Case Report

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. Positron emission tomography (PET) using [C11]PK11195, a marker of activated microglia, provides a means to visualize neuroinflammation in vivo in humans. We hypothesize that in patients with active epilepsy, [C11]PK11195 PET (PK-PET) may be able to identify areas of focally increased inflammation corresponding to the seizure onset zone.

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 18F-fluorodeoxyglucose (FDG)-PET and EEG. Routine brain magnetic resonance imaging (MRI) was initially 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 cortical dysplasia, and may therefore have a clinical role in guiding epilepsy surgery for patients with difficult-to-localize seizure foci.

Keywords: Positron emission tomography, epilepsy, inflammation, focal cortical dysplasia, microglia, pk11195.

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Case Report

A 31-year-old woman had a 7-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 (Fig 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 (Fig 1B). An 18F-fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) performed at this time, considered to be an ictal study, showed intense right frontal hypermetabolism (Fig 2A). A subsequent FDG-PET performed during a seizure-free period after treatment with lorazepam showed right frontal hypometabolism (Fig 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.[2-4] Using a two-parameter linearized reference tissue model[5] implemented in PMOD (PMOD Technologies, Zurich, Switzerland), images of tracer uptake (relative to cerebellum) were generated (Fig 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.

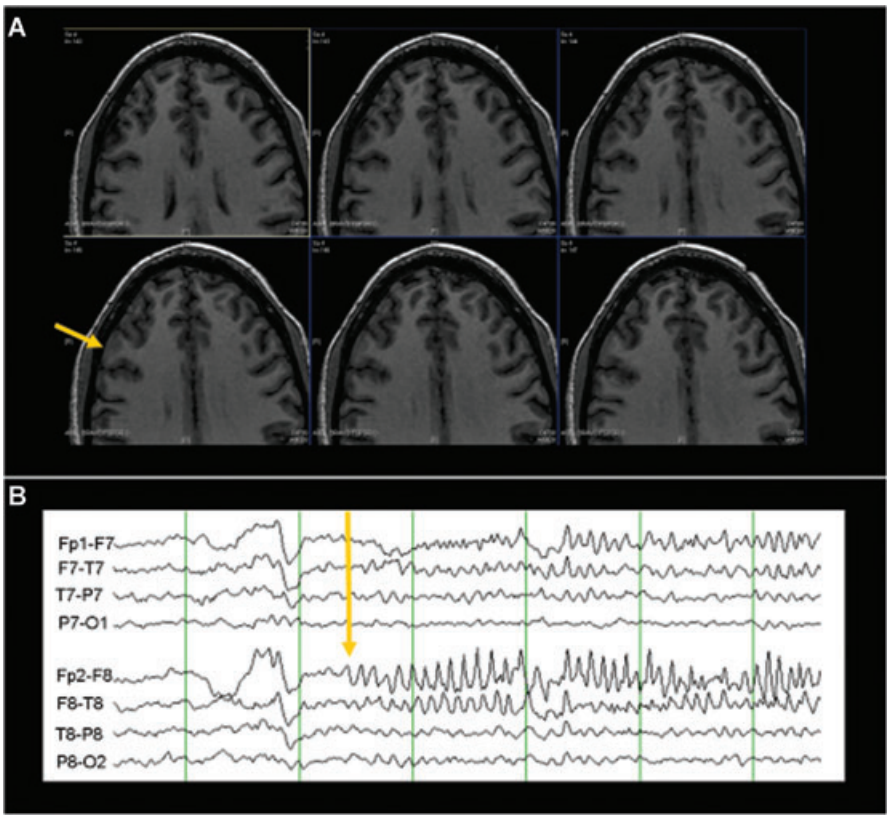

Fig 1. (A) A 3T MRI showing possible subtle right frontal lobe cortical dysplasia. (B) Electroencephalogram obtained at the time of the patient's first (ictal) FDG-PET study, showing a typical right frontal electrographic seizure (onset marked by arrow.) These seizures recurred every 5-30 seconds throughout the 1-hour scanning session.

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 (Fig 3). The patient is seizure free 1 year after surgery.

