

Can SPECT Predict the Future for Mild Cognitive Impairment?

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The clinical role of Single Photon Emission Computed Tomography (SPECT) in the diagnosis and prognostication of dementing illnesses remains controversial. Numerous studies have compared SPECT in patients with Alzheimer's Disease (AD) and other dementias, and age-matched controls. The typical abnormality in AD is bilateral posterior temporal/parietal hypoperfusion, which often correlates with mental status, and can be asymmetrical. This pattern is found in approximately 60-90% of Alzheimer's patients,^{1,3} but other patterns have been identified including frontal involvement with or without parietal-temporal deficits and unilateral parietal/temporal hypoperfusion.⁴ Some studies have shown good correlation between such SPECT patterns and autopsy diagnosis.^{5,6} Generally speaking, however, the sensitivity and specificity of these patterns have varied in different series depending on the severity of the patient sample and the comparison group, which usually includes normal age-matched controls or patients with other types of dementia. The situation is further complicated by the confounding effects of factors, such as age of onset, years of education, duration of illness, severity of disease, etc., on perfusion ratios.⁷ The effect of disease severity on sensitivity and specificity was well-illustrated in a sample of 48 AD patients classified as mild, moderate or severe and 60 normal controls drawn from a population-based study by Claus *et al.* (1994). ROC curve analysis was used to determine the value added by semiquantitative SPECT in clinical diagnosis of AD.⁸ With specificity set at 90%, sensitivity was 42% in mild, 50% in moderate and 79% in severe AD. In mild dementia where diagnosis may be in doubt (i.e. *a priori* probability of 50%), the diagnostic gain was substantial (34%) for an abnormal scan, but poor when the scan was negative. Thus, depending on the results of the particular series, some authors continue to advocate the use of SPECT in the differential diagnosis of dementia,^{1,2,9} while others reject it as not cost-effective.^{8,10,11}

The clinical application of SPECT has also been further hampered by lack of standardization.¹² Acquisition parameters including the camera used, reconstruction algorithms and image display can all influence interpretation. Brain-dedicated triple-head cameras have better spatial resolution than single-head cameras; this can affect sensitivity in small regions targeted in AD such as the hippocampus. Whether visual or semiquantitative analysis is used can also affect results. With semiquantitative analysis, group differences can often be discerned, but the problem for the clinician is the application of such results to the individual case. Visual analysis is still the primary mode of interpretation in the clinical setting, even though automatic, semiquantitative methods could be applied quickly and efficiently by properly developed computerized algorithms. Semiquantitative methods usually increase sensitivity but may decrease specificity. Furthermore, lack of agreement on how best to measure regions of interest, what reference regions to use and software discrepancies between different camera system

manufacturers continue to retard optimal application of the SPECT method.

Despite these difficulties, the question has arisen whether SPECT would also be useful in subjects with mild cognitive impairment (MCI) to predict who will progress to dementia. MCI, a term derived from the DSM-III-R and ICD-10, refers to mild memory or other cognitive impairments in the absence of functional disabilities.¹³ Similar terms, all with slightly differing criteria, have included age-associated memory impairment (AAMI), age-associated cognitive decline (AACD), and cognitive impairment not demented (CIND) but MCI is emerging as the preferred designation and so will be used in this. According to the recent Canadian study of Health and Aging, 30% of Canadians over 65 have MCI, including 8% who had no obvious systemic or psychiatric illnesses contributing.¹³ This MCI population appears to be bimodal; approximately 50% will decline to dementia within three years and the remainder have stable, mild cognitive impairments that do not appear to progress.¹⁴⁻¹⁶ It may be that if such individuals are observed long enough they will decline, but few studies have gone beyond two or three years of follow-up. In one study where participants were followed for seven years, the conversion rate to dementia was 69%, with decline occurring in all subjects within four years of observation.¹⁵ Clearly, as therapies that may delay progression in AD become available, MCI will be an important target group for intervention since a successful delaying strategy could postpone clinically significant disease for some years or at least until the person dies of other causes.

