Positron Emission Tomography in the Differential Diagnosis of Dementia in Young Adults: A Prospective, Community-Based Study

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Abstract

**Background:** The aim of this study was to evaluate the diagnostic accuracy of positron emission tomography (PET) in the differential diagnosis of young onset Alzheimer’s disease (AD) and other dementias in a community-dwelling population.

**Methods:** A prospective sample of 102 individuals presenting consecutively to a primary care centre for examination of suspected dementing diseases in young adults. The mean age of symptom onset of dementia in our patients was 60.06 ± 4.28 years (mean ± 1SD, 95% lower confidence intervals (CI) 54.75, upper 63.37). Patients were evaluated using standard clinical criteria for the diagnosis of dementia. Functional neuroimaging data was obtained and nuclear medicine physicians blind to the clinical diagnosis generated PET diagnoses. Final clinical diagnoses based on all available data were then established and compared against PET diagnoses.

**Results:** Forty-nine patients received a final clinical diagnosis of early-stage AD (MMSE score 20.97 ± 5.10). There were 29 non-AD demented patients, 11 depressed patients and a miscellaneous group of 13 patients. Among patients with AD, the sensitivity and specificity of PET was 78% (95% CI: 66-90%) and 81% (95% CI: 68-86%), respectively. The specificity of PET in the differential diagnosis of other dementias, including frontotemporal dementia, was greater than 95%.

**Conclusion:** Recruitment methods in this study provide a sample that may be more representative of patients in the general population and indicate that PET imaging can contribute to the diagnosis of AD in younger adults. The high specificity of PET suggests this technique might help in the diagnosis of other forms of dementia in young adults.
Background

Clinical, pathologic, and genetic evidence indicates that the various dementias have different underlying aetiologies and pathogenetic mechanisms. Treatment approaches will therefore be different for each of these conditions and accurate diagnosis is critical in order to maximize the efficacy and appropriateness of specific regimes. At present, precise differential diagnosis of dementia relies on histopathological observations, only available at autopsy. Thus, when faced with a patient with a potential dementia condition, currently the clinician must establish a probable diagnosis based on evidence available from longitudinal clinical assessment, blood tests, neuropsychological evaluation, and structural brain imaging. Although in more advanced stages of dementia a pre-mortem differential diagnosis typically becomes more secure, accurate clinical diagnosis in the early stages continues to be difficult. Furthermore, with the prospect of the introduction of pharmacological therapies that might slow the rate of neurologic deterioration, dependence on the progression of disease to a more advanced stage for accurate diagnosis may subject patients to unnecessary treatment delays. Establishing valid and reliable clinical markers of dementia capable of identifying differential pathognomonic change during the early clinical stages and with young onset is required.

Early differential diagnosis and management of dementia may benefit from precise functional neuroimaging information. In disease states of the central nervous system including dementia, the ability of neurons to take up metabolites such as glucose is impaired. By identifying regions of hypometabolism, functional neuroimaging
techniques, including positron emission tomography (PET), can theoretically assist in the clinical evaluation and differentiation of dementia syndromes [1-5].

**PET and Dementia**

A number of PET studies have identified distinct patterns of brain metabolic abnormalities indicative of a disruption of neuronal function in individuals diagnosed with various dementia syndromes, including Alzheimer’s disease (AD) [6-8]; frontotemporal dementia (FTD) [9-11]; vascular dementia (VD) [12]; primary progressive aphasia (PPA) [13,14]; dementia with Lewy bodies (DLB) [15-17]; and depression [18,19]. PET studies are therefore increasingly being used as an adjunct in the clinical evaluation of patients with suspected dementia, particularly to aid in early detection [1,17,20], or when a clinical diagnosis is problematic [2,7,16,21,22]. However, the actual sensitivity and specificity of PET in the diagnosis of dementia in young adults with the onset of dementia syndrome prior to the age of 65 years is unclear.

**Diagnostic Accuracy of PET**

Multiple PET studies have shown that individuals diagnosed with AD demonstrate a characteristic pattern of glucose hypometabolism, and the condition can be distinguished from healthy controls with 93-94% sensitivity and 93-99% specificity [23,24]). The capability of PET to differentiate AD from other types of dementia is more variable, with sensitivity values as high as 93-94% [21,25] but as low as 44% [1], and specificity values ranging from 63 to 80% [1,22,25].
While the majority of functional neuroimaging research has focused on identifying AD, the sensitivity and specificity of PET in diagnosing other dementia conditions has also been investigated. PET distinguished FTD from AD or DLB with 78% sensitivity and 71% specificity [3]. DLB has been differentiated from AD with 85-90% sensitivity and 80-91% specificity [3,16,26].

