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The Value of PET in Mild Cognitive Impairment, Typical and Atypical/Unclear Dementias: A Retrospective Memory Clinic Study

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Abstract

This retrospective study examined the role of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis of atypical/unclear dementias in a memory clinic setting. A total of 94 patients with a diagnosis of mild cognitive impairment (MCI) or dementia, who had a PET study within 2 months of their diagnosis, were reevaluated at 5 and 18 months. Results showed that PET was associated with a change in diagnosis in 29% of patients and a 64% increase in the use of cholinesterase inhibitors (ChEIs). PET significantly lowered the number of atypical/unclear diagnoses from 39.4% to 16% and nearly 30% of these were found to have a typical Alzheimer's disease (AD) pattern of hypometabolism. In conclusion, the addition of PET to the investigation of atypical/unclear cases of dementia helped generating a more accurate diagnosis and initiating earlier treatment. PET was of limited contribution to typical AD and frontotemporal dementia (FTD) cases. This study provides guiding evidence about the true value of PET imaging in the day-to-day challenge of dementia diagnosis.

Keywords

positron emission tomography, Alzheimer's disease, atypical dementia, memory clinic, mild cognitive impairment, frontotemporal dementia

Introduction

In recent years, the measurement of regional cerebral glucose metabolism ($rCMR_{glc}$) using [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) has been increasingly used to support the clinical diagnosis of patients with suspected neurodegenerative disorders such as Alzheimer's disease (AD), dementia with Lewy Bodies (DLB), vascular dementia (VD), and frontotemporal dementia (FTD).[1-6] Numerous studies have shown that adding PET to the clinical investigation increases diagnostic sensitivity and accuracy in AD, DLB, FTD, and asymptomatic individuals at risk of AD.[5,7-9]

In 2007, Jagust and colleagues compared the accuracy of FDG-PET to the accuracy of clinical and pathological diagnosis of 44 individuals with dementia, cognitive impairment, or normal cognitive function.[10] Participants underwent an initial clinical evaluation and PET scanning and were followed up until death and autopsy. Sensitivity of the initial evaluation for the pathologic diagnosis of AD was 0.76, and specificity was 0.58; PET had values of 0.84 and 0.74, and final evaluation had values of 0.88 and 0.63. Positive predictive values for initial evaluation, PET, and final evaluation were 0.70, 0.81, and 0.76. Negative predictive values were 0.65, 0.78, and 0.80. The diagnosis of AD at the initial evaluation was associated with a 70% probability of detecting AD pathology; with a positive PET scan, this probability increased to 84%, whereas a negative PET scan decreased the probability to 31%. A diagnosis of "Not AD" at the initial evaluation was associated with a 35% probability of AD pathology, increasing to 70% with a positive PET scan. The authors suggested that as a diagnostic tool, PET is superior to a baseline clinical evaluation and similar to an evaluation performed after 4 years of evolution. A PET study by Silverman and colleagues classified patients according to whether they were likely to progress, and contrasted the clinical prediction of progression with the FDG-PET prediction of progression.[11] The clinical prediction

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of subsequent course had a sensitivity of 77% and specificity of 76%, whereas the sensitivity of PET was 95% and its specificity was of 79%.

Based on evidence showing that FDG uptake patterns differ across dementing disorders, other studies have demonstrated that PET is very useful in the differential diagnosis of dementia. For example, compared to historical normal controls, patients with AD show an abnormally low uptake in the posterior cingulate, precuneus, medial temporal lobe, temporoparietal regions and frontal cortex, whereas patients with FTD show an early and more severe frontal and anterior/mesial temporal hypometabolism pattern that is often asymmetrical.[12-15] In the United States, this led to the approval in 2004 of FDG-PET as a routine examination tool for the differential diagnosis of AD from FTD (Expert Panel of the National Institute of Aging/Centers for Medicare and Medicaid Services). Dementia with Lewy Bodies patterns closely mirror those observed in AD with added reduction in the occipital lobe, particularly in the primary visual cortex.[16,17] Whether PET can accurately differentiate hypometabolism in mild cognitive impairment (MCI) from healthy aging or dementia remains unclear at present.[3,4,8]

Despite such eloquent demonstrations, routine use of PET in clinical management has not received wide acceptance in practice.[18] The value of adding PET to an MCI workup also remains controversial. Availability and cost-effectiveness issues are inevitable, even though some authors have shown that the use of PET for evaluating early dementia can add valuable information without adding to the overall costs.[19,20] In a review of the literature published between 1975 and 2001, Gill and colleagues found little evidence to support the addition of PET to the routine clinical evaluation of patients with suspected or established dementias.[21] Galasko et al reported that clinical diagnoses of AD made by using the National Institute of Neurological and Communicative Disorders and Stroke— Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria are accurate in up to 90% of the cases.[22] Even Jagust and colleagues (2007; cited above) concluded that the value of this technique in the current clinical environment with limited therapeutic options is likely to be modest.[10] Finally, the most recent Canadian Consensus Conference on the Diagnosis and Treatment of Dementia reiterates that dementia can be accurately diagnosed through clinical evaluation, cognitive screening, basic laboratory evaluation, and structural imaging, and that there is insufficient evidence to recommend routine functional neuroimaging.[23]

