

# Case Report

## Imaging Cerebral Vasculitis in Refractory Epilepsy Using [<sup>11</sup>C](R)-PK11195 Positron Emission Tomography

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**P**K11195 (1-[2-chlorophenyl]-N-methyl-N-[1-methylpropyl]-3-isquinoline carboxamide) is a specific ligand for the peripheral benzodiazepine binding site (PBBS), which is particularly abundant on cells of mononuclear phagocyte lineage. The PBBS is not normally expressed in healthy brain tissue. However, areas containing brain macrophages or activated microglia, the brain's resident and normally dormant population of macrophages, show a significant disease-induced increase in the expression of PBBS [1, 2]. Positron emission tomography (PET) with [<sup>11</sup>C](R)-PK11195 has previously been used to image focal accumulation of macrophages or activated microglia in patients with intractable epilepsy due to Rasmussen's encephalitis [3]. The radionuclide [<sup>123</sup>I]iodo-PK11195 is currently under investigation for use in single-photon emission computed tomography (SPECT) [4].

These earlier studies suggested that the expression of the PBBS closely corresponds to the functional deficits observed clinically in cases in which standard MR imaging either is unrevealing or shows large-scale changes, such as the atrophy of an entire hemisphere. In this report, we describe a patient with persistent partial seizures in whom the onset and progression of disease

suggested that the pathologic process was primarily within the posterior left hemisphere.

### Case Report

A 30-year-old woman had a 12-year history of simple partial seizures, which typically began with the patient's perceiving flashing light on the right side of the visual field. At the time of scanning, occasional secondarily generalized seizures had been occurring once every 3–4 months. Examination of the patient revealed a right-sided homonymous hemianopia, severely impaired verbal memory, dyscalculia, and finger agnosia. An electroencephalogram revealed generalized slow background activity and evidence of left hemispheric dysfunction with irregular  $\theta$  waves. During the entire scan time, we monitored the patient by continuous electroencephalography. She remained free of seizure and showed her usual interictal electroencephalogram activity. MR imaging and [<sup>11</sup>C](R)-PK11195 PET were performed on the same day.

### MR Imaging

T1-weighted spin-echo sequences with and without IV contrast material (gadopentetate dimeglumine) were obtained on a 1.5-T scanner (Signa; General Electric Medical

Systems, Milwaukee, WI). T1-weighted MR imaging (TR/TE, 35/6) revealed atrophy in the left hemisphere that was most pronounced in the occipital and temporoparietal region. No gadolinium-enhancing lesions were shown (Figs. 1A–1C). T2-weighted MR imaging (2500/80) showed increased signal in the left posterior temporal and occipital lobes (Fig. 1G). These images did not show any obvious change in brain volume when compared with MR images obtained 12 months earlier.

### PET

To obtain a PET scan of the patient, we operated the scanner (ECAT HR++ PET; CTI/Siemens, Knoxville, TN) in the high-sensitivity three-dimensional mode after injecting the patient with a bolus of 218.2-MBq single enantiomer [<sup>11</sup>C](R)-PK11195 (36.5 GBq/mmol). During the scan, the patient had no seizures, and electroencephalographic monitoring showed no epileptic discharges. Dynamic data were collected over 60 min as 17 temporal frames. Attenuation correction factors were derived from a transmission image segmented to eliminate the effect of scatter in the raw data (derived from an uncollimated rotating <sup>137</sup>C point