Whether SPECT can contribute to this predictive exercise was addressed in the study reported in this issue by McKelvey *et al.*¹⁷ A well-documented group of subjects with MCI, were followed over a mean period of three years. The authors used the term AACD for this group, who were defined as having a history of mild memory decline, evidence of mild memory impairment on standardized neuropsychological testing and an assigned rating of 0.5 (questionable dementia) on the Clinical Dementia Rating (CDR) scale.¹⁸ SPECT scans were analyzed visually, with good inter-rater agreement, using a dichotomous classification of the abnormalities seen typically in AD. The results showed that 64% of these subjects had abnormal scans and that there were no differences in demographic or neuropsychological factors at study initiation between those with or without abnormalities on their scans. The exception was clinical depression, which was more highly represented in the subjects with normal scans (62%) compared to those with abnormal scans (20%). If the subjects with depression were eliminated, the frequency of abnormal scans (78%) was virtually identical to a study published by the same group in subjects with probable AD, in whom 76% were found to have abnormal scans.¹⁰ The high incidence of abnormal scans in this patient population, with a distribution of abnormality quite typical for AD, is noteworthy; it may be that a CDR of 0.5 based on a structured interview

actually selecting a higher proportion of patients with pre-clinical AD than other criteria that have been used for MCI. Of the 34 survivors available for follow-up, 27 were followed for more than two years and seven for less than two years. Fifty-three percent of the subjects showed decline to dementia. There were no differences in age, education, and duration of follow-up or performance on initial neuropsychological tests in those who did or did not decline. The presence of an abnormal SPECT initially did not accurately predict decrease on the Mini Mental State score or who would decline to dementia. Specifically, 67% (12/18) of those who progressed had an abnormal scan initially, but 31% (5/16) with normal scans also progressed. Overall, the positive and negative predictive values were approximately 50%. It is not clear from the data provided if elimination of the depressed patients would have improved these odds.

In this clinician-friendly, well-conducted study, visual SPECT interpretation was applied in a standardized fashion to a clearly defined cohort of individuals at potential risk for developing dementia. The authors conclude quite definitively that visual analysis of SPECT in this population is not at all useful in predicting who will progress to dementia. There are some limitations to this study, however, which must be taken into account when assessing the generalizability of these results. The sample size, although respectable, was still relatively small, with too few subjects to allow for epidemiological and other factors that may influence SPECT patterns and rate of decline to be taken into account. Unlike other studies, performance on delayed recall did not apparently have any predictive value. The role played by depression in this particular sample is also unclear. The authors do not indicate how depressive symptoms were assessed, but depressive symptoms were apparently not an exclusion criterion for participation in the study. Since depression can be a reversible cause of cognitive impairment, this is of some note, particularly since 62% of the patients with clinical depression (8/13) had normal SPECT scans. In this context it is notable that in a longitudinal SPECT study of cognitively impaired subjects, reversible deficits on SPECT in patients followed over one year were associated with resolving clinical depression while persisting deficits were more likely to be seen in patients with true dementia.¹⁹ In the current study,¹⁷ the length of follow-up was limited, and while the majority were followed for at least two years, it is still possible that some patients would have converted to dementia with longer follow-up. Another limitation is that visual interpretation of scans was used with a dichotomous classification as normal or abnormal. While this has the advantage of easy applicability, semiquantitative measures may have been more predictive.