Although typical cases of dementing disorders may not benefit from routine PET imaging, we hypothesized that complex and atypical/unclear cases with MCI or dementias who present an unusual profile may represent the ideal situation where PET is indicated. The primary goal of this study was therefore to explore the value of PET in the evaluation of MCI, typical and atypical/unclear dementias. More specifically, we postulated that PET helps generating a more accurate diagnosis and initiating earlier treatment in complex atypical cases but that its value in typical dementias is limited. Our secondary goal was to explore this issue in a specialized Memory Clinic setting where patients are not seen in the context of a first-line screening for memory problems but represent a selected cohort of complex patients referred by neurologists, geriatricians, geriatric psychiatrists, and family physicians familiar with cognitive problems. This last feature is unique in that despite a growing body of literature on PET imaging in dementia, very few authors have addressed this issue in the context of the day-to-day challenges of a third-line specialized referral clinic.[4,9,21,24]

Methods

Patient Selection and Diagnosis

We retrospectively reviewed the files of all patients who had been seen at our memory clinic between January 2006 and June 2008 (ie, 1498 files, including 554 new consultations). Patients were referred by family physicians, neurologists, geriatricians, and geriatric psychiatrists. Inclusion criteria were (1) a clinical diagnosis of MCI, typical dementia, or atypical/unclear dementia, and (2) an FDG-PET scan within 2 months of the clinical diagnosis. Exclusion criteria were absence of a PET study or a PET study conducted >2 months after the initial clinical diagnosis. All patients had a PET study within 2 months of their initial clinical diagnosis, were re-evaluated within 3 months of their PET, and again on average 1.5 years after their initial clinical diagnosis.

"Typical dementias" included AD, DLB, FTD, VD, and corticobasal degeneration (CBD), whereas "Atypical/unclear dementias" included cases where the initial clinical diagnosis was uncertain, unclassified, and the clinician listed several possible hypotheses for the diagnosis. Clinically probable or possible dementias were considered equivalent.

All of the initial clinical diagnoses were made by 2 experienced cognitive neurologists (LV, RWB) and an experienced geriatric psychiatrist (MH). All of the diagnoses were clinical diagnoses made using standard criteria based on clinical interview, functional assessment, neurological examinations, neuropsychological screening, magnetic resonance imaging, and laboratory studies.

MCI. The diagnosis of MCI was clinical and based on a standardized interview with the patient and a reliable informant, reporting evidence of some cognitive decline from a prior level of functioning, normal activities of daily living (ADL), normal general intelligence, absence of dementia, Clinical Dementia Rating (CDR) = 0.5 or Global Deterioration Scale (GDS) = 3, and Mini-Mental State Examination (MMSE) score $\geq$24. Fixed cut-off scores on neuropsychological testing were not used for the clinical diagnosis of MCI.

Dementing Disorders. All patients fulfilled the *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition* (*DSM-IV*) criteria for dementia, showed significant ADL impairments, had deficits in 2 or more cognitive domains, and had CDR $\geq$1 or GDS $\geq$4.[25] All clinicians were familiar and knowledgeable of the consensus criteria for the diagnosis of AD (NINCDS-ADRDA), FTD, VD, and DLB when making their clinical diagnoses.[26-29] The FTD group included patients

with the frontal variant, semantic dementia, and primary progressive aphasia.

PET Imaging and Image Evaluation

The patients fasted for at least 4 hours before administration of 18F-FDG. The serum glucose level was measured for all patients. The 18F-FDG brain PET was obtained with a dual-head coincidence camera (Vertex MCD-AC, Phillips, Milpitas, California). After a 30-minute rest in a dimly lit room, eyes closed, 111 MBq (3 mCi) 18F-FDG were injected in a venous catheter. Another 30 minutes rest was observed before starting the acquisition ($64 \times 64 \times 16$ matrix, 64 steps, mean of 25 seconds/steps with decay correction). Measured attenuation and scatter correction were applied to the iterative reconstruction method.

Images were evaluated by a unique rater (N.P.) who was not blind to the clinician's diagnostic hypotheses. This rater has extensive experience in reading FDG-PET scans in research and clinical settings. The rater was asked to make a judgment about whether the image reflected the presence of MCI, a typical dementia (including the specific type), or an atypical/unclear pattern. The scan obtained before April 2007 were analyzed visually using the criteria mentioned thereafter. Each scan obtained after April 2007 was analyzed and compared to a group of 18 normal elderly controls using SPM2 (Wellcome Department of Neurology, Institute of Neurology, University College London, UK) with MATLAB (Mathworks, Sherbon, Massachusetts), with a level of significance of $P < .001$. This comparison allowed the determination of the area with significant hypometabolism as compared to normal elderly controls.

