

Perfusion and Receptor SPECT in the Dementias—George Taplin Memorial Lecture

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It is a great honor for me to be giving the Taplin Lecture this year. George Taplin possessed a unique quality in the field of nuclear medicine, a quality that is in limited supply in a high technology specialty such as ours, and one that we cannot afford to lose. Taplin was, first of all, a clinician. He identified areas of his practice where clinically important problems were going unsolved and posed the question: Can a radiotracer method be designed to provide the functional information necessary to root out a solution? I will endeavor to apply the Taplin approach to an area of increasing concern in clinical practice, the assessment and management of patients with dementia.

Lewis Thomas has called Alzheimer's disease the disease of the century (1). The increasing interest in the disease has come about as awareness of its malignancy and prevalence has heightened (2). Alzheimer's disease is the primary cause of the severe dementia affecting at least 5% of Americans over the age of 65 and 20% over the age of 80 (3). The disastrous impact of the disease on the lives of its patients and their families is compounded by its enormous financial cost to society. Half of the nursing care in the United States, worth over 20 billion dollars, goes to the treatment of Alzheimer's disease and the other dementias. Over 50 million dollars is spent annually for research on the dementias in the U.S. alone (4). Perhaps most importantly, millions of dollars are spent annually on psychometric and clinical testing in only a marginally successful attempt to diagnose and stage the disease.

The signs and symptoms of Alzheimer's disease are nonspecific: (a) dementia without prominent focal neurologic defects and (b) a steadily progressive course. Neurofibrillary tangles and senile plaques are present,

but may be seen in other conditions including trauma and normal aging. It is impossible to make the diagnosis of Alzheimer's disease before death or without a brain biopsy to document the density and distribution of the plaques and tangles.

More than 15 years ago, investigators using the inert gas washout method observed that blood flow was reduced in Alzheimer's disease (5,6). Studies carried out at various positron emission tomography (PET) facilities suggested that these abnormalities in flow and metabolism were focal and most extensive in the parietal area (7-11). Several years ago at The Society of Nuclear Medicine meeting in St. Louis, Cohen and his group showed that the changes in metabolism seen with PET could be repeated with the single photon tracer [¹²³I]IMP (12). The potential for using single photon emission computed tomography (SPECT) perfusion imaging in the assessment of patients with dementia has been further explored by Cohen et al., Sharp et al., and Johnson et al. (13-15). While these studies begin to document the potential role that SPECT imaging may play in the diagnosis and assessment of Alzheimer's disease, it is useful to examine the dilemmas facing the clinician dealing with patients with memory loss and to explore the process that must be followed before we fully appreciate the value and the limitations of SPECT imaging in the workup of these patients.

DEMENTIA vs. DEPRESSION

Depression is usually reversible with appropriate medical management. Frequently, depression masquerades as dementia. In one study of 200 patients admitted with the provisional diagnosis of dementia 20 patients (10%) had depression and 16 had a chronic brain syndrome with a much more benign course than typical Alzheimer's disease (16).

Phelps and the group at UCLA have observed abnormalities in glucose metabolism in some patients with unipolar depression particularly in the frontal lobe of

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the dominant hemisphere (17). Preliminary data from Hill and the group at the New England Deaconess Hospital suggest similar findings with SPECT and [²⁰¹Tl]DDC. In most patients with depression, the perfusion pattern is normal, however. In either case, the perfusion maps obtained from patients with depression can be distinguished from the bilateral parietal perfusion abnormalities seen in patients with Alzheimer's disease.

ALZHEIMER'S DISEASE vs. VASCULAR DEMENTIA

Another clinical dilemma is the differentiation of Alzheimer's disease from the vascular dementias. In Tomlinson's autopsy study, over half the patients with ischemic dementia had cerebrovascular disease (18). In the elderly, 50% of dementia is due to Alzheimer's disease, 17% is vascular, 18% is a combination, and 15% is due to other causes.

Vascular dementia can present in a number of ways. Bilateral anterior cerebral artery occlusion occurs when a common trunk gives off both anterior cerebral arteries; occasionally behavioral disturbances may result. Rarely, unilateral anterior cerebral artery occlusion may produce dementia if it involves the dominant hemisphere. Bilateral anterior cerebral artery infarction is easily distinguishable from Alzheimer's disease by SPECT perfusion imaging. Anterior cerebral artery infarction results in decreased perfusion to the anterior head of the caudate nucleus as well as the medial aspect of the frontal lobe: parietal uptake is normal.