Discussion

Inflammation is increasingly recognized to play a critical role in the pathogenesis of epilepsy.[6] 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[2-4] to include patients

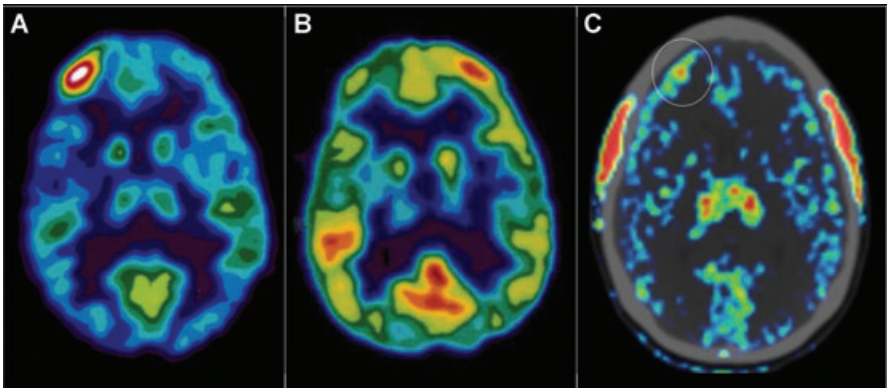

Fig 2. (A) Ictal FDG-PET showing right frontal hypermetabolism. (B) Interictal FDG-PET showing right frontal hypometabolism. (C): PK11195-PET overlaid on CT showing increased tracer uptake in right frontal lobe (as well as thalamus, a normal finding).

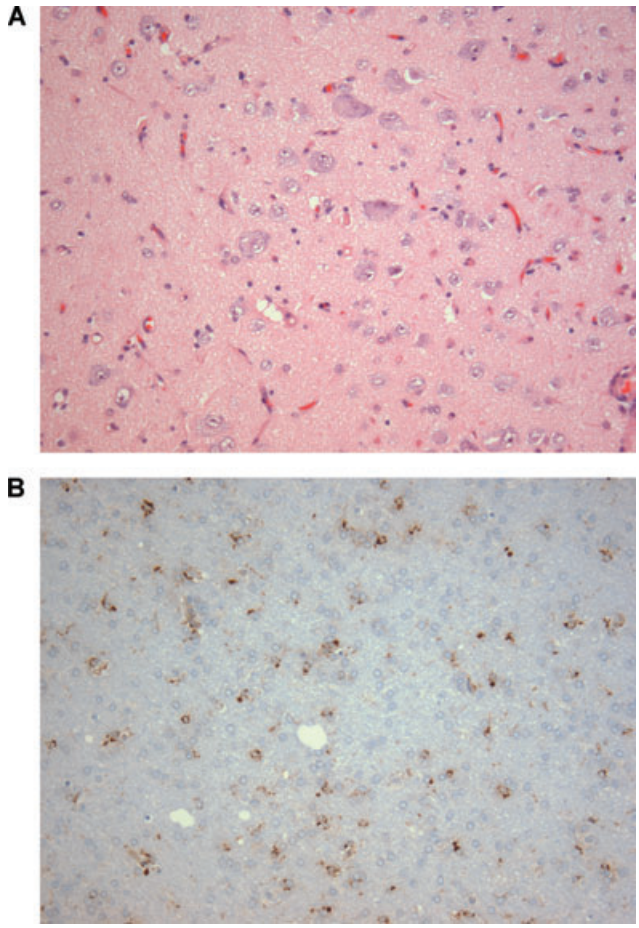

Fig 3. (A) A 100× magnification H&E stain of right frontal lobe tissue showing enlarged, bizarrely shaped, dysplastic neurons consistent with focal cortical dysplasia. (B) A 100× magnification CD68 (KP1) stain showing excess microglia with activated morphology.

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.[7] It is a common pathological diagnosis in patients with normal brain MRIs who undergo epilepsy surgery, indicating that it is often not visible in routine neuroimaging studies.[8] Neuropathologically, FCD is a class of disorders involving abnormal neuronal morphology (eg, balloon cells), organization (eg, disrupted lamination), and/or location (eg, ectopic neurons within white matter).[9] 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.[10] 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.[9] 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.

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