Dementias were classified using generally accepted criteria: (1) AD: uni- or bilateral parietotemporal hypometabolism or bilateral parietal and precuneal hypometabolism, more or less dorsolateral frontal hypometabolism of less importance than the parietotemporal defects,[1,3,5] (2) DLB: same criteria as AD with added hypometabolism in the occipital lobes,[1,3] (3) FTD: uni- or bilateral frontotemporal hypometabolism, with or without less severe parietal hypometabolism,[1,3,5] (4) semantic dementia: isolated bilateral temporal hypometabolism,[30] (5) primary progressive aphasia: unilateral fronto-parieto-temporal hypometabolism,[31] and (6) VD: well-defined focal defects not respecting the above described patterns.[32] Mild cognitive impairment being a clinical diagnosis, the FDG-PET study was used to assess whether it was a pattern at risk of conversion into AD (ie, hypometabolism in the precuneus-posterior cingulate region, with or without mild parietotemporal hypometabolism) or whether it was a pattern at low risk of conversion into AD (normal scan).[33-34] In the context of cognitive deterioration, the diagnosis of MCI was attributed when there was isolated hypometabolism in the precuneus-posterior cingulate region.[35]

Impact of PET Imaging

The impact of PET imaging on the diagnosis (ie, confirmation of the clinical diagnosis, clarification of the diagnosis, change in the diagnosis, was of no help, had no impact, etc) was scored retrospectively using 2 general categories: (1) PET contribution ("None" [ie, when PET results were entirely incompatible with the clinical presentation and did not contribute at all to the clinical diagnosis], "Helps, clarifies, orients" [ie, when PET imaging contributed in some way to the clinical diagnosis], "Confirms clinical impressions" [ie, when PET and clinical diagnosis were identical]), and (2) Diagnostic change following PET imaging ("Yes" or "No"). The impact of PET imaging on the prescription of cholinesterase inhibitors (ChEIs) was also analyzed.

PET Imaging in Typical Dementia

Positron emission tomography imaging is not routinely recommended in typical dementias and very few clinicians will order such costly examination when the diagnosis is very clear. In this retrospective study, a total of 16 patients with AD and 12 patients with FTD underwent PET scans despite clear clinical diagnoses. The reason for this was that when PET brain imaging became available at our center in 2006, we wanted to document a few clear-cut, typical, classical cases of AD and FTD to ensure that our imaging unit was valid and accurate for the study of dementias. Finding out the degree of reliability of our PET unit in classic cases of dementia was a way for us to ensure that PET imaging might be helpful in clarifying the diagnosis in difficult cases. Because of the retrospective nature of this design, this became prospective to the current study.

Statistical Analyses

Statistical Package for the Social Sciences ([SPSS] version 12.0) was used for data analyses. Most of the analyses in this study consisted of descriptive statistics. Concordance rates were calculated using Cohen's kappa coefficient (κ). This is a statistical measure of interrater agreement for categorical items. It is generally thought to be a more robust measure than simple percentage agreement calculation since κ takes into account the agreement occurring by chance. κ is considered an overly conservative measure of agreement. The interpretation of the κ was based on current statistical interpretation charts where <0 = *No agreement*, 0.0 to 0.20 = *Slight agreement*, 0.21 to 0.40 = *Fair agreement*, 0.41 to 0.60 = *Moderate agreement*, 0.61 to 0.80 = *Substantial agreement*, and 0.81 to 1.00 = *Almost perfect agreement*.

Results

Participants

A total of 96 files were retrospectively selected from our database. Two patients were excluded because their functional imaging studies were performed over 1 year after the initial clinical diagnosis. The composition of the group is shown in Table 1. At the initial clinical diagnosis, a total of 39.4% (n = 37) of the patients were diagnosed with an atypical/unclear dementia, which is due to the complexity of the cases that are referred

Table 1. Patient Characteristics[a]

Gender	
Men	41 (43.6)
Women	53 (56.4)
Age at initial diagnosis	64.7 (9.8)
Education	12.7 (4.3)
MMSE score	23.5 (5.0)
Initial clinical diagnosis	
Typical dementias	33/94 (35.1)
AD	16/94 (17.0)
FTD	12/94 (12.8)
Others (CBD, DLB, VD)	5/94 (5.3)
Atypical/unclear dementias	37/94 (39.4)
MCI	17/94 (18.1)
Psychiatric	7/94 (7.4)
Medications[b]	
Vascular	54 (57.4)
Psychiatric	31 (32.9)
Memory	13 (13.8)

Abbreviations: MMSE, Mini-Mental State Examination; AD, Alzheimer disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; VD, vascular dementia.
[a] Values are mean (SD). For gender, initial clinical diagnosis, and medications, number of participants in each category with percentages in parentheses.
[b] Medications: "Vascular" included antiplatelets, anticoagulants, statins, hypoglycemiants and antihypertensives; "psychiatric" included antidepressants and benzodiazepines; and "memory" included cholinesterase inhibitors and memantine.

to our memory clinic and the fact that these are often the cases where we order functional neuroimaging. Among the typical dementias, there were 16 patients with AD and 12 with FTD. The remaining 5 cases included 2 patients with CBD, 2 with DLB, and 1 patient with VD. There were 17 patients with a clinical diagnosis of MCI. Finally, there were 7 patients with a purely psychiatric condition. A total of 13.8% of patients were taking memory-enhancing drugs at the moment of the PET scan.

