Focal High Uptake of HM-PAO in Brain Perfusion Studies: A Clue in the Diagnosis of Encephalitis

Case Presentation and Discussion by Michael A. Meyer
Guest Editor: Heinz W. Wahner

From the Case Records of the Mayo Clinic, Rochester, Minnesota

J Nucl Med 1990; 31:1094–1098

CASE PRESENTATION

A 71-yr-old right-handed housewife presented to the Mayo Clinic in June 1989 with the chief complaint of cognitive function decline.

CLINICAL HISTORY

The patient was well until 6 mo prior to her evaluation when she developed an upper respiratory tract infection associated with mild forgetfulness. She was treated with ciprofloxacillin, 500 mg bid. Her upper respiratory tract infection resolved, but recurred 5 mo later, and was again treated with the same antibiotic. Over the next few weeks, she developed increased forgetfulness for names, dates, and places. She was described as becoming irritable and was having difficulty getting along with family members. She became withdrawn and complained that her husband had no compassion for her. She also believed that her neighbors did not like her and began making errors with both her daughter's and son-in-law's name. Family members noted that she stopped smiling, her hands would tremble, and that she had progressive difficulty in finding words. Her cooking and shopping became slow and laborious, and she complained of being tired and nauseated. By the fourth week of her progressive illness, she could not put together a meal and had fairly significant trouble with short-term memory and word finding. Episodes of confusion and incoherent speech also developed.

Neurologic examination was significant for deficits in short-term memory and attention span, with a mini-mental status score of 21/38 (30/38 or less indicative of dementia by the Kokmen mental status scale (*1*). Her speech displayed an expressive dysprodia, and she had trouble with spatial constructions. Since she had been previously cognitively normal and had developed a progressive dementia over one month's time, an extensive neurologic evaluation was undertaken. A single-photon emission computed tomography (SPECT) brain perfusion scan was ordered. A technetium-99m-hexamethyl-propyleneamine oxime (^{99m}Tc-HM-PAO) SPECT scan was performed 1 hr after injecting 20.9 mCi of tracer (Fig. 1), which revealed an unusually "hot" focus of uptake in the left hippocampus and amygdala, which matched an area of abnormally bright T2 signal on subsequent MR images (Fig. 2). The SPECT scan was interpreted as suggesting an active seizure focus, even though her history was negative for any previous seizures. An awake and sleep electroencephalography (EEG) was subsequently performed the day after her SPECT scan, and showed an active seizure focus in the left temporal-occipital region (Fig. 3). Rhythmic 3-4Hertz left posterior temporal-occipital discharges occurred in 20-sec bursts. During hyperventilation, a 35-sec 3-4Hz rhythmic slow discharge with 2Hz sharp and slow wave complexes were noted, during which time she was mildly dysphasic. Her EEG was considered to be consistent with complex partial seizures.

Since the SPECT and magnetic resonance (MR) scans had pinpointed the left hippocampus as the focus responsible for her subacute, progressive memory deficits, stereotactic biopsy of this area was performed to determine the etiology of her problem, and rule out possible malignancy. Pre-operative intra-arterial digital subtraction angiogram showed no abnormal vascularity or blush of contrast dye in the region of the left temporal lesion, and was otherwise unremarkable (Fig. 4). Biopsy of the lesion using computerized stereotactic techniques revealed benign hippocampal tissue with changes suggestive of chronic encephalitis. Pathologic features included microglial proliferation, sparse peri-vascular inflammation and gliosis. No viral inclusions were noted. The pathology resembled changes seen in a paraneoplastic disease process.

Received Dec. 28, 1989; revision accepted Mar. 28, 1990.
For reprints contact: Michael M. Meyer, MD, Department of Neurology, Mayo Clinic, Rochester, MN 55905.

