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# SPECT Imaging in Alzheimer's Disease

B. Leonard Holman

*Brigham and Women's Hospital*

Keith A. Johnson

*Massachusetts General Hospital*

*and*

Thomas C. Hill

*New England Deaconness Hospital*

A number of radiotracers have recently been developed that accumulate in the brain proportional to cerebral blood flow. These compounds are lipophilic, moving across the blood-brain barrier with nearly complete extraction during a single passage through the cerebral circulation. Once inside the brain, they are either bound to nonspecific receptors or metabolized to nonlipophilic compounds. As a result, they maintain this distribution within the brain for some time after injection. The development of these commercially available tracers promises to bring into general medical practice the remarkable diagnostic advances that have been limited to the small number of centers that can afford the costly on-site cyclotrons and technical support required for positron emission tomography. This review will describe the radiopharmaceuticals and instrumentation which may be expected to provide useful clinical information about cerebral perfusion, and will describe the authors' initial experience with these techniques in memory disorders.

While it is possible to diagnose Alzheimer's disease in some patients with 90% certainty based on a constellation of clinical and laboratory observations, approximately half the patients with Alzheimer's disease cannot be accurately categorized at the time of their initial visit. In these patients, it may require years of follow-up study before these patients can be correctly diagnosed.

Radiotracer methods have been used to measure blood flow and metabolism in patients with Alzheimer's disease for several decades. Initially, investigators using the inert gas washout method observed that blood flow was reduced globally in Alzheimer's disease. More recently, studies carried out at a number

Requests for reprints should be sent to: B. Leonard Holman, M.D., Department of Radiology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115.

provide absolute measurements of cerebral flow, it can provide clinically useful indices for the detection and evaluation of diseases which attack the brain regionally.

## Image Acquisition

Careful quality control is essential with SPECT. The relatively low photon flux from the target organ, the scattered radiation from the high energy gamma rays of I-123 and I-124, and the low photon energies associated with T1-201, stretch the imaging process to its limits.

Between 3–5 mCi I-123 IMP is injected intravenously (3–4 mCi of T1-201 DDC and 10–20 mCi of Tc-99m HMPAO is used as the tracer). Imaging begins 10–20 minutes after injection with the patient supine and the head centered in the field of view. The patient's head should be placed in a holder to ensure that it does not move during the 30–40 minutes of data acquisition. The patient should be placed on a comfortable couch so that movement is reduced to a minimum during data acquisition.

For the rotating gamma camera, a sixty-four frame, 360 degree study is acquired with the detector as close to the head as possible using a collimator optimized to the energies of the radionuclide. The total image is 20–30 minutes.

Reconstruction is performed after correcting the 64 frames with a 60 million count flood source image and after correcting for photon attenuation. Attenuation correction is more straightforward for imaging of the head than for imaging of the thorax or abdomen. Since the attenuation constant does not vary significantly throughout the brain, attenuation corrections such as those introduced by Sorenson or Chang are quite suitable for brain perfusion tomography.

Reconstruction is performed using a ramp filter. A three-dimensional Butterworth filter is then applied to the reconstructed images to reduce the noise introduced from the out-of-slice planes as well as from the plane of the image. Image reconstruction from the 3D data set may be performed along any plane of interest, depending on the clinical situation. Typically, reconstructions are performed along the plane parallel to the orbitomeatal line and in the coronal and sagittal planes.

## Normal Patterns

Patients without central nervous system disease and with normal X-ray CT examination demonstrate bilaterally symmetrical activity on the SPECT perfusion images (Figure 1). Activity is greatest along the convexity of the frontal, temporal, parietal, and occipital lobes corresponding anatomically to cortical gray matter. Activity is also high in the regions corresponding to the

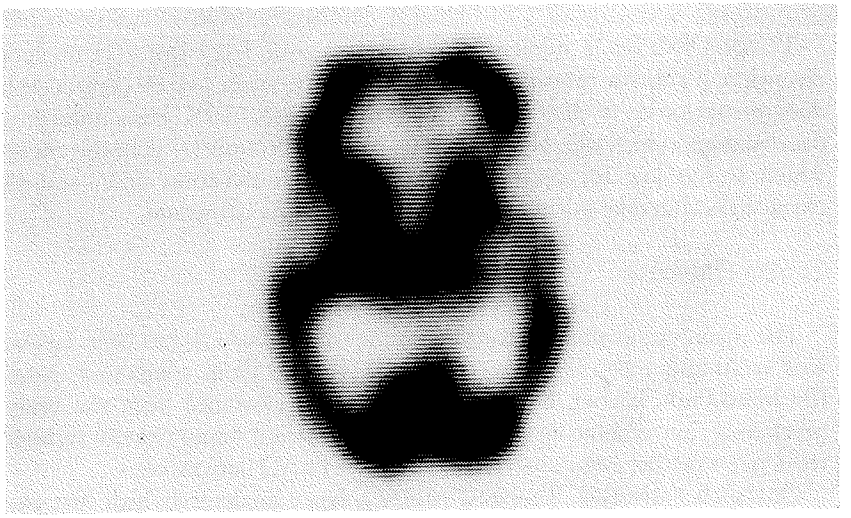

Figure 1: Normal transaxial I-123 IMP SPECT at level of basal ganglia and thalamus.

basal ganglia and thalamus. The regions between the basal ganglia and the convexity corresponding anatomically to cortical white matter and the ventricles have less activity.