Initial Clinical Diagnosis, Nuclear Medicine Physician's Diagnosis, and Most Recent Diagnosis

Figure 1 illustrates the initial clinical diagnosis, the Nuclear Medicine Physician's (NMP) diagnosis (using FDG-PET), and the most recent diagnosis for each clinical subgroups (ie, atypical/unclear, MCI, AD, and FTD).

Atypical/unclear cases. The number of cases considered atypical/unclear by the NMP was significantly lower than the clinicians (6.4% vs 39.4%). Among the atypical/unclear cases at the initial clinical evaluation, 29.7% showed typical AD patterns of hypometabolism on FDG-PET, 21.6% were normal, 16.2% showed patterns of VD, and 13.5% were compatible with FTD. The large number of AD patterns of hypometabolism on FDG-PET in the atypical/unclear category (ie, 29.7%) explains the significant difference in prevalence between the initial clinical diagnosis and the NMP diagnosis of AD (ie, 17% vs 33%; see Figure 1; see also Figure 2A for an example of an "atypical/unclear" case at the initial clinical diagnosis later identified as "AD" by the NMP diagnosis using FDG-PET). At the end of the study, a total of 16% of the 94 cases remained atypical/unclear despite clinical evolution of the disease and extensive investigation, which in some cases included serial functional imaging studies.

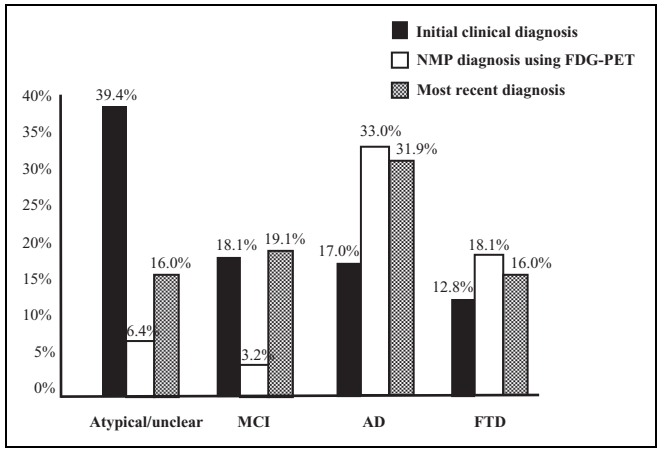

Figure 1. Initial clinical diagnosis, NMP diagnosis using FDG-PET, and most recent diagnosis. Atypical/unclear = cases where the initial clinical diagnosis was uncertain, unclassified, and the clinician listed several possible hypotheses for the diagnosis; AD indicates Alzheimer's disease; FTD = frontotemporal dementia; MCI = mild cognitive impairment; NMP = nuclear medicine physician; FDG-PET = [^{18}F]fluorodeoxyglucose positron emission tomography.

MCI cases. The number of MCI cases at risk of conversion identified by the NMP was significantly lower than the total number of MCI cases diagnosed by the clinicians (3.2% vs 18.1%; see Figure 1; see also Figure 2B for an example of an "MCI" case at the initial clinical diagnosis identified as "normal" on FDG-PET). Among this 18.1%, only 11.8% were identified as MCIs at risk of conversion on FDG-PET. The remainder of the sample was composed of 52.9% with a normal PET, 29.4% with a typical pattern of AD, and 5.9% with a pattern of FTD. Altogether, these results may reflect the different categories of patients with MCI, where a pattern of parietotemporal hypometabolism is being associated in the literature with a greater risk of conversion to AD as compared to a normal PET study which is of good prognosis, and the FTD pattern being associated with a risk of conversion to FTD.[33-34] However, this was not formally evaluated in the current work. At the end of the study, 19.1% of this cohort had a diagnosis of MCI and the concordance rate between the initial clinical diagnosis and the most recent diagnosis was high, reaching 70.6% (Kappa = .61, $P < .0001$, substantial agreement).