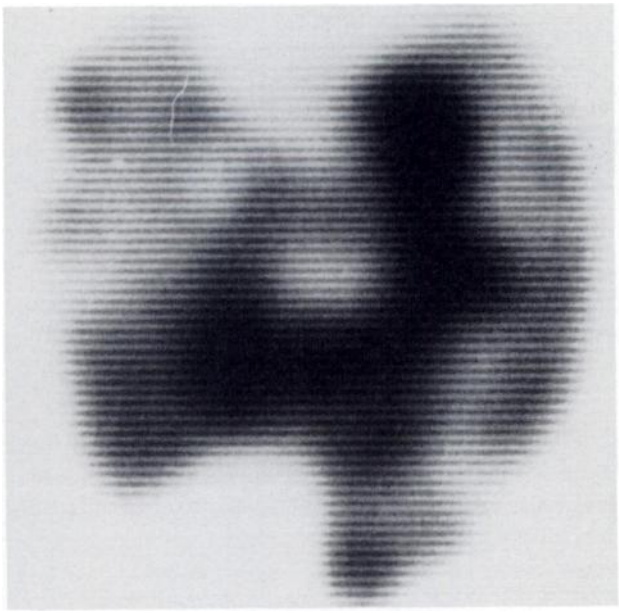

FIGURE 1
SPECT brain perfusion scan obtained 1 hr after injecting 20.9 mCi of ^{99m}Tc-HMPAO. This transaxial section through the temporal lobes demonstrates an unusually "hot" focus of tracer uptake in the left hippocampus and amygdala.

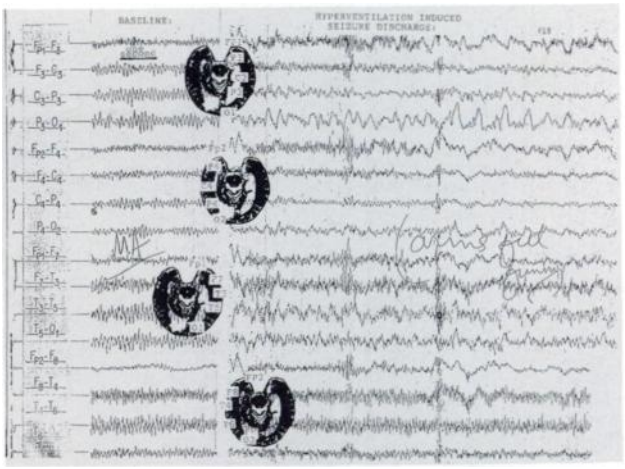

FIGURE 3
Sixteen-channel EEG recording demonstrating fairly normal interictal baseline activity over the left parasagittal regions. During hyperventilation, epileptiform discharges can be noted in the left posterior temporal-occipital region (evident in the 4th, 11th, and 12th channels), corresponding to the general region of abnormally high HMPAO accumulation seen on the SPECT scan.

An extensive search was therefore made to look for an underlying malignancy. Computed tomography (CT) of the abdomen showed a benign cyst of the left kidney and was otherwise negative. Mammogram was normal. Purkinje cell antibody testing was negative, and CEA was negative with a normal hemoquant value of 1.2. Urine and serum protein immunoelectrophoresis did not reveal any monoclonal protein, and was normal. Cerebral spinal fluid (CSF) failed to show any malignant cells, with normal beta-glucuronidase levels. CSF protein and glucose 1 mo after biopsy was 47 and 77 mg/dl, respectively. CSF VDRL was negative, and all cul-

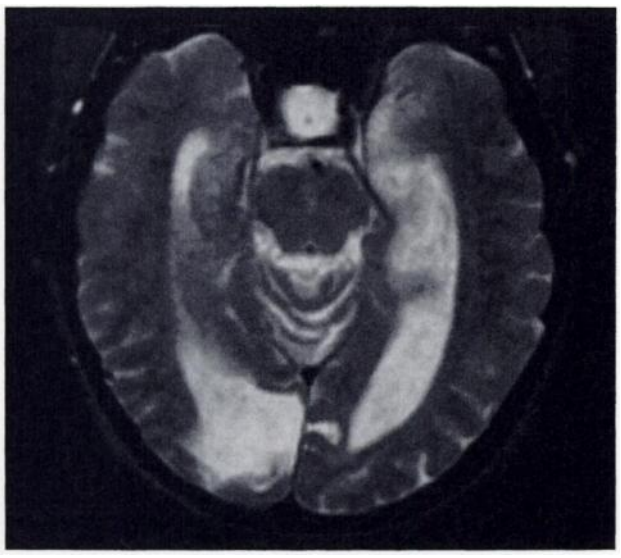

FIGURE 2
Corresponding T2-weighted MR image demonstrating an abnormally bright T2 signal from the left hippocampus. The area of abnormal MR signal is more circumscribed and restricted than the relatively large SPECT abnormality. A chronic, perhaps congenital porencephalic cyst evident in the posterior right occipital region, was noted incidentally.