Attention must be paid to achieving a reproducible baseline state. We inject the tracer with the patient's eyes open, with the room dimly lit and with white noise in the background. This state of activation is maintained during the 10–20 minutes before image acquisition. Strong arguments have been made for covering the patient's eyes and ears in order to reduce outside stimulants which might increase blood flow and metabolism. The injection protocol will depend on the information that is being sought but, once the protocol is established, it must be followed diligently.

## SPECT in the Dementias

More than 15 years ago, investigators using the inert gas washout method, observed that blood flow was reduced in Alzheimer's disease (Obrist, Chivian, Cronquist, and Ingvar, 1970; Simard, Olesen, Paulson, Lassen, and Skinhoj, 1971). Studies carried out at various PET facilities suggested that these abnormalities in flow and metabolism were focal and most extensive in the parietal area (Benson, Kuhl, Phelps, Cummings, and Tsai, 1981; Cutler et al., 1985; Foster et al., 1983; Frackowiak et al., 1981; Friedland et al., 1983). A number of groups have suggested that the changes in metabolism seen with PET could be repeated with the single photon tracer I-123 IMP (Cohen et al, 1986; Johnson et al., 1985; Sharp et al., 1986).

Tl-201 DDC has a number of advantages over I-123 IMP: (1) no lung retention, (2) on-site preparation, (3) ease of preparation, and (4) considerable documentation on its distribution and toxicity. Tl-201 DDC has a number of disadvantages which will prevent its wide-scale application: (1) a photon energy which is too low for optimal imaging, (2) high radiation dose, and (3) extracerebral uptake in the muscles surrounding the calvarium.

*Tc-99m-HM-PAO*

The macrocyclic amine, propyleneamine oxine (PnAO), has been labeled with technetium-99m (Holmes et al., 1985). This lipophilic compound crosses the blood:brain barrier, but it has a very rapid clearance from the brain, precluding tomographic imaging. However, significant improvements in brain residence time has been observed with newer PnAO derivatives.

One such derivative, Tc-99m-HM-PAO, has a moderately high first pass extraction through the cerebral circulation and has an initial cerebral distribution similar to IMP (Ell et al., 1985; Holmes et al., 1985). Unlike IMP, Tc-99m-HM-PAO does not appear to redistribute within the brain for up to 4.5 hours after injection. Tc-99m-HM-PAO has significant advantages over either I-123 IMP or Tl-201 DDC: (1) on-site preparation, (2) lower radiation dose, (3) lower cost, (4) ideal physical characteristics, and (5) higher photon flux.

Ultimately, a Tc-99m labeled tracer will be necessary for cerebral perfusion imaging to achieve a high level of clinical acceptance. The limited availability and high cost of I-123 and Tl-201 labeled agents will prevent them from competing effectively with a Tc-99m agent which can be prepared routinely from a kit on-site, provided that the Tc-99m labeled agent yields images of comparable quality. Nevertheless, experience with I-123 labeled amines and Tl-201 DDC provides us with the tools necessary to establish the clinical utility of cerebral perfusion imaging.

## Instrumentation

Single photon emission computed tomography (SPECT) of the brain can be performed using either multidetector or rotating gamma camera systems. Each imaging system has its advantages; the choice of equipment depends on the level of utilization and on the purposes to which the technique will be applied.

The high collection coefficiency of the multidetector system makes rapid scanning (5–7.5 minutes) of an entire slice possible. The primary advantage of this system is its high sensitivity, resulting in high spatial resolution and rapid imaging. As a result, SPECT perfusion images of the brain can be obtained with a spatial resolution of 10 mm (full-width at half-maximum) in the plane of the slice. The multidetector system would, therefore, be the preferred instrument

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reduced. In a patient with biopsy proven Jacob-Creitzfeld disease, IMP uptake was markedly reduced uniformly throughout the cortex; the parietal areas were affected to the same extent as elsewhere in the brain. The perfusion pattern in Korsakoff's psychosis is patchy, but without focal defects (Sharp et al., 1986). Early indications would, therefore, suggest that most dementias can be distinguished from the dementia of Alzheimer's disease.