AD cases. The number of AD cases identified by the NMP was significantly higher than the number diagnosed by the clinicians (33.0% vs 17.0%; see Figure 1). This partly reflects the high number of atypical/unclear patients who presented a pattern of AD hypometabolism on FDG-PET. Among patients with AD at the initial clinical evaluation, 68.8% showed an

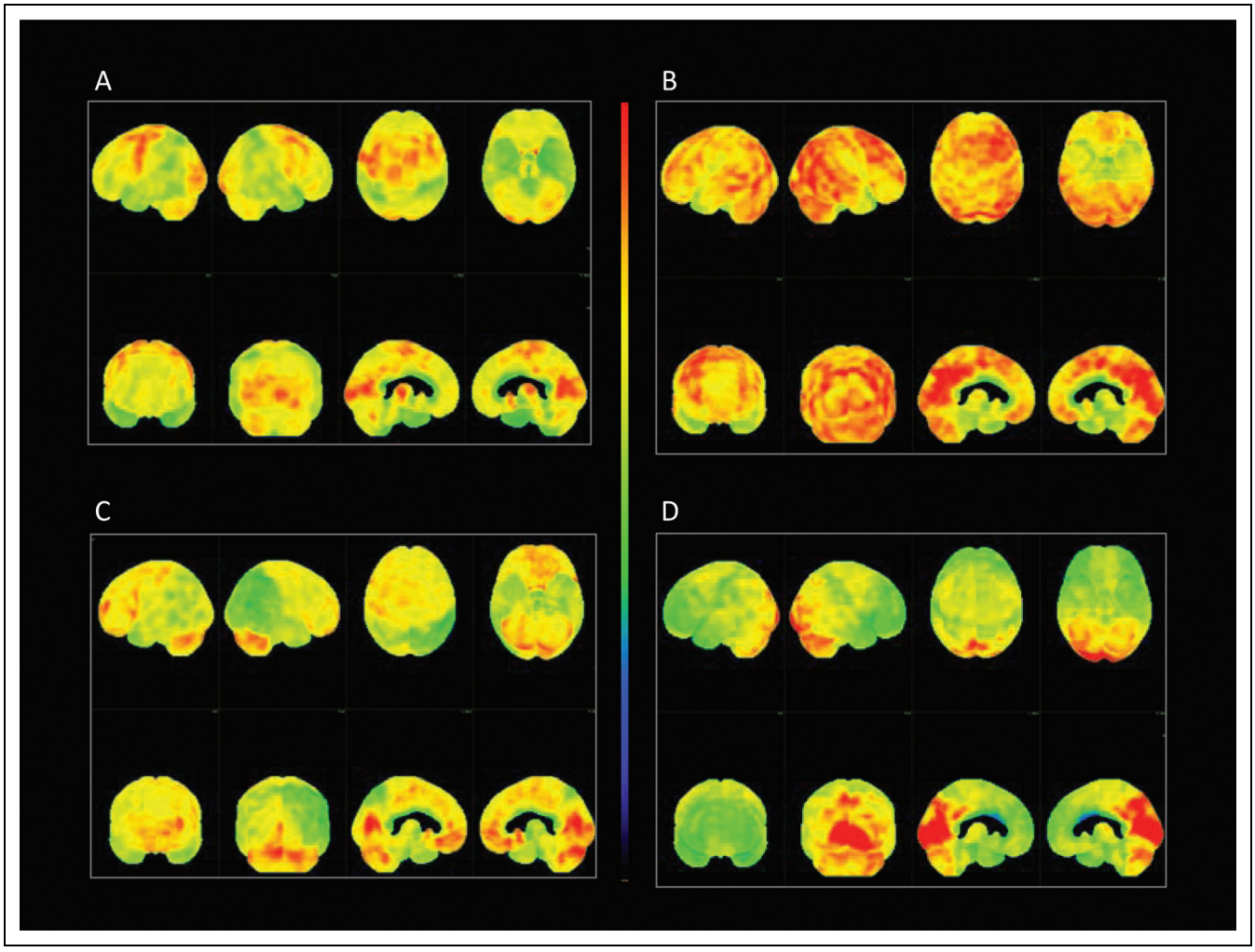

Figure 2. Representative SPM2 images related to 18F-FDG PET scans for MCI, typical, and atypical/unclear cases. A, A 72-year-old man with 5 years of education, MMSE = 16, presented with cognitive symptoms, diagnosed as atypical/unclear at initial clinical evaluation, PET scan read as AD, started on ChEIs, most recent diagnosis is AD. B, A 66-year-old woman with 11 years of education, MMSE = 30, MOCA = 28, presented with memory complaints, diagnosed as MCI at initial clinical evaluation, PET scan read as normal, no ChEIs, most recent diagnosis is MCI. C, A 59-year-old man with 18 years of education, MMSE = 19, presented with memory deficits, diagnosed as AD at initial clinical evaluation, PET scan read as AD, started on ChEIs, most recent diagnosis is AD. D, A 49-year-old man with 15 years of education, MMSE = 30, presented with cognitive and behavioural changes, diagnosed as FTD at all clinical evaluations, PET scan read as FTD, most recent diagnosis is FTD. AD indicates Alzheimer's disease; FDG-PET = [^{18}F]fluorodeoxyglucose positron emission tomography; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MOCA = Montreal Cognitive Assessment; ChEIs = cholinesterase inhibitors; FTD = frontotemporal dementia

AD pattern on FDG-PET (see Figure 2C for an example of an "AD" case at the initial clinical diagnosis identified as "AD" on FDG-PET). The remainder of the sample included 12.5% with a typical FTD pattern, 6.3% with a typical DLB pattern, 6.3% with MCI, and 6.3% with normal brain metabolism. At the end of the study, 31.9% of all cases remained with a diagnosis of AD, which was congruent with the NMP diagnosis.