Twenty percent of patients with middle cerebral artery occlusion appear demented. It is frequently difficult to evaluate the dementia because of superimposed aphasia. The perfusion abnormality in a middle cerebral artery occlusion is distinctive, however, involving the temporal, posterior frontal and parietal lobes unilaterally.

Perhaps the greatest clinical dilemma occurs with multi-infarct dementia (MID) because (a) evidence of stroke does not rule out Alzheimer's disease, (b) computed tomography (CT) and angiography correlate with the ischemic score in only 40% of cases (19), so that CT and angiography by themselves are of limited value, (c) a high ischemic score identifies patients who have had a stroke but does not indicate that the stroke either caused or contributed to the dementia, and (d) in patients with MID, it is imperative to prevent more strokes.

The usual appearance of multi-infarct dementia on perfusion SPECT is two or more asymmetric perfusion defects, but without bilateral parietal deficits. Both Cohen et al. and Sharp et al. demonstrate distinctive perfusion patterns in MID in most patients (13,14), but there are problem cases. Patients with bilateral parietal

defects may have other perfusion deficits due to stroke. These patients cannot be classified as MID simply because they have a high ischemia score. Other questions must be answered first. Do these patients have Alzheimer's disease superimposed on stroke? Does stroke lower the threshold for Alzheimer's disease? Or do some strokes result in a dementia-like picture with decreased parietal uptake, but without Alzheimer's disease? We do not have all of the answers at this time and it will require long term follow-up of these patients to get them.

ROLE OF PERFUSION SPECT

Can perfusion SPECT imaging play a role in the evaluation of Alzheimer's disease? To answer that question properly requires that we dissect it into smaller pieces. The first, and easiest, question to answer is: Can we separate Alzheimer's-like patients from age-matched controls? The normal brain shows uniform distribution of [¹²³I]IMP throughout the cerebral cortex. In patients with Alzheimer's disease, marked decreases in blood flow are seen particularly in the parietal area, suggesting that we might have a signature that could be helpful in the identification of the disease (Fig. 1). We studied a group of patients with severe Alzheimer's disease in which the diagnosis was highly probable based on clinical criteria and compared them with age-matched controls (15). We compared the [¹²³I]IMP activities in the parietal, frontal, temporal and striate cortex with the activity in the cerebellum. We normalized the tracer activity to the cerebellum because the cerebellar activity was the same in Alzheimer's disease as it was in the age-matched controls, and because the cerebellum is not pathologically involved in Alzheimer's disease.

In our study, the cortical:cerebellar ratios were significantly lower for most regions of the cortex in patients with Alzheimer's disease than in the control subjects. Relative [¹²³I]IMP uptake was decreased in the posterior parietal (73% of control), frontal (77%), and lateral (76%), medial (82%), and posterior temporal (83%) cortex. Smaller reductions were seen in the striate cortex (91%). The posterior parietal cortex was the most sensitive marker of 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 SPECT correlate with the severity of the dementia? PET studies using FDG have demonstrated that the severity of the metabolic abnormality correlates with the severity of disease as determined by clinical and psychometric testing (11). It would appear likely that similar observations will be made with SPECT, but this question must be studied more thoroughly.

