A BRIEF REVIEW OF THE UTILITY OF SPECT PERFUSION NEUROIMAGING IN THE EVALUTION OF DEMENTIA AND MILD COGNITIVE IMPAIRMENT

Theodore A. Henderson, MD, PhD
The Synaptic Space
Consultant to CereScan Corporation
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While roughly 5.1 million Americans are afflicted with Alzheimer's disease (AD) or related dementias, the incidence of new-onset AD is expected to double in the next forty years. As America ages, an estimated 10-20% of those over the age of 65 years will develop mild cognitive impairment (MCI). A slight memory decline, often only subjective, but often detectible by neuropsychological testing, characterizes MCI. Cognitive decline with MCI is too subtle to be detected by Mini Mental Status Examination (MMSE), Draw-A-Clock, or other tests for profound cognitive decline.

Several prospective longitudinal studies with large samples have examined the progression from MCI to AD. Studies, such as Boyle and colleagues (Neurology, 2006 Vol 67:441) which followed 221 subjects with MCI over 2.5 years and Bennett and colleagues (Neurology 2002, Vo 59:198) which followed 211 subjects with MCI and 587 controls over 4.5 years, have shown that roughly 35% of patients with MCI progress on to AD over the course of 5 years. Thus, the ability to identify MCI accurately will help target those at risk of progressing to AD. Given that medications can now potentially slow the progression of AD, earlier detection is a critical step. Moreover, some studies have suggested that MCI with a different prognosis shows different perfusion patterns on SPECT scan. Specifically, Johnson and colleagues (J Neurol Neurosurg. Psychiatry 2007, Vol 78:247) showed that patients with progression to AD over 5 years demonstrated a pattern of decreased perfusion in the posterior cingulate gyrus and the parietal and temporal lobes. In contrast, patients who had declining MCI did not show decreased perfusion in the posterior cingulate gyrus. Patients with stable MCI showed no decreased perfusion in the temporal or parietal lobes. Nobili and colleagues (J. Neurology 2008 Vol 255:1344) similarly found that SPECT perfusion patterns were predictive of the type of MCI experienced. Patients with subjective experience of MCI who tested in the normal range on psychometric testing showed perfusion patterns on SPECT which were indistinguishable from controls. Patients with nonamnestic MCI demonstrated bilateral perfusion deficits in the temporal lobes, while patients with amnestic MCI demonstrated bilateral perfusion deficits in the parietal lobes, temporal lobes and the posterior cingulate and precuneus area.

Clinical studies have examined the sensitivity and specificity of SPECT perfusion scans for the diagnosis of AD. Perhaps the earliest studies were by Bonte and colleagues (J. Compute Asst. Technol. 1986 Vol 10:579) in which they documented decreased temporal lobe perfusion in 37 patients with AD using $Xenon^{133}$ perfusion SPECT. Hanya and colleagues (Gerontology 1993, Vol 39:260) examined a group of 219 patients and were able to distinguish 56 of whom had AD based on decreased perfusion of the temporal and parietal lobes (sensitivity 82%, specificity 89%). Matsuda and colleagues (AJNR 2007, Vol 28:731) utilized Z-score analysis of perfusion of the posterior cingulate and precuneus to distinguish 40 patients with AD from 40 controls with an

accuracy of 86%. Michael Devous hypothesized that posterior cingulate hypoperfusion was a predictive measure of AD (Eur J Nucl Med Mol Imaging 2002 Vol 29:1685). This conclusion is supported by the work of Bonte and colleagues (e.g., J Nucl Med 2004 Vol 45:771). When patients were followed to autopsy, using neuropathological findings as the gold standard for AD, SPECT functional neuroimaging had a sensitivity of 87%, a specificity of 89.5%, a positive predictive value of 93% and a negative predictive value of 81% (Bonte et al., Clin Nucl Med 2006 Vol 31:376).

As part of the Oxford Study to Investigate Memory and Aging, Jobst and colleagues (Internat Psychogeriatr 1997, Vol 9:191) followed 200 patients with dementia and 119 controls over 7 years. Each patient received annual cognitive examinations, annual SPECT scans, and annual temporal lobe CT scans to evaluate the hippocampus. All deaths among the subjects were autopsied for the gold standard diagnosis of pathological findings of AD. Clinical evaluation yielded a sensitivity of 96%, specificity of 61% and 85% accuracy, while SPECT scans combined with temporal lobe CT yielded 89% sensitivity, 93% specificity and 88% accuracy.

Fluorodeoxyglucose positron emission tomography (FDG-PET) is often used for diagnostic evaluation of AD and is FDA-approved for this purpose. It has also been the subject of intense efforts to increase its sensitivity and specificity. FDG-PET as it is standardly used in clinical practice has a sensitivity of 92% and a specificity of 85% (McMurtray et al, Euro Neurol, 2008 59:31). Haense and colleagues (Dement Geriatri Cogn Disord, 2009, 28:259) evaluated an automated statistical analysis method and found that it only increased sensitivity to 78-83% and specificity to 78-93% depending on the method. Multivariate image analysis has enhanced the discriminatory value of FDG-PET to a sensitivity of 90% and specificity of 97% based on one groups findings (Markiewicz et al, Neuroimage, 2009 46:472).