FTD cases. The number of FTD cases identified by the NMP was slightly higher than the clinicians (18.1% vs 12.8%). Among patients with FTD at the initial clinical evaluation, 75.0% were indeed compatible with FTD on FDG-PET (see Figure 2D for an example of an "FTD" case at the initial clinical diagnosis identified as "FTD" on FDG-PET). The remainder of the sample included 16.7% of atypical/unclear patients and 8.3% with a normal PET. At the end of the study, a total of 16.0% of all cases remained with a diagnosis of FTD, which was overall homogeneous across evaluation modalities.

Concordance Rates

Figure 3 illustrates the global concordance rate between the initial clinical diagnosis and the NMP diagnosis using FDG-PET (31.9%, Kappa = .23, $P < .0001$). This fair degree of agreement is mainly explained by the very low concordance rate observed in patients with atypical/unclear presentations (5.4%). When

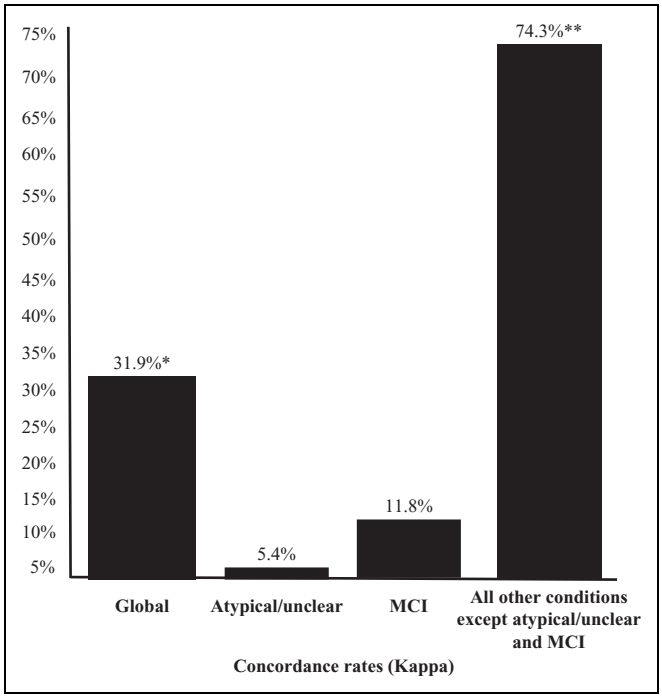

Figure 3. Concordance rates between the initial clinical diagnosis and the Nuclear Medicine Physician's diagnosis all conditions combined (ie, global), in atypical/unclear, in MCI, and in all other conditions, except atypical/unclear and MCI. *31.9%, Kappa = .23, $P < .0001$, fair agreement. **74.3%, Kappa = .52, $P < .001$, moderate agreement. MCI indicates mild cognitive impairment.

the latter cases were excluded, the concordance rate rose to 52.8% (Kappa = .39, $P < .001$), which is very close to a moderate level of agreement (0.40 to 0.60). This figure includes MCI cases which are also known to show a poor concordance rate of 11.8% likely due to the different subtypes of MCI, particularly the ones with good prognosis who do not show any impairment in their brain metabolism. When patients in the "atypical/unclear" and "MCI" groups were excluded, the concordance rate rose to 74.3% with an even greater Kappa (Kappa = .52, $P < .001$, moderate agreement).

Impact of PET Imaging

Clinicians' impression of the contribution of FDG-PET to the diagnosis was analyzed. Results show that PET overall helped, clarified, and oriented diagnosis in 56% of cases; confirmed clinical impressions in 16% of cases; and had no impact in 28% of cases. Moreover, FDG-PET findings were associated with a change in clinical diagnosis in 29% of cases.

Figure 4 allows a more in-depth view of the differential contribution of PET imaging in MCI, as well as typical and atypical/unclear dementias. Data suggest that PET imaging was very helpful for atypical/unclear cases (81.1% of cases) and patients with MCI (88.2% of cases), yet in a very different way. Indeed, atypical/unclear patients were more likely to be involved in a diagnostic change following PET (59.5% of cases) while, not surprisingly, patients with MCI were seldom involved in such