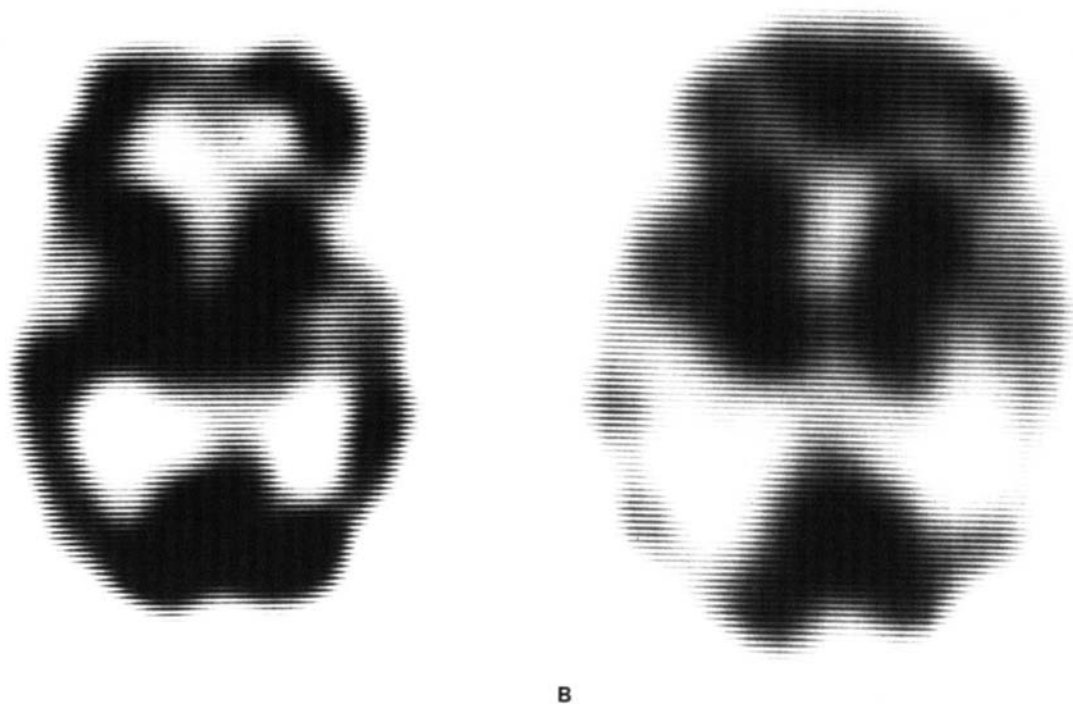


FIGURE 1

A: Normal perfusion pattern obtained using [^{123}I]IMP, rotating gamma camera, and long bore collimator. SPECT reconstruction was obtained in plane perpendicular and 2 cm above orbitomeatal line. B: Diminished [^{123}I]IMP uptake in posterior temporal and posterior parietal lobes bilaterally in patient with autopsy-proven Alzheimer's disease

Does the perfusion pattern correlate with clinical symptoms? Most patients with Alzheimer's disease present with parietal perfusion deficits, memory loss, and cognitive abnormalities. However, there are interesting subsets. Patients with memory and language dysfunction have asymmetric abnormalities in glucose metabolism with marked reduction in the dominant frontal, temporal, and parietal cortex. Patients in whom the memory disorder is the dominant abnormality have a more symmetrical reduction in metabolism (10). A small group of patients with Alzheimer's disease present with aphasia as their predominant clinical symptom. In one of these patients, we observed a marked decrease in perfusion in the inferior temporal pole of the dominant hemisphere. Occasionally, patients with Alzheimer's disease may have visuospatial cognitive dysfunction. While most patients with Alzheimer's disease have normal metabolism and blood flow to the occipital area, one of our patients with visuospatial problems had profound perfusion defects in the parieto-occipital cortex. 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 more 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 (20). The several patients with Parkinson's disease that we studied had normal perfusion patterns. As more severely demented patients with Parkinson's disease are studied, it is likely 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 Parkinson's disease requires careful study before SPECT perfusion imaging is used routinely as a screening tool in the dementias.

Other dementias have more characteristic appearances. Huntington's dementia presents the choreiform movements and atrophy of the caudate nuclei accompanied by decreased perfusion to the basal ganglia. We have observed decreased [^{123}I]IMP uptake in the basal ganglia using SPECT and a long-bore collimator while

Sharp et al. report normal uptake using more standard collimation (14). Progressive supranuclear palsy is a dementia that presents with parkinsonism and a disorder of gaze. This disease is characterized by plaques and tangles in the deep midline structures. Iodine-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 motor areas is reduced. In a patient with biopsy-proven Jacob-Creutzfeldt disease, IMP uptake was markedly reduced uniformly throughout the cortex; the parietal areas were affected to the same extent as the rest of the brain. The perfusion pattern in Korsakoff's psychosis is patchy, but without focal defects (13). Early indications would, therefore, suggest that most dementias can be distinguished from the dementia of Alzheimer's disease.

Is the abnormal perfusion 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 the standard criteria for the diagnosis of Alzheimer's disease, and who had mild to moderate dementia, ten 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 many patients can be classified early in their clinical course as probable Alzheimer's disease, many others remain diagnostic dilemmas until their disease process has been clarified by time or by autopsy. An early warning system to either alert the patient, his family, and his clinician to the future needs of his Alzheimer's disease or, alternatively, to provide reassurance to the patient that his course will be a benign one, would be a priceless addition to our diagnostic techniques, even though effective treatments for Alzheimer's disease are only in their infancy.