Is the abnormal pattern seen early in the course of the disease? It will require several years before we have defined the diagnostic accuracy of SPECT in early Alzheimer's disease. Our preliminary data is promising, however. In a group of patients studied during the early phase of their clinical workup, who met NINCOS-ADRDA criteria for the diagnosis of probable Alzheimer's disease, and who had mild to moderate dementia, 10 out of 13 had decreased perfusion to the parietal cortex. In 18 patients in whom the diagnosis of Alzheimer's disease could not be made with certainty, seven had reduced uptake in the parietal lobes similar in appearance to the perfusion pattern seen in patients with probable Alzheimer's disease; four patients had parietal abnormalities in addition to focal defects elsewhere suggesting combined vascular and Alzheimer's disease. Only one patient in this group had the findings of multi-infarct dementia with multiple asymmetric defects. Six patients had a normal perfusion scan. While it is possible that patients with normal perfusion have a slower deterioration in their cognitive function (if they have Alzheimer's disease at all), long term follow-up will be necessary to properly classify these patients and to determine the accuracy of perfusion SPECT in this large group of patients who cannot be classified by current techniques.

These data underscore the need to provide more objective screening tests in patients with memory disorders. While some patients can be recognized early in their clinical course as probable Alzheimer's disease, many others remain diagnostic dilemmas until their disease process has advanced or until post mortem confirmation is obtained. An "early warning" system to either alert the patient, his or her family and clinician to the future needs of the patient or, alternatively, to provide reassurance to the patient that his or her course will be a benign one, would be a significant addition to our diagnostic armamentarium. Pharmacologic therapy for Alzheimer's disease is a subject of active investigation and an objective marker of cerebral function may aid in the testing of drug efficacy.

## Receptor Imaging

While perfusion SPECT may be useful in the differential diagnosis and staging of the dementias, the functional information that it provides may be quite limited for uncovering the underlying mechanisms of Alzheimer's disease and for detecting the disease before it becomes symptomatic. The perfusion changes that we see in the posterior temporoparietal and posterior frontal

lobes are probably secondary and indirect consequences of the disease although these regions have been described as the most heavily laden with plaques and tangles. Much interest has focused on the profound decrease in the neurotransmitter acetycholine in the basal forebrain, probably resulting from degeneration of the acetycholine containing cells originating in the medial septum and basal nucleus of Meynert. The hippocampus and other parts of the limbic and paralimbic systems are thought to play a crucial role in memory and learning; these areas are necessary for imprinting memory templates for storage and the rekindling of these templates during retrieval (Mesulam, 1985). Lesions involving these structures might severely affect memory without structurally affecting the parietal and frontal association areas; blood flow and metabolism would nevertheless be reduced in association cortex secondary to disuse.

To help us better understand the mechanism of the disease, it will be necessary to image aspects of receptor function directly. Until recently, it has only been possible to measure receptor function at autopsy and, even then, only indirectly by counting the number of receptor sites. The development of radiotracer techniques, using high-specific-activity radioisotope-labeled neurotransmitter antagonists and emission tomography, has made the in vivo assessment of receptor binding possible in living patients. Studies of dopamine receptor binding and, in a normal subject, muscarinic acetylcholine receptor binding have already been reported (Eckelman et al., 1984; Wong et al., 1984).

We imaged a patient with clinically diagnosed Alzheimer's disease using I-123 QNB, a muscarinic antagonist whose distribution is primarily receptor mediated (Holman et al., 1985). We used the ratio of I-123-QNB activity between the cerebellum and the caudate nucleus as an index of the specificity of the tracer for muscarinic binding sites. The concentration of muscarinic acetylcholine receptor sites in the human is 950 pmole/g of protein in the caudate, but only 15 pmole/g in the cerebellum (Wastek and Yamamura, 1978). Therefore, our finding of a 15-fold greater concentration of tracer in the caudate than in the cerebellum 15 hours after injection (and with approximately the same blood flow to the two structures) confirms the high specificity of the tracer for muscarinic receptor sites in vivo. The decreasing activity in the cerebellum relative to the caudate with time after injection suggests that the selectivity of the tracer for muscarinic receptor sites increases with time, probably due to washout of the tracer from nonspecific binding sites. Along with the increase in receptor specificity, IQNB receptor binding appears to increase with time, with a greater than threefold increase in brain activity between two to 15 hours after injection.