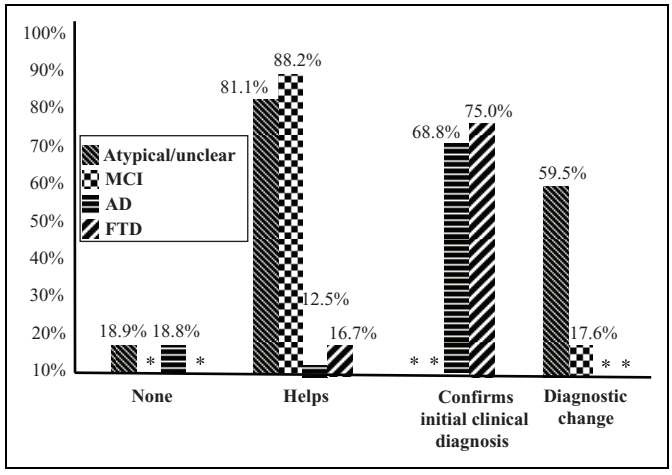

Figure 4. Differential contribution of PET imaging in MCI, typical, and atypical/unclear dementias. This figure shows that PET (1) was helpful in generating a more precise diagnosis in atypical/unclear cases, (2) was helpful in providing a clarification of the risk of conversion into AD for MCI cases, and (3) was of limited usefulness to both typical AD and FTD cases other than confirming the clinical diagnosis. The symbol * means that the percentage for this category was below 10% and therefore is not shown on the graph. AD indicates Alzheimer's disease; PET = positron emission tomography; MCI = mild cognitive impairment.

a process (17.6%). Despite relatively similar levels of usefulness from FDG-PET imaging in atypical/unclear and MCI cases, this additional examination allowed increased diagnostic accuracy in atypical/unclear cases whereas the benefit in MCIs lied in providing a clarification of the risk of conversion into AD as well as evidence that a primary neurodegenerative disease was less likely. Finally, the usefulness levels were low in both typical AD and FTD cases, but high levels of confirmation were reported (68.8% for AD and 75.0% for FTD), hence suggesting that PET's contribution in typical dementias lied in confirming clinical impressions rather than generating diagnostic change.

Finally, the prevalence of use of a ChEIs before and after PET imaging was computed. Numbers increased significantly from 13.8% to 38.3% following PET scan, partly reflecting the impact of PET on atypical/unclear cases that turned out to be potentially treatable patients with AD.

Discussion

This retrospective study adds to the growing evidence suggesting that use of PET in the evaluation of patients with cognitive impairments and dementia can improve diagnostic accuracy and lead to an earlier treatment, a better planning for future care, and less suffering for patients and their families.[1,9] More specifically, results show that PET helped in the clinical diagnosis of dementia in 56% of cases, led to a change in diagnosis in 29% of patients, lowered the number of atypical/unclear diagnoses from 39.4% to 16%, and was associated with a 64% increase in use of ChEIs (partly as a result of clearer diagnoses).

Although typical AD and FTD dementia cases may not benefit from routine PET imaging, we hypothesized that atypical/unclear and complex cases with MCI or dementia, who present an unusual profile may represent the ideal situation where this technology is indicated. A total of 39.4% of patients were diagnosed with an atypical/unclear dementia profile versus 35.1% with a typical dementia. The high numbers of atypical/unclear cases reflect the fact that selected cohorts of more complex cases are referred to our specialized memory clinic and many typical dementia cases are diagnosed and cared for by family physicians nowadays. Results showed that one of the main advantages of PET was to lower the number of atypical/unclear cases (from 39.4% to 16% at the end of the study), hence providing more accurate diagnoses. Almost 30% of these patients were found to have a typical AD pattern of hypometabolism on FDG-PET. Such influence from PET significantly contributed to seal the final diagnoses which were maintained throughout the study. In the end, only 16% of the cases remained atypical/unclear.

As for MCI cases, PET only identified 3.2% of them compared to 18.1% using initial clinical evaluation with a multidisciplinary approach. Over half of this 18.1% were identified as normal on PET, indicating a good prognosis and low likelihood of conversion to AD while a third were at risk of conversion. Concordance rates were high between the initial clinical diagnosis and the most recent diagnosis, despite negative findings on PET. Altogether, the latter data is consistent with the fact that there is no MCI-specific pattern of hypometabolism, MCI being a clinical syndrome with different heterogeneous cognitive deficits and clinical outcomes.[3]

Consistent with previous reports, PET was very good at confirming an initial clinical diagnosis of AD (68.8%) or FTD (75.0%). In FTD, the "initial clinical diagnosis," "NMP diagnosis," and "most recent diagnosis" gravitated around the same prevalence. However, PET allowed the identification of significantly more cases of AD than the clinician and this was partly due to the proportion of atypical/unclear patients who showed a pattern of AD hypometabolism on PET imaging. At the end of the study, the total number of cases who remained with a diagnosis of AD was similar to that obtained by PET imaging. These results are interesting because recent data suggests that PET findings have a high concordance rate with autopsy findings.[10]

Although the global concordance rate between the initial clinical diagnosis and the NMP diagnosis was only fair at 31.9%, this was largely explained by the impact of the "atypical/unclear" and "MCI" groups. When the latter cases were excluded from the equation, the concordance rate rose to 74.3% and showed moderate agreement.

