Published in final edited form as:

Arch Neurol. 2009 October ; 66(10): 1288–1289. doi:10.1001/archneurol.2009.208.

Stroke incidentally identified using improved positron emission tomography for microglial activation

William C. Kreisl, MD¹, Gilbert Mbeo, MD², Masahiro Fujita, MD, PhD¹, Sami S. Zoghbi, PhD¹, Victor W. Pike, PhD¹, Robert B. Innis, MD, PhD¹, and Justin C. McArthur, MBBS, MPH²

¹Molecular Imaging Branch, National Institute of Mental Health, Bethesda, MD, U.S.A.

²Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, U.S.A.

A 42-year-old man enrolled in a research study using [¹¹C]PBR28, an improved positron emission tomography (PET) radioligand to measure microglial activation. History included HIV infection, diabetes, hypertension, hypercholesterolemia, 12 pack-year smoking history, and remote use of cocaine and heroin. Medical and neurological exam were normal except for elevated blood pressure of 157/100 mmHg. Brain MRI showed occasional foci of mild chronic white matter ischemia but was otherwise unremarkable (Fig A).

The patient then underwent PET imaging of the brain with [¹¹C]PBR28. Surprisingly, a small (1.3 cm³) focus of increased signal in the right basal ganglia was apparent on the PET scan (Fig B). Modeling of radioligand kinetics revealed that the total distribution volume (V_T) of [¹¹C]PBR28 in the right basal ganglia was 76% higher than in the left. V_T is proportional to the amount of microglial activation.

Based on the PET findings, the patient returned to the referring center, where he recalled a previously unreported episode of mild weakness in his left face and left hand. This weakness occurred 12 days before the PET scan and had resolved completely within twenty-four hours.

Repeat MRI demonstrated a new lesion in the same region as the increased PET signal (Fig C, D). The MRI findings were consistent with a subacute infarction occurring between the first MRI and the PET scan.

COMMENT

This case represents the unusual occurrence of a stroke presenting as an incidental finding on PET imaging, and the first time a stroke has been imaged in humans using [¹¹C]PBR28.

Ischemic brain injury results in activation of microglia, which in turn over-express the 18 kDa translocator protein (TSPO, formerly known as the peripheral benzodiazepine receptor).¹ TSPO is consequently a marker of brain injury and inflammation. PET imaging can quantify microglial response to brain injury using radioactive ligands that bind to TSPO. [¹¹C]PBR28 is an improved radioligand for microglial activation, as it has higher specific and lower nonspecific binding to TSPO than the older radioligand [¹¹C] (R)-PK 11195.² [¹¹C]PBR28 is therefore capable of measuring microglial activation with high sensitivity and specificity. In

Corresponding author: William Charles Kreisl, M.D., Molecular Imaging Branch, National Institute of Mental Health, 31 Center Drive, Room B2B34, Bethesda, MD 20892, Phone: (301) 451-8894, Fax: (301) 480-3610, Email: kreislw@mail.nih.gov.
Requests for reprints: Robert B. Innis, MD, PhD, Molecular Imaging Branch, National Institute of Mental Health, 31 Center Drive, Rm. B2/B37, Bethesda, MD 20892-2035, Phone: (301) 594-1089, Fax: (301) 480-3610, E-mail: robert.innis@nih.gov

fact, [^{11}C]PBR28 has high enough signal-to-noise to localize inflammation to relatively small areas, such as the peri-ischemic penumbra in a rat stroke model.³

Although [^{11}C]PBR28 had never before been used to image stroke in humans, we identified an infarct, without a *priori* knowledge that the lesion existed. The lacunar size of the lesion demonstrates that [^{11}C]PBR28 is sensitive for measuring changes in TSPO density in small areas of infarction. Without the [^{11}C]PBR28 PET scan, we would not have obtained the second MRI and the diagnosis of stroke may have been missed. Instead, we were able to identify and modify the patient's risk of future stroke. [^{11}C]PBR28 can identify inflammation in stroke in humans, and may have clinical use in measuring microglial response to ischemia.

ACKNOWLEDGEMENTS AND FUNDING

We thank the staff of the NIH PET Department for successfully performing the PET studies; Jinsoo Hong, Cheryl Morse, and Yi Zhang for production of radioligand; and Kimberly J. Jenko for metabolite analysis.

This research was supported by the Intramural Research Program of NIMH project # Z01-MH-002795-04 (RBI), # Z01-MH-002793-04 (VWP), and by 1PO30MH075673 (JCM).

Dr. Kreisl had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Stephenson DT, Schober DA, Smalstig EB, Mincy RE, Gehlert DR, Clemens JA. Peripheral benzodiazepine receptors are colocalized with activated microglia following transient global forebrain ischemia in the rat. *J Neurosci* 1995 Jul;15(7 Pt 2):5263–5274. [PubMed: 7623150]
2. Imaizumi M, Briard E, Zoghbi SS, et al. Brain and whole-body imaging in nonhuman primates of [^{11}C]PBR28, a promising PET radioligand for peripheral benzodiazepine receptors. *NeuroImage* 2008 Feb 1;39(3):1289–1298. [PubMed: 18024084]
3. Imaizumi M, Kim HJ, Zoghbi SS, et al. PET imaging with [^{11}C]PBR28 can localize and quantify upregulated peripheral benzodiazepine receptors associated with cerebral ischemia in rat. *Neurosci Lett* 2007 Jan 16;411(3):200–205. [PubMed: 17127001]

Figure 1.

(A) The original T1-weighted MRI has mild white matter ischemic changes (not seen at the level shown) but is otherwise unremarkable. (B) [^{11}C]PBR28 PET scan performed 6 weeks later shows increased binding in right basal ganglia. Repeat T1-weighted (C) and FLAIR (D) images show a new stroke (arrows). V_T = Total distribution volume.