Our preliminary study suggests that muscarinic acetylcholine receptor concentrations may be relatively preserved in patients with Alzheimer's disease despite the profound decrease in blood flow to the temporoparietal cortex. The I-123-QNB activity ratio between the temporoparietal cortex and

Along with the introduction of non-invasive imaging techniques, such as CT and MR, neuroradiologists have always strived to make cerebral angiography as safe as possible. A major impetus for the development of digital subtraction angiography (DSA) was the desire for less invasive imaging of the carotid bifurcation in the stroke-prone patient. Compared to conventional film arteriography, DSA offers improved contrast resolution at the expense of less spatial resolution; this compromise is acceptable in many cases because the exquisite detail obtainable with conventional arteriography is not always necessary for one to make appropriate diagnostic and therapeutic decisions. Initially, the DSA technique was used in conjunction with intravenous (IV) injections of contrast material to image the extracranial vessels. Intravenous DSA can evaluate the carotid artery bifurcations with a high degree of accuracy and a success rate of about 80% (Chilcote et al., 1981; Christensen et al., 1980: Strother et al., 1980; Wood, Lukin, Tomsick, and Chambers, 1983). This new technique also has been applied to the intracranial vasculature with some success (Modic et al., 1981; Strother et al., 1981).

Digital imaging can also be used in conjunction with selective arterial catheterization (Brant-Zawadzki, Gould, Norman, Newton, and Lane, 1982; Crummy et al., 1982). The technical part of the procedure is the same as for conventional arteriography; the only difference is that the digital image is substituted for the film image. This method provides much better image quality than IV DSA, but still does not equal the resolution obtainable with film screen angiography.

*The Digital System*

The digital angiographic system consists of an X-ray fluoroscopic system connected to a computer. For digital imaging, the image intensifier must be of the highest quality and the TV camera should have a signal to noise ratio of at least 500:1 and preferably 1000:1. The signal from the TV camera passes through an analog/digital converter and enters the image memories and central processing unit of the computer. The signal is logarithmically amplified and mask mode subtraction is performed. The final subtracted image is displayed on a monitor. The digital image can also be transferred to hard copy film for convenient viewing and long-term storage.

The image processing of DSA allows visualization of vessels containing a concentration of iodine as low as 2–3%; by comparison, conventional film screen arteriography requires an iodine concentration of 40–50%. The increased contrast sensitivity of digital angiography makes possible the imaging of arteries with an intravenous injection. In addition, the contrast and brightness can be adjusted and optimized after the examination is completed.

Alzheimer's disease; uptake was decreased in 13 of 15 patients. The frontal and lateral temporal cortices were decreased in 10/15 and 6/15, respectively. Uptake of tracer in the striate was the least affected of the cortical regions and was decreased in only one of 15 patients with Alzheimer's disease.

Does the perfusion pattern correlate with clinical symptoms? The majority of patients with Alzheimer's disease present with bilateral parietal perfusion deficits. Some patients have a marked language dysfunction and have asymmetric abnormalities in perfusion and glucose metabolism: marked reduction in the left frontal, temporal, and parietal cortex. Others have spatial cognitive difficulties and have right hemisphere deficits (Foster et al., 1983). In one patient with a severe aphasia we observed a marked decrease in perfusion in the inferior temporal pole of the left hemisphere. In another patient having visuospatial symptoms, profound perfusion defects in the occipital lobes were seen. There is, therefore, good correlation between gross clinical patterns and the perfusion patterns we see in patients with Alzheimer's disease. Correlation between perfusion patterns and subtle classifications of behavioral disorders awaits further study using higher resolution imaging equipment and more sophisticated psychological testing.

Can Alzheimer's disease be distinguished from other dementias? Kuhl and his group have shown that the parietal:caudate ratio of glucose metabolism in Parkinson's disease is very similar to Alzheimer's disease (Kuhl et al., 1985). The several non-demented patients with Parkinson's disease that we studied had normal perfusion patterns. As more severely demented patients with associated Parkinson's disease are studied, it is possible that perfusion patterns similar to those seen in Alzheimer's disease will be observed. Several questions come to mind: How many of these patients have superimposed Alzheimer's disease? Are there distinctive features in the perfusion pattern of Parkinson's disease that will allow us to distinguish it from the pattern of Alzheimer's disease? The population of patients with both diseases require careful study before SPECT perfusion imaging is used routinely as a screening tool in the dementias.

Other dementias have more characteristic appearances. Huntington's disease is a progressive disintegration of movement and cognition associated with a gross atrophy of the caudate nucleus and putamen, and accompanied by decreased perfusion to these structures. We have observed decreased I-123 IMP uptake in the basal ganglia using SPECT and a long-bore collimator while Sharp reports normal uptake using more standard collimation (Sharp et al., 1986). Progressive supranuclear palsy is associated with dementia and presents with a parkinsonism disorder of gaze. This disease is associated neuropathologically with senile plaques and neurofibrillary tangles in the deep midline structures. I-123 IMP SPECT results in decreased tracer uptake in the basal ganglia, less symmetrically than with Huntington's disease. In both conditions, parietal perfusion is normal while perfusion in the frontal areas is

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