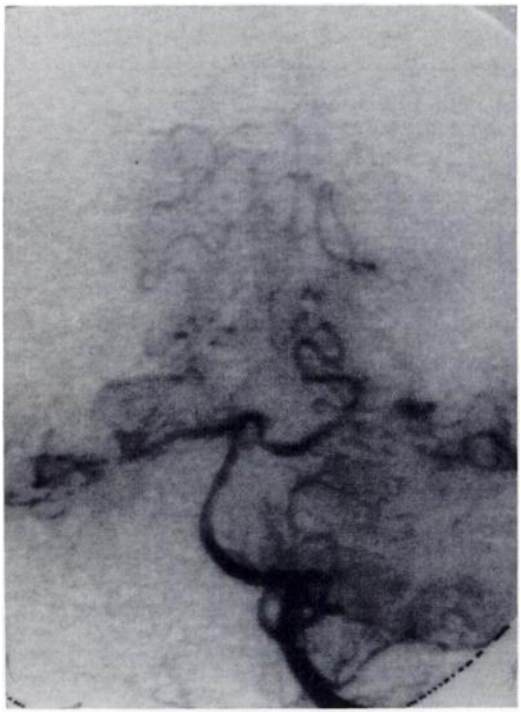

FIGURE 4
Intra-arterial digital subtraction angiogram was unremarkable. Shown above is the arterial phase after contrast dye injection into the left vertebral artery. Normal caliber and size of the basilar artery are noted, as well as the paired posterior cerebral arteries. No abnormal vascularity noted.

tures showed no growth with negative blastomyces and cryptococcal serologies. One WBC/microliter and 1 RBC/microliter was found in the CSF with an unremarkable differential. Heme group, folate, B12, thyroxine, cholesterol, triglycerides, RPR, bleeding time, sensitive TSH and chemistry group were unremarkable with the exception of a mildly elevated glucose at 131 mg/dl, and a serum calcium of 10.2 mg/dl. ANA was positive at 1:20 with a speckled pattern. Urinalysis was negative.

A chest CT revealed a tiny indeterminate nodular density in the left lateral lobe in addition to a calcified granuloma in the left lung base. One month later, the patient stabilized with a slightly improved mental status score of 28/38, and continues to be followed with a diagnosis of dementia secondary to a chronic encephalitis which may be based upon a paraneoplastic effect. However, no definite systemic malignancy has yet been identified.

DISCUSSION

Detection of a high activity (hot) focus on the brain perfusion scintigram with HM-PAO in this case was quite unusual, since normal temporal lobes usually display less avid uptake and retention of tracer than other brain regions. In comparing the patient's SPECT scan through the horizontal plane with her MRI at a comparable level of section, it appears that the unusually high uptake pattern is limited to the mesial left temporal lobe in the region of the left hippocampus.

Both HM-PAO and iodoamphetamine (IMP) brain perfusion studies typically show the temporal lobes normally have lower uptake than other regions of brain cortex, including the cerebellar cortex. Since local cerebral blood flow is coupled to the local cerebral metabolic rate, it is also not surprising to find that temporal lobe glucose metabolic rates are not as high as other brain regions in the normal state. Monkey deoxyglucose autoradiographic studies demonstrate that the normal amygdala and hippocampus have cerebral glucose metabolic utilization rates of 25 and 39 μmole/100 g/min, respectively, versus 47, 59, and 79 μmole/100 g/min for parietal, visual, and auditory cortices, respectively (*2*). A recent normal adult fluorinedeoxyglucose (FDG) study by Evans et al. correlated local metabolic rates with an MRI-based region of interest atlas and found that the hippocampus had one of the lowest metabolic rates of all gray matter structures analyzed (*3*). The metabolic rates were ~30 μmole/100 g/min versus 50 μmole/100 g/min for the hippocampus and striate cortex, respectively. Inferior, middle, and superior temporal gyri averaged ~44, 46, and 37 μmole/100 g/min, respectively. Developmental differences in this relative temporal lobe hypometabolism have also been demonstrated by a fluorodeoxyglucose study which demonstrated a higher temporal lobe glucose utilization rate in 3–8-yr-old patients of 49 μmole/100 g/min versus 24μmole/100 g/min in an older group of 19–30-yr-old adults (*4*).

