinflammation including activated microglia, with the extent of microglial activation correlating with seizure frequency.⁹ It is not known whether activated microglia are an intrinsic aspect of FCD, or a reactive phenomenon reflecting the near-constant epileptic activity typically associated with FCD lesions.⁸ In either scenario, results from this case support the utility of PK-PET in identifying subtle FCD.

In conclusion, this case demonstrates that PK-PET, by identifying localized inflammation, can aid detection of subtle epileptogenic abnormalities such as FCD in the context of clinical evaluations for epilepsy surgery. PK11195-PET could also be used to inform development of novel anti-inflammatory strategies to combat refractory epilepsy.

I considered including this paragraph, but think I will wait to see if reviewers ask about this:

A possible limitation of this study is the absence of EEG monitoring, which makes it difficult to know whether this patient was experiencing subclinical seizures at the time of PK-PET acquisition. The relative blood flow image (Figure 2D) shows no marked perfusion abnormalities, making an ongoing seizure less likely (and also indicating that changes in blood flow do not account for results.) Furthermore, as noted above, FCD is associated with near constant electrocorticographic epileptic activity,⁸ which calls into question the distinction between the ictal and interictal state in asymptomatic patients.

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Figure 1.

1A: 3T MRI showing possible subtle right frontal lobe cortical dysplasia.

1B: Electroencephalogram obtained at the time of the patient's first (ictal) FDG-PET study, showing a typical right frontal electrographic seizure (onset marked by arrow.) These seizures recurred every 5–30 seconds throughout the one hour scanning session.

Figure 2.

2A: Ictal FDG-PET showing right frontal hypermetabolism.

2B: Interictal FDG-PET showing right frontal hypometabolism.

2C: PK11195-PET overlaid on CT showing increased tracer uptake in right frontal lobe (as well as thalamus, a normal finding).

Figure 3.

3A: 100x magnification H&E stain of right frontal lobe tissue showing enlarged, bizarrely-shaped, dysplastic neurons consistent with focal cortical dysplasia.

3B: 100x magnification CD68 (KP1) stain showing excess microglia with activated morphology.