Finally, which tracer will be used for SPECT perfusion imaging? The largest experience has been garnered with [^{123}I]IMP, but imaging has been reported using [^{123}I]HIPDM (21), [^{201}Tl]DDC (22), and [$^{99\text{m}}\text{Tc}$]HMPAO (23). The agent that will be used in the future will most likely be labeled with $^{99\text{m}}\text{Tc}$ because of its physical characteristics, cost, and availability. The biologic characteristics of the tracer will be important, however. The $^{99\text{m}}\text{Tc}$ radiotracer must have high first-pass extraction and rapid blood clearance coupled with slow metabolism and back-flux into the blood, features seen with [^{123}I]IMP and [^{201}Tl]DDC, but not with [^{123}I]HIPDM (24). The tracer distribution must also reflect regional cerebral perfusion from the time of injection until the completion of the study. The relationship between tracer uptake and blood flow should not be affected by disease or by pharmacologic or physiologic manipulations. While some of these relationships have been described for [^{123}I]IMP, they have not yet been reported for [^{201}Tl]DDC and [$^{99\text{m}}\text{Tc}$]HMPAO. Needless to say, the effects of time, disease, and drugs on tracer uptake must be well understood before the routine application of SPECT perfusion imaging for the diagnosis of Alzheimer's disease.

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. Much interest has focused on the profound decrease in the neurotransmitter acetylcholine in the basal forebrain, probably resulting from degeneration of the acetylcholine containing cells originating in the medial septum and basal nucleus of Meynert. The hippocampus and other parts of the limbic and paralimbic systems 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 (25). Lesions involving these structures might severely affect memory without affecting the memory banks of the parietal and posterior frontal associative areas. Blood flow and metabolism would nevertheless be reduced in the memory banks 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 recep-

tor 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 (26,27).

We imaged a patient with clinically diagnosed Alzheimer's disease using [¹²³I]QNB, a muscarinic antagonist whose distribution is primarily receptor mediated (28). We used the ratio of [¹²³I]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 pmol/g of protein in the caudate, but only 15 pmol/g in the cerebellum (29). Therefore, our finding of a 15-fold greater concentration of tracer in the caudate than in the cerebellum 15 hr after injection (and with approximately the same blood flow to the two structures) indicates the high specificity of the tracer for muscarinic receptor sites. 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 2 and 15 hr 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 [¹²³I]QNB activity ratio between the temporoparietal cortex and the caudate was, nevertheless, lower than the corresponding ratio in the age-matched normal subject. It is quite provocative that the extent of reduction is similar to that reported by Mash et al. for the loss of presynaptic (M₂) receptors in the cortex of patients with Alzheimer's disease when determined by postmortem in vitro studies (30).

Recent work has raised questions concerning the primacy of the acetylcholine defect in Alzheimer's disease. Somatostatin receptors are significantly reduced in number in the frontal and temporal cortex and the hippocampus (31). Because the receptor sites themselves are depleted, studies using labeled somatostatin antagonists would likely find reduced uptake in these regions, perhaps outstripping the reduction in perfusion. Similar receptor mapping could be carried out using the binding sites for corticotropin-releasing factor, a hypothalamic-releasing hormone that is the major physiologic mediator of adenylyl cyclase, corticotropin and beta-endorphin secretion. This hormone has been reported to be depleted in the frontal and temporal

lobes and the hippocampus in patients with Alzheimer's disease (32).

These studies may provide very useful in vivo maps of receptor binding. To complement the anatomic information that they provide, it will be necessary to supplement these studies with pharmacologic interventions to more clearly define receptor function. For example, the use of a postsynaptic acetylcholine muscarinic antagonist followed by IQNB imaging would permit assessment of the more interesting presynaptic (M₂) binding sites.

Finally, receptor site labeling alone doesn't tell us how effectively that receptor is activating the postsynaptic neuron. It may be that we will have to develop a family of compounds that can measure aspects of receptor function beyond its binding activity.

At least for the immediate future, SPECT imaging with tracers that assess cerebral perfusion offers the greatest opportunity for the clinical management of the dementias because the perfusion patterns are discriminating and sensitive, because the test is easily performed and because SPECT perfusion imaging may lead directly to the solution of a number of clinical dilemmas in the diagnosis and management of the disease. In the more distant future, however, chemical SPECT imaging may take its place as a complement to physiologic SPECT imaging in the community hospital as well as in the tertiary medical center for the routine workup of patients with dementia.

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