Aside from the left hippocampal abnormality and the expected perfusion defect over the region of the right occipital porencephalic cyst, the remainder of the patient's SPECT scan was unremarkable. Relatively high uptake was also seen in the cerebellum, which is a normal feature seen on routine HM-PAO scans of normal individuals. Since the high activity focus on the SPECT scintigram matched the abnormal area found on MRI, it was assumed that the left hippocampus was the area of the brain responsible for her symptoms. A stereotactic biopsy of the lesion was therefore performed based on the matching SPECT and MRI information.

A hot spot on a SPECT brain perfusion scintigram does not lead to a specific diagnosis but does suggest that a number of pathologic processes should be considered. Since PET studies have confirmed that central nervous system tumors have high blood flow, it is tempting to extrapolate from the positron emission tomography (PET) studies to SPECT and speculate that HM-PAO or IMP SPECT scintigrams might display areas of malignancy with abnormally high uptake of tracer. A review of the current literature on SPECT imaging of primary brain tumors shows this apparently is not always true. A great number of iodine-123-IMP ([^{123}I]IMP) studies and a smaller number of ^{99m}Tc-HM-PAO studies show that primary CNS tumors more often appear as cold spots on SPECT brain scintigrams. This also appears to be the case for HIPDM. Looking at the cumulative published experience to date, only one of 26 low-grade gliomas (4%) had increased [^{123}I]IMP uptake versus one of 23 patients with high-grade gliomas (all 23 patients with unclassified gliomas failed to show increased tracer uptake). Whereas only 2 of 72 patients had increased [^{123}I]IMP uptake, 10 of 50 glioma patients had increased HM-PAO uptake. High-grade gliomas showed increased HM-PAO uptake in 8 of 32 cases, and 2 of 7 unclassified gliomas had high uptake patterns (25% and 29%, respectively). All 11 patients that have been cumulatively reported with low-grade gliomas failed to show increased HM-PAO uptake. Meningiomas appear to behave differently, showing increased HM-PAO in 11 of 14 cases (79%) versus only 8 of 47 cases with increased [^{123}I]IMP uptake (17%). In one study by Nakano et al. (*5*), on 12 meningioma patients, low uptake of [^{123}I]IMP at 20 min postinjection can be associated with high flow patterns found by dynamic SPECT scanning, suggesting that there is no mechanism for tracer uptake and/or retention by meningiomas. A similar situation probably exists for astrocytomas as well.

Important exceptions to the predominantly normal or low uptake of [^{123}I]IMP by brain tumors include metastatic melanoma and metastatic carcinoid tumors.

Holman and colleagues studied 47 patients with a variety of primary and metastatic tumors, and found 4 of 5 patients with brain metastasis from melanoma had increased iodoamphetamine uptake in the tumor (*6*). Increased uptake of IMP might also occur for small cell tumors of the lung, but this is not as well known. A recent study clearly demonstrates that carcinoid tumors metastatic to brain accumulate and retain IMP at 1, 5, and 24 hr after injection (*7*).

Our patient's MRI exam was interpreted as being worrisome for neoplasm, which influenced the decision to biopsy the lesion to rule out glioma. However, based on the collected experience with HM-PAO, the prebiopsy probability of tumor was low.

Seizure activity is another important cause for an unusually high focal uptake of tracer in the brain. It has been shown by both PET and SPECT scintigraphy that a seizure focus has elevated metabolic rates and high blood flow during the ictal phase, and accumulated high amounts of iodoamphetamine or HM-PAO at that time (*8,9*). In contrast, the inter-ictal phase is associated with depressed metabolism and blood flow, resulting in a low activity focus on SPECT brain scintigrams. The abnormally high activity on the HM-PAO scintigrams in the left hippocampus of this patient was consistent with unrecognized complex-partial seizure activity. The subsequent EEG confirmed that an active seizure focus did indeed exist in the left temporal lobe (Fig. 3). The patient was subsequently placed on Carbamazepine, 200 mg tid. Although no clinically apparent seizure activity has been noted, another EEG one month after biopsy again showed electrographic seizure activity, now centered over the right temporal region. Although a follow-up SPECT scintigram has not been performed, it is interesting to note that the posterior right mesial temporal lobe of the patient's scan also appears to show elevated tracer uptake and might reflect the site of the epileptiform activity that was to develop later on.