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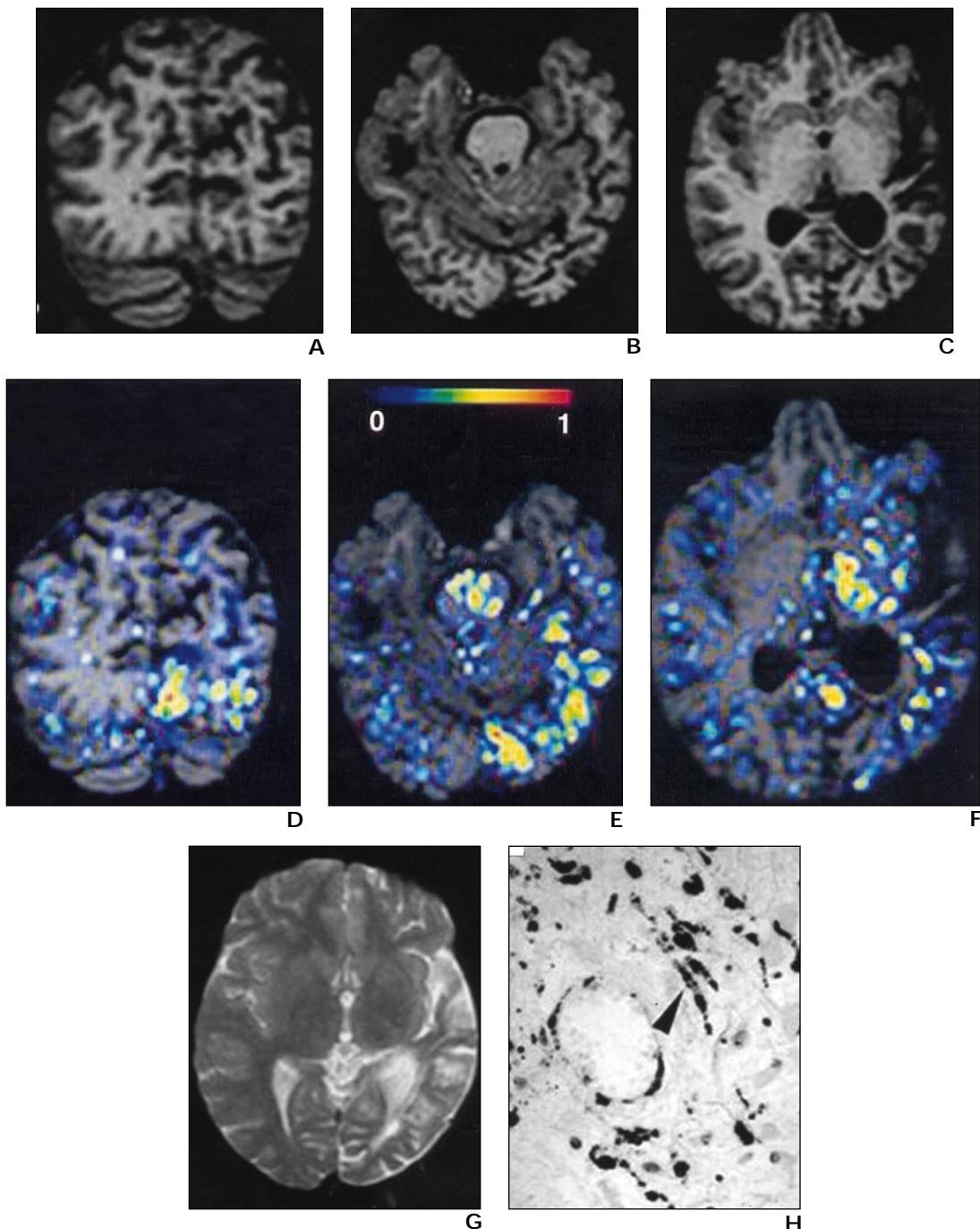
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**Fig. 1.**—MR images (TR/TE, 35/6) and positron emission tomography (PET) images of 30-year-old woman with chronic cerebral vasculitis pathology show unilateral atrophy, particularly of left occipital and temporo-parietal lobes. Images of unaffected right hemisphere show no significant regional increase in  $[^{11}\text{C}](R)\text{-PK11195}$  binding, but images of affected left occipital and temporal lobes reveal regionally increased binding.

**A–C**, Coronal (A) and transverse (B and C) unenhanced T1-weighted MR images.

**D–F**, Coronal (D) and transverse (E and F) images from  $[^{11}\text{C}](R)\text{-PK11195}$  PET.

**G**, T2-weighted MR image (2500/80) shows increased signal intensity in left posterior temporal and occipital lobes.

**H**, Photograph of histopathologic specimen obtained from patient's left occipital lobe stained immunocytochemically with antibody against macrophage epitope CD68 and counterstained with H and E reveals collection of microglia (arrowhead) and macrophages in vicinity of small blood vessel. ( $\times 375$ )

source). Scatter correction was achieved by an analytic calculation of the scatter distribution derived from the raw emission image

(activity distribution) and transmission image (density distribution). Data were subsequently reconstructed with a Hanning filter

producing an image resolution of 6.9 mm (full width at half maximum) at the center of the field of view.

A simplified reference tissue model was used to generate a parametric image of the regional binding potential, which is a measure of specific radionuclide binding [5]. The model was applied to  $[^{11}\text{C}](R)\text{-PK11195}$  PET as described recently in a study of epilepsy patients [3] using the cerebellum as a reference region devoid of any significant binding.

For accurate anatomic localization of  $[^{11}\text{C}](R)\text{-PK11195}$  binding, the binding potential map was coregistered with and superimposed onto the patient's own T1-weighted MR images using a previously described mutual information algorithm [6]. The regional binding of  $[^{11}\text{C}](R)\text{-PK11195}$  in the occipital and temporal lobes of the affected hemisphere (binding potential = 0.40; focal maxima in the occipital lobe > 0.80; variance of binding potential for normal occipital and temporal lobe = 0.002 and 0.004, respectively) and in the ipsilateral thalamus (binding potential = 0.53) (Fig. 1) was significantly increased as compared with healthy tissue where binding potential values are close to zero [3]. Increased  $[^{11}\text{C}](R)\text{-PK11195}$  binding was also seen in the white matter of the left hemisphere containing the fiber tracts of the optic radiation and the internal capsule and in deep gray matter, such as the ipsilateral thalamus and brainstem.