Statistical parametric analysis has enhanced the prognostic value of SPECT scans for AD. Kogure and colleagues (J Nucl Med 2000 Vol 41:1155) evaluated 32 subjects with MCI compared to 45 controls. At baseline, MCI subjects demonstrated decreased perfusion of the posterior cingulate and precuneus which was only detectable by statistical parametric analysis. At 24 month follow-up, all MCI subjects had progressed to AD clinically. Repeat SPECT scans showed progression of the hypoperfusion in the posterior cingulate and precuneus, as well as involvement of the hippocampus and parietal lobes. Huang and colleagues (BMC Neurol. 2002 Vol12:9) demonstrated a similar progression of hypoperfusion in the posterior cingulate in subjects with MCI followed over two years. Ishiwata and colleagues found a similar progression over three years in a study of 18 subjects with 10 controls (Acta Neurol Scand 2006 Vol 114:91). One group did not find posterior cingulate hypoperfusion to have the same predictive value (Caroli et al., J. Neurol, 2007, V254:1698).

The diagnostic validity of SPECT for AD is no longer in question (Matsuda, Neuropathology, 2007, 27:570; Johnson et al, J Neurol Neurosurg Psychiatry, 2007 78:240; Dougall et al, Am J Geriatr Psychiatry, 2004 12:554 – but limited to non-statistical analysis studies). Indeed, the ability of SPECT to accurately diagnose MCI is now well-established. As detailed above, SPECT studies have

shown that MCI can be differentiated into three distinct entities – progressing to AD, declining without progression, and stable – each strongly correlated with a distinct perfusion pattern revealed by SPECT. The questions now have become: 1) how early can SPECT detect MCI at risk for progression to AD, 2) can SPECT differentiate AD from other forms of dementia (Pick's disease or frontotemporal {FTD}, and Dementia with Lewy bodies{DLB}), and 3) how early can SPECT differentiate these pathological conditions? These questions have only been partially answered.

Recently, several groups have focused on novel methods of image analysis to enhance the identification of prodromal AD among patients with MCI. Habert and colleagues (Neurobiol. Aging, 2009, epub) utilized statistical analysis in a sample of 83 patients with memory complaints who were followed over three years. They found similar sensitivity and specificity as described above. Pagoni and colleagues (Psychiatry Res, 2009, 173:8) used principal component analysis to differentiate mild and moderate AD. Again, the hippocampus, parietal cortex, and posterior cingulate emerged as discriminative features for the severity of AD. Chaves and colleagues (Neurosci Lett, 2009 V461:293) found linear kernel support vector analysis significantly increased the diagnostic power of SPECT in identifying early mild AD. In a sample of 38 patients with mild AD, the approach yielded a sensitivity of 97%, a specificity of 100% and an accuracy of 99%.

Shimizu and colleagues examined the differentiation of DLB and AD using statistical parametric analysis to evaluate cortical, as well as deep nuclei, perfusion. They found that while hypoperfusion in the occipital lobe was predictive of DLB, the additional findings of increased perfusion in the thalamus and bilateral striatum strengthened the accuracy of the diagnosis of DLB. Goto and colleagues (Am J Neuroradiol. 2009 31:720) also found striatal parameters useful in differentiating early mild DLB from early mild AD. They found striatal volume to be reduced in early DLB, along with reduced occipital perfusion. The sensitivity of these parameters was 89%, while the specificity was 84%. They confirmed that reduced hippocampal perfusion and volume distinguishes early AD from early DLB.

Several different linear and non-linear analysis methods were tested by Horn and colleagues (Artif Intell Med, 2009 47:147) to aid the differentiation of FTD from AD. They found support vector machine and partial least sequence regression was most accurate in differentiating mild AD from mild FTD (88% accurate). Tranfaglia and colleagues (Hell J Nucl Med, 2009 12:110) utilized commercially available statistical parametric analysis software to differentiate FTD from AD and MCI. The software allowed the evaluation of separate Brodmann areas with statistical comparison to a normal database. Statistically significant decreases in perfusion in Brodmann areas 37 (temporal gyrus), 39 (angular gyrus) and 40 (supramarginal gyrus) distinguished AD from FTD and from MCI. In contrast, decreased perfusion in area 47 (frontal association cortex) distinguished FTD.

In summary, SPECT is a valuable tool in the identification of AD, the differentiation of other dementias, and the detection of MCI. In several studies, SPECT detected MCI functional patterns prior to the onset of neuropsychological impairment. SPECT, alone or in combination with genetic testing, has the potential to provide prognostic information and differentiate those at risk for progression of MCI to AD.