A focal area of markedly elevated uptake of HM-PAO is distinctly unusual in routine dementia evaluations when Alzheimer's disease is clinically suspected. Our clinical experience with Alzheimer's disease agrees with the published literature that focal posterior parietal perfusion defects are commonly found (*10*). When dementia is due to a multi-infarct state, corresponding patchy deficits in perfusion are likewise noted. Diminished uptake of tracer in patients with recent and progressive dementia would also be consistent with HIV related dementia (*11*). However, secondary lesions in immunosuppressed AIDS patients might lead to focal hot spots, especially if viral encephalitis has occurred (see below). Other less frequent causes for dementia such as Huntington's chorea are not known to be typically associated with focally increased tracer uptake. Although advanced Huntington's chorea has been associated with diminished HM-PAO or IMP uptake in the caudate (*12*), we have seen a case of early Huntington's chorea with progressive memory trouble and bilaterally increased IMP uptake in the temporal lobes. Brain CT was unremarkable in this patient.

Focally increased IMP or HM-PAO uptake in the temporal lobe can be associated with viral encephalitis. In six patients with herpes simplex encephalitis, focal increases in HM-PAO uptake at the site of infection have been reported when the brain CT is initially negative (*13*). This initially high uptake pattern has been reported to normalize after therapy. Launes et al. (*13*) claim this to be specific to herpes simplex encephalitis, yet a case report by Duncan et al. (*14*) demonstrated that increased uptake can also be seen in non-herpes encephalitis, and even decreased uptake was noted in one patient with acute herpes encephalitis (*15*). A recent study by Lane et al. (*16*) demonstrates both MRI and SPECT findings which are very similar to our presented case. Whereas their patient had herpes encephalitis with focally elevated HM-PAO uptake in the left temporal lobe 53 days after onset of the illness, our patient had biopsy-proven encephalitis though no viral inclusions could be found.

Limbic encephalitis, also known as paraneoplastic encephalomyelitis, is usually found to be a remote effect of small cell lung carcinoma. Inflammatory infiltrates of cytotoxic/suppressor T lymphocytes and neuronal loss has been demonstrated in not only the hippocampus but also in the brainstem, spinal cord, and dorsal root ganglia (*17*). Both serum and CSF of afflicted patients will selectively stain only neuronal nuclei at dilutions up to 1:20,000 and 1:400, respectively, and appear to be directed against a 35–40-kd molecular weight neuronal antigen (*18*). Although a malignancy is usually discovered at autopsy in these patients, cases have been reported where a malignant tumor cannot be identified in patients with limbic encephalitis. In Brierly's initial description of limbic encephalitis, two of his three cases failed to show any systemic malignancy (*19*). A recent report by Ingenito et al. found biopsy and autopsy changes consistent with limbic encephalitis in a 59-yr-old man with only a benign thymoma and no malignancy (*20*). DNA probe analysis for herpes simplex types 1 and 2 virus, cytomegalovirus, and HIV virus were all negative in their reported case. Therefore, failure to identify a malignancy in our patient's case would not be inconsistent with a pathologic diagnosis of limbic encephalitis.

CONCLUSION

This case, with the unusual diagnosis of limbic encephalitis, demonstrates how brain perfusion studies can be helpful in the diagnostic evaluation of patients presenting with complex focal brain disease. The findings shown here are entirely nonspecific and can be seen in any type of acute or chronic viral encephalitis

involving the temporal lobe. Since hippocampal blood flow and metabolism are normally low relative to other brain regions, finding high HM-PAO uptake in this area on SPECT scans is unusual and should therefore raise suspicion for the possible existence of encephalitis and/or a very recent temporal lobe seizure.