How does this study based on visual inspection of SPECT scans compare to other series that have examined the predictive value of SPECT in patients with MCI? In a longitudinal study of 18 subjects with MCI studied by quantitative Xenon SPECT and followed over two years, Celsis *et al.* (1997) reported that reduced parietal-temporal perfusion and the degree of right-left parietal-temporal asymmetry were intermediate in the MCI group compared to normal controls and patients with probable AD.²⁰ Although initial mean parietal-temporal flow differed significantly in patients with MCI compared to the other two groups, it did not distinguish between the five subjects who did and the 13 who did not become demented over two years. The

degree of parietal-temporal asymmetry, however, did predict conversion to dementia.²⁰ In a larger sample, using HMPAO as tracer in a brain-dedicated, high resolution SPECT camera, Johnson *et al.* (1998) were able to distinguish four groups of subjects based on regional SPECT perfusion ratios, including normal controls (N = 34), subjects with AD (N = 56) and subjects with questionable AD (CDR 0.5) at baseline, 18 of whom progressed and 27 of whom did not progress to AD over two years of follow-up.²¹ Using a sophisticated statistical technique, singular value decomposition, these authors were able to identify regional decreases in perfusion that were most predictive of conversion to AD. The four main regions were the hippocampal-amygdaloid complex, the anterior and posterior cingulate, and the anterior thalamus. Such studies demonstrate that with semi-quantitative analysis and a spatial resolution adequate to detect perfusion in limbic structures, areas known to be targeted early in AD, differences can be detected between MCI patients who will and will not progress to dementia. To apply such findings to individual cases in the clinical context, however, simple, automated algorithms to quantify perfusion in these regions and larger samples to determine normal cut-offs and confidence intervals would be needed.

Properly applied, SPECT can also be useful in detecting heterogeneity in AD subjects and potentially provide an individualized profile of perfusion changes over time which may be helpful in documenting progression rates and evaluating response to new therapies. It is unlikely that SPECT alone, however, will be adequate to diagnose and track progression of AD pre-clinically or clinically. This is partly because of factors we do not yet understand which determine blood flow ratios in relation to pathological changes in different brain regions. Work in progress in our laboratory, mapping limbic system atrophy and perfusion changes using co-registered SPECT and MRI, has shown that regional structural atrophy is actually more discriminatory between AD and normal control subjects than perfusion ratios.²² Also many series have reported a small incidence of normal SPECT scans in clinically diagnosed probable AD patients (for example, in 11% of the Black *et al.* series⁷). It may be that individuals vary in their capacity to compensate for pathological change and can maintain regional perfusion, at least in early stages of disease.

The utility of SPECT in predicting development of dementia in MCI needs to be considered in the context of other modalities as well. Certain biological markers such as the presence of APO E4^{21,23} or a positive tropicamide eye-drop test^{24,25} have not proved to be helpful. The most cost-effective measure may be simple neuropsychological tests. Several studies have indicated that impairments in delayed recall and mental control are good predictors of later development of disease.^{14,16,26,27} Atrophy of the medial temporal structures, as quantitatively measured on MRI, may also be predictive. Even though there is considerable cross-sectional overlap between normal aged controls and AD subjects, smaller volumes of temporal lobe structures are also associated with a higher risk of conversion to dementia.^{28,29}

Because of the considerable disease heterogeneity in AD, it is likely that more than one modality may be needed to differentiate AD from normal aging and other dementias. For example, performance on selected neuropsychological tasks used in conjunction with brain measures on MRI and SPECT may improve

predictive accuracy. This has yet to be determined, however. In cross-sectional diagnosis of AD, a combination of SPECT perfusion and medial temporal lobe measures appears to be more powerful than either method alone.^{22,30,31} Serum or CSF markers may also eventually contribute to this differentiation,³² but it is likely that some type of brain imaging will still need to be used in conjunction with daily function, cognitive and behavioural assessment to provide information for individual staging and to monitor progression of disease. More research is required to determine the optimal combination of these biomarkers. Clearly for the imaging tools to become clinically relevant and cost-effective, reliable, automatic or semi-automatic analysis procedures must be developed so they can be applied in a time-efficient manner. The potential is certainly there to do this already, but more effort to achieve consensus on the best measures to use will be necessary if progress is to be achieved in applying these powerful image techniques successfully to daily practice.

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