Subsequent biopsy from the left occipital lobe revealed a chronic cerebral vasculitis with perivascular accumulations of mononuclear cells, with small areas of ischemic necrosis; activated microglia; an occasional microglial nodule; and collections of macrophages (Fig. 1H). In addition, there were small gliotic scars suggestive of previous involvement. The patient was subsequently treated with prednisolone and azathioprine, which, at follow-up examination 7 months later, were associated with a marked reduction in the patient's seizures and stabilization of her neurologic and cognitive deficit.

## Discussion

In the reported patient, MR imaging revealed the atrophy in the occipital and tem-

poroparietal region but not the nature of the underlying process. The latter is relevant particularly with respect to potential therapeutic interventions, such as immunosuppressant treatment. In the absence of gadolinium-enhancing lesions indicating disturbance of the blood-brain barrier,  $[^{11}\text{C}](R)\text{-PK11195}$  confirmed the presence of an active inflammatory process with perivascular infiltrates and activated microglia.

Microglia are of mononuclear phagocyte lineage and, being resident in the normal brain, form part of the brain's intrinsic immune system. When activated by neuronal damage or inflammation, microglia de novo express the PBBS [2]. Microglial activation occurs at primary lesion sites as well as in remote projection areas of the lesioned neuronal pathway. Hence, remote microglial activation can regularly be observed in the thalamus ipsilateral to a primary (e.g., ischemic) lesion of the cortex [7]. The associated increase in PBBS expression at these projection sites is associated with a significant rise in  $[^{11}\text{C}](R)\text{-PK11195}$  binding albeit not to the same high levels as is observed in the primary disease foci (such as in the occipital lobe of our patient).

In accordance with the dominant clinical features—unilateral visual-field defect and seizure-associated visual abnormalities since the onset of the disease—the lesions detected in our patient on  $[^{11}\text{C}](R)\text{-PK11195}$  PET involved predominantly the occipital (including the visual cortex) and temporal lobes as well as ipsilateral thalamus and white matter containing visual tract fibers. It is likely that in our patient, the secondary increases in deep gray matter were largely caused by Wallerian-type degeneration resulting from the widespread damage to corticothalamic and corticospinal fiber tracts in the left hemisphere. However, it should be noted that in some brainstem areas that do not have a blood-brain barrier, such as the floor of the fourth ventricle, microglia are not entirely quiescent and, therefore, some constitutive binding of PK11195 is expected.

In summary, the increased  $[^{11}\text{C}](R)\text{-PK11195}$  binding in this patient indicated the presence of macrophages and activated microglia, thus providing additional information about the cellular nature of the brain lesion revealed on MR imaging and a rationale for anti-inflammatory treatment. In patients with vasculitic disease with normal or ambiguous findings on MR imaging,  $[^{11}\text{C}](R)\text{-PK11195}$  PET may also be helpful. Based on the cell biologic phenomenon of microglial activation that is uniquely sensitive to subtle brain lesions [8],  $[^{11}\text{C}](R)\text{-PK11195}$  PET provides a marker of the site and progression of active disease in the brain.

## References

1. Benavides J, Cornu P, Dennis T, et al. Imaging of human brain lesions with an omega 3 site radioligand. *Ann Neurol* **1988**;24:708-712
2. Banati RB, Myers R, Kreutzberg GW. PK ("peripheral benzodiazepine")-binding sites in the CNS indicate early and discrete brain lesions: microautoradiographic detection of  $[^3\text{H}]PK11195$  binding to activated microglia. *J Neurocytol* **1997**;26:77-82
3. Banati RB, Goerres GW, Myers R, et al.  $[^{11}\text{C}](R)\text{-PK11195}$  PET-imaging of activated microglia in vivo in Rasmussen's encephalitis. *Neurology* **1999**;53:2199-2203
4. Dumont F, De Vos F, Versijpt J, et al. In vivo evaluation in mice and metabolism in blood of human volunteers of  $[^{123}\text{I}]jido\text{-PK11195}$ : a possible single-photon emission tomography tracer for visualization of inflammation. *Eur J Nucl Med* **1999**;26:194-200
5. Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ. Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **1997**;6:279-287
6. Studholme C, Hill DLG, Hawkes DJ. Automated three-dimensional registration of magnetic resonance and positron emission tomography images by multiresolution optimization of voxel similarity measures. *Med Phys* **1997**;24:25-35
7. Pappata S, Levasseur M, Gunn RN, et al. Thalamic microglial activation in ischemic stroke detected in vivo by PET and  $[^{11}\text{C}]PK11195$ . *Neurology* **2000**;55:1052-1054
8. Kreutzberg GW. Microglia: a sensor for pathological events in the CNS. *Trends Neurosci* **1996**;19:312-318