ACKNOWLEDGMENT

I would like to thank Dr. H.W. Wahner (Nuclear Medicine) for helpful suggestions and review of this manuscript.

REFERENCES

1. Kokmen E, Naessens JM, Offord KP. A short test of mental status: description and preliminary results. *Mayo Clin Proc* 1987; 62:281–288.
2. Kenedy C, Sakurado O, Shinohara M, et al. Local cerebral glucose utilization in the normal conscious macaque monkey. *Ann Neurol* 1978; 4:293–301.
3. Evans AC, Beil C, Marrett S, Thompson CJ, Hakim A. Anatomical-functional correlation using an adjustable MRI based region of interest atlas with positron emission tomography. *J Cereb Blood Flow Metab* 1988; 8:513–530.
4. Chugani HT, Phelps ME, Maziotta JC. Positron emission tomography study of human brain development. *Ann Neurol* 1987; 22:487–497.
5. Nakano S, Kinoshita K, Jinnouchi S, Hoshi H, Watanabe K. Dynamic SPECT with iodine-123 IMP in meningiomas. *J Nucl Med* 1988; 29:1627–1632.
6. Nagel J, Ichise M, Mueller S, et al. Increased iofetamine I-123 brain uptake in metastatic melanoma. *Arch Neurol* 1988; 45:1126–1128.
7. Nishizawa S, Higa T, Kuroda Y, Sano A, Mrakami M, Takahashi Y. Increased accumulation of N-isopropyl-I123-p-iodoamphetamine in bronchial carcinoid tumor. *J Nucl Med* 1990; 31:240–242.
8. Lee B, Markand O, Wellman H, et al. HIPDM-SPECT in patients with medically intractable complex partial seizures: ictal study. *Arch Neurol* 1988; 45:397–402.
9. Stefan H, Pawlik G, Bocher-Scharz H, et al. Functional and morphological abnormalities in temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *J Neurol* 1987; 234:377–384.
10. Smith F, Besson J, Gemmell H, Sharp P. The use of technetium-99m-HMPAO in the assessment of patients with dementia and other neuropsychiatric conditions. *J Cereb Blood Flow Metab* 1988; 8:S116–S122.
11. Costa D, Ell P, Burns A, Philpot M, Levy R. CBF tomograms with 99mTc-HMPAO in patients with dementia (Alzheimer type and HIV) and Parkinson's disease—initial results. *J Cereb Blood Flow Metab* 1988; 8:S109–S115.
12. Nagel J, Johnson K, Ichise M, et al. Decreased iodine-123 IMP caudate nucleus uptake in patients with Huntington's disease. *Clin Nucl Med* 1988; 13:486–490.
13. Launes J, Nikkinen P, Lindroth L, Brownell A, Liewebdahl K, Iivanainen M. Diagnosis of acute herpes simplex encephalitis by brain perfusion single photon emission computed tomography. *Lancet* 1988; ii:1188–1191.
14. Duncan R, Patterson J, Bone I, Kennedy P. Single photon emission computed tomography in diagnosis of herpes simplex encephalitis. *Lancet* 1988; ii:516.
15. Nara T, Nozaki H, Nishimoto H. Single photon computed tomography in diagnosis of herpes simplex encephalitis. *Lancet* 1988; ii:516.
16. Lane R, Kirkibride V, Hughes P, Jones B, Costa D. Diagnosis of herpes simplex encephalitis by single photon emission tomography. *Lancet* 1989; ii:778–779.
17. Henson RA. Encephalomyelitis with carcinoma. In: Henson RA, Urich H, eds. *Cancer and the nervous system.* Oxford, UK: Blackwell Scientific; 1982:314–345.
18. Graus F, Ribata T, Campo E, Monferte R, Urbano A, Rozman C. Immunocytochemical analysis of the immune reaction in the nervous system in paraneoplastic encephalomyelitis. *Neurology* 1990; 40:219–222.
19. Brierley JB, Corsellis JAN, Hieron R, et al. Subacute encephalitis of later adult life, mainly affecting the limbic areas. *Brain* 1960; 83:357–368.
20. Ingenito GG, Berger JR, David NJ, Norenberg MD. Limbic encephalitis associated with thymoma. *Neurology* 1990; 40: 382.