Unfortunately, these studies of the diagnostic accuracy of PET are fraught with a number of methodological limitations. It is therefore difficult to assess the applicability of the reported diagnostic values to routine practice [27,28].

Foremost, studies retrospectively recruited patients non-consecutively from specialty clinics, often resulting in cohorts composed entirely of individuals with manifest dementia of one specific type [6,22,23,25,26]. This method of recruitment resulted in homogeneous patient samples that are not generally representative of those individuals who undergo dementia evaluations in primary health care settings. Furthermore, when only those patients who have tested positive on clinical grounds are used to evaluate the accuracy of a diagnostic test, verification bias can occur, leading to substantial bias in the estimates of test performance [29]. To be more clinically applicable, a study should include a spectrum patients ranging from those at risk for a particular disease (such as mild cognitive impairment) to those with manifest disease [30]. Assessing only a subset limits the clinical applicability of the results. While no formal description of patient recruitment was provided, one study appeared to consecutively recruit its sample from a primary care centre [1]. Not unexpectedly, this study reported PET diagnosed AD with 44% sensitivity, a much
lower value than reported in those studies with homogeneous, retrospectively selected sample populations.

Second, confidence of the results in a number of studies is limited by small numbers of patients [1,3,16,21,26]. To address the problems associated with small sample sizes, two large, multi-centred studies have been conducted [24,25]. However such a research design lacks standardization, and the lack of uniformity of procedures among contributing sites for recruiting participants, collecting clinical data, and recording and categorizing PET presents a potentially significant confound [27].

Third, the highest diagnostic values have come from studies investigating the ability of PET to distinguish dementia from healthy controls [23,24], while values generated when differentiating amongst various dementia conditions are generally lower and more variable [1,21,25]. The highest sensitivity and specificity values may not therefore generalize to clinical practice, where the clinician is often faced with the difficult task of differentiating between multiple potential conditions, rather than simply dissociating between manifest dementia and general good health.

Finally, accuracy of PET diagnosis is frequently discussed only in terms of sensitivity and specificity. Sensitivity refers to the probability of a positive test among patients with disease, while specificity refers to the probability of a negative test among patients without disease. However, clinicians don’t generally know whether or not a patient has disease, hence the need for ordering the test. Thus, while sensitivity and specificity are among the most commonly reported methods for communicating the diagnostic value of a particular test, they do not convey the information needed to
interpret test results. Ideally, one would like to know what the probability of disease is given a positive or negative test. For this, likelihood ratios can be calculated to assess the post-test likelihood of disease. The positive likelihood ratio (PLR) indicates the increase in probability of disease following a positive test, while the negative likelihood ratio (NLR) represents the reduction in probability of disease following a negative test result.

**Aims of the Current Study**

It is uncertain whether the diagnostic sensitivity and specificity of PET is suitably high enough to be of value in the diagnosis of dementia. The aim of the current study was therefore to evaluate the value of PET imaging in supporting the clinical diagnosis of common dementia syndromes in a sample of individuals presenting consecutively to a primary care centre for examination of suspected neurological impairment in young adults. Such a community-based case series is more representative of the type of patients presenting for dementia investigation and the results of the data analysis more appropriate for guiding diagnosis.

**Methods**

**Participants**

All individuals referred to a young onset dementia clinic for specialist neurologic investigation of suspected dementia over the years from 1998 to 2002 were included in the current study. The cohort was composed of 102 consecutively presenting patients, and included 55 males and 47 females. The mean age of symptom onset of dementia in our patients was 60.06 ± 4.28 years (mean ± 1 standard deviation (SD);
95% lower CI 54.75, upper 65.34) (Table 1). Patients received a diagnosis based on standardized clinical assessment [31] utilizing widely accepted diagnostic criteria, including longitudinal clinical assessment, blood tests, neuropsychological evaluation, EEG analysis, and structural brain imaging [32-35].

Final clinical diagnoses were: 49 patients with AD; 17 patients with FTD; 11 patients with depression; six patients with DLB; six patients with PPA; and a miscellaneous group of 13 patients (4 patients with non-neurodegenerative neurological conditions; 2 patients with mild cognitive impairment; 2 patients with VD; 2 patients with PSP; 2 normal patients; and 1 patient with corticobasal syndrome). The PET diagnoses were then compared with the final clinical diagnoses.

Presenting complaints included cognitive decline (85.29%), speech disturbance (8.82%), behavioural change (4.90%), and gate abnormality (0.98%). Twenty-eight patients (27.45%) self-reported a positive family history of dementia.

**PET Imaging and Data Analysis**

Flurodeoxyglucose (FDG) was synthesised by automated synthesis modules: IBA $^{18}$F-FDG Module with GE TracerLab Mx Module. All patients were imaged utilising an Allegro GSO PET scanner (Philips Medical Systems). Patients were instructed to fast for at least six hours, before FDG administration weight and height was measured and euglycaemia was confirmed. A surface area adjusted dose (XMBq/m$^2$) was used. All
patients were imaged at rest in a quiet room with dim lights and minimal
environmental stimulation.

The FDG PET images were reported off the Siemens work stations following
reorientation and windowing using the Siemens “cool” colour scale. Software analysis
using the Neurostat package was performed. Two experienced nuclear physicians
reviewed the images and the Neurostat SSP-Z score maps without the patients’
clinical data. Each case was classified as either normal or possible AD, FTLD, LBD,
PPA or Depression.

<INSERT FIGURE 1>

Sample sizes in each of the diagnostic groups were quite different; therefore, one-way
analysis of variance could not be used to evaluate MMSE performance across groups.
Rather a Kruskal-Wallis test (a non-parametric method) indicated there was no
significant difference in MMSE performance between individuals diagnosed with
AD, FTD, DLB, PPA or depression [F(4, 6.55) = 3.68, p = 0.07].

FDG PET data was evaluated in terms of the ability to differentially diagnosis the
most common dementia syndromes. Sensitivity and specificity values were
calculated by comparing the blind consensus diagnosis from the PET scan against the
consensus final clinical diagnosis. For all values, a 95% confidence interval (CI) was
calculated according to the methods provided by Simel and colleagues [36].

Likelihood ratios (LR) were interpreted according to the general guidelines provided
by Jaeschke and colleagues [37].
Results

Alzheimer’s Disease

Of the 49 patients who received a final clinical diagnosis of AD, the PET diagnosis correctly identified 38 of these individuals, for a sensitivity of 78% (95% CI: 66-90%). Of the 53 patients who received a final diagnosis other than AD, the PET diagnosis incorrectly classified 43 of these individuals as not having AD, for a specificity of 81% (95% CI: 68.86%). The LR for a PET scan considered consistent with AD was 4.11 (95% CI: 2.29-7.32%), suggesting a small increase in the likelihood of a final diagnosis of AD when diagnosed on PET with AD. The LR of PET findings negative for AD was 0.27 (95% CI: 0.16-0.46%), suggesting a small decrease in the likelihood of a final diagnosis of AD when PET findings are negative for AD.

Additional Dementia Syndromes

An analysis of the diagnostic accuracy of PET in other forms of dementia was also performed (Table 2). Unfortunately, the small number of patients in each diagnostic category limited the statistical confidence associated with the sensitivity results. However, these preliminary findings indicated that the specificity of PET for FTD, DLB, PPA, and depression was greater than 95%

<INSERT TABLE 2>
Conclusion

In a community-based case series of young older adults presenting with symptoms of dementia, AD was detected by PET with 78% sensitivity and 81% specificity. The specificity is comparable with previously reported values, while sensitivity was slightly lower [21,25]. However, the current study group provide a sample of the general population, rather than the utilized in most previous studies. Clinicians in primary care settings can therefore take greater confidence from the findings of the current study, which demonstrates a significant increase or decrease in the likelihood of AD depending on whether PET is consistent with or not suggestive of AD.

Cognitive status as measured by the MMSE was equivalent across the AD and non-AD dementia groups, and the patients were considered similar in terms of disease severity. Differential PET diagnoses therefore cannot be interpreted as simply reflecting differences in severity of disease. Rather, functional disturbances in AD appear sufficiently characteristic to allow PET to be beneficial in differential diagnosis.

With the introduction of disease modifying agents that may delay cognitive decline and maintain functional level, accurate and early diagnosis of dementia is a critical component of care. Based on performance on the MMSE, our patients with AD were considered to be in a relatively early clinical stage. The current results clearly suggest PET can contribute in the differential diagnosis of early-stage AD. This functional technique can therefore be recommended to not only support the diagnosis of dementia, but hasten accurate diagnosis.
Unfortunately the small number of patients in additional diagnostic categories limits the statistical confidence associated with analysis of the sensitivity and specificity of PET in identifying non-AD dementia syndromes. However, the diagnostic specificity of PET was exceptional in all the subgroups analysed. None of the 17 non-demented patients were misdiagnosed as having AD or a non-AD dementia, indicating the chance of a healthy patient being misdiagnosed with PET as having a young onset dementia syndrome is substantially unlikely. PET scanning therefore appears to be highly useful in ruling out potential dementia syndromes, and may be of significant clinical value in atypical or uncertain cases.

In the current study, none of the patients diagnosed with a dementing syndrome has undergone post-mortem confirmation of diagnosis. Rather, widely accepted diagnostic criteria were used as the standard of reference for patient diagnoses. Admittedly, there is the potential for discrepancy between the clinical diagnosis and the true nature of a dementia syndrome if pathological confirmation is not obtained, and it is not possible to provide unequivocal diagnostic accuracy data. However, even pathological confirmation is not beyond reproach. There is no universally accepted set of pathological criteria, and the various diagnostic algorithms place discordant degrees of reliance on varying diagnostic factors [21]. Depending on the criteria utilized, a patient may not always receive the same autopsy diagnosis [38].

In conclusion, attempts to differentiate potential dementia syndromes based on clinical grounds alone can be difficult, particularly when patients present with few or an atypical profile of symptoms. In addition, clinical assessment typically involves multiple examinations and tests over months and years, which may lead to
unnecessary delay in diagnosis and introduction of an appropriate treatment regime should these become available.

Little more than a decade ago, the American Academy of Neurology [39] regarded computed tomography and magnetic resonance imaging as “optional” examinations for the diagnosis and evaluation of dementia. However, structural imaging techniques have now become a widely accepted and highly valued component in the diagnosis and management of dementia [40]. A similar paradigm shift is underway with respect to the role of functional imaging, as the contribution of rapidly evolving techniques such as PET is becoming increasingly realized. The current study takes another step forward in validating the utility of functional imaging in the diagnosis of dementia, and suggests that in a clinical environment, PET may be an effective adjunct for the early diagnosis and differentiation of various dementia syndromes, especially in young adults, a conclusion supported by recent studies [41-43].
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Table 1: Characteristics of the Patient Sample

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Number (men/women)</th>
<th>Age at Symptom Onset*</th>
<th>Age at PET Scan*</th>
<th>MMSE Score (max = 30)†</th>
<th>Disease Duration (years)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>102 (55/47)</td>
<td>60.06 (4.28)</td>
<td>64.04 (8.90)</td>
<td>25 (5-30)</td>
<td>5.74 (2.75)</td>
</tr>
<tr>
<td>AD</td>
<td>49 (24/25)</td>
<td>61.75 (9.73)</td>
<td>65.65 (9.41)</td>
<td>20.97 (5.10)</td>
<td>5.34 (2.08)</td>
</tr>
<tr>
<td>FTD</td>
<td>17 (10/7)</td>
<td>59.87 (6.72)</td>
<td>63.42 (7.80)</td>
<td>25.44 (3.32)</td>
<td>5.19 (2.27)</td>
</tr>
<tr>
<td>DLB</td>
<td>6 (6/0)</td>
<td>64.47 (5.13)</td>
<td>69.19 (4.65)</td>
<td>27.40 (1.82)</td>
<td>6.68 (2.85)</td>
</tr>
<tr>
<td>PPA</td>
<td>6 (3/3)</td>
<td>61.18 (8.66)</td>
<td>67.54 (7.59)</td>
<td>21.00 (10.65)</td>
<td>7.28 (3.37)</td>
</tr>
<tr>
<td>Depress</td>
<td>11 (6/5)</td>
<td>53.02 (8.28)</td>
<td>56.29 (7.92)</td>
<td>27.11 (2.89)</td>
<td>5.34 (1.85)</td>
</tr>
</tbody>
</table>

Note: Depress = Depression. *Values are Means (SD). † Values are Medians (Range)
### Table 2: Diagnostic Accuracy of PET in other forms of Dementia

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontotemporal Dementia</td>
<td>17</td>
<td>53% (29-77%)</td>
<td>95% (90-100%)</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>6</td>
<td>83% (53-100%)</td>
<td>99% (97-100%)</td>
</tr>
<tr>
<td>Primary Progressive Aphasia</td>
<td>6</td>
<td>50% (10-90%)</td>
<td>100% (99-100%)</td>
</tr>
<tr>
<td>Depression</td>
<td>11</td>
<td>18% (0-41%)</td>
<td>100% (99-100%)</td>
</tr>
</tbody>
</table>

Note: Values in parenthesis represent 95% confidence intervals
**Figure 1:** Representative PET images from patients with AD showing biparietal hypometabolism (a); FTD with frontal hypometabolism (b); PPA with predominant left temporal and left hemisphere hypometabolism (c); and DLB with occipital and parietal hypometabolism (d).
Figure 1: Representative PET images from patients with AD showing biparietal hypometabolism (a); FTD with frontal hypometabolism (b); PPA with predominant left temporal and left hemisphere hypometabolism (c); and DLB with occipital and parietal hypometabolism (d).