The impact of PET imaging was assessed in various other ways. First, results showed that PET overall helped, clarified, and oriented the clinical diagnosis in over half of the cases. Second, PET provoked a change in clinical diagnosis in one third of the patients. It is important to mention that the post-PET visit was conducted within 5 months of the initial clinical diagnosis, therefore limiting the confounding impact of disease progression on diagnostic change. Third, it appeared very clearly that the cases benefiting the most from PET were atypical/unclear presentations. In this category alone, 59.5% of the patients underwent a change in diagnosis. Positron emission tomography imaging was considered helpful in 81.1% of the atypical/unclear cases and in 88.2% of the patients with MCI, despite the fact that the latter group did not undergo a significant diagnostic change following PET (17.6%). In MCI, the usefulness from PET was reported because it either clarified the risk of conversion to AD or indicated that a primary neurodegenerative disease was less probable at this stage, both of them without requiring diagnostic change. In some cases, of course, it helped to uncover AD or another primary condition such as FTD. The usefulness from PET was low in both AD and FTD cases because the examination essentially confirmed the initial clinical diagnosis. Finally, it was interesting to note that the use of ChEIs increased significantly from 13.8% to 38.3% after PET imaging. This is another indirect indicator of the impact of PET, again predominantly on atypical/unclear cases where the largest increase in the identification of treatable dementias was seen.

Limitations of the Study

This study has several limitations, the most important one being its reliance on clinical diagnosis due to the retrospective nature of the design. The use of a single and unblinded FDG-PET rating is also a limitation. Despite the fact that our rater is an experienced NMP with fellowship training in the area of dementia and FDG-PET imaging, it is well known that reliance on qualitative interpretation of images by visual reading depends heavily on the observer's experience and training. Another limitation related to functional imaging is the lack of specific PET criteria for the diagnosis of MCI. Other limitations include the fact that structural brain imaging was not considered a separate variable but factored into the diagnosis of clinicians. The relatively short window of observation (ie, 1½ year) between the initial clinical diagnosis and the most recent diagnosis probably limits our chance of capitalizing on disease evolution to obtain a more precise final clinical diagnosis. By contrast, the short delays between the initial clinical diagnosis and PET imaging, as well as with the standard post-PET evaluations are the strengths of this study.

Also of concern is the fact that the entire study was based on clinical diagnoses and no postmortem confirmatory analyses with histologically proven material were obtained. As mentioned by Jagust and colleagues, most existing studies compare PET to a clinical diagnosis, which may be inaccurate and therefore not an ideal gold standard.[10] This is mainly because the use of clinical diagnosis as a criterion does not permit the comparison of the relative accuracy of the PET diagnosis and the clinical diagnosis to the neuropathological diagnosis. Jagust and colleagues pointed out that when PET disagreed with the clinical diagnosis, the correct pathological diagnosis was more likely to be congruent with PET than with the diagnosis at the initial clinical evaluation.[10] Finally, because the study was conducted in a retrospective fashion on 94 individuals with a diagnosis of MCI or dementia, no

sensitivity or specificity values could be generated. Despite these shortcomings, we believe this study realistically reflects the day-to-day collaboration between clinical and nuclear medicine in dementia.

Conclusions

Altogether, this study shows that PET can play a key role in the evaluation of complex atypical/unclear cases with MCI or dementia. Positron emission tomography imaging helped in providing more accurate diagnoses and often was superior to the clinical diagnosis. Because the incidence of AD, DLB, and FTD are expected to increase dramatically as the baby-boomer generation ages, accurate diagnosis is important particularly in the early and mild stages of dementia where treatments are most effective. We believe that incorporating routine PET imaging in complex atypical/unclear cases can have a significant impact on early pharmacological management of patients with AD which in turn may delay cognitive decline, maintain patients' functional level longer, and delay institutionalization. Ultimately, this may help families who have to deal with the anxiety of an ambiguous diagnosis and repeated investigations.

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Declaration of Conflicting Interests

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References

1. Herholz K, Carter SF, Jones M. Positron emission tomography imaging in dementia. *Br J Radiol*. 2007;80(2):160-167.
2. Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. FDG-PET studies in MCI and AD. *Eur J Nucl Med Mol Imaging*. 2005;32(4):486-510.
3. Mosconi L, Tsui WH, Herholz K, et al. Multicenter standardized FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med*. 2008;49(3):390-398.
4. Pakrasi S, O'Brien JT. Emission tomography in dementia. *Nucl Med Commun*. 2005;26(3):189-196.
5. Silverman DH, Small GW, Chang CY, et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA*. 2001;286(17):2120-2127.
6. Whitwell JL, Jack CR. Neuroimaging in dementia. *Neurol Clin*. 2007;25(3):843-857.
7. Mendez MF, Shapira JS, McMurtray A, Licht E, Miller BL. Accuracy of the clinical evaluation for frontotemporal dementia. *Arch Neurol*. 2007;64(6):830-835.
8. Mosconi L, Brys M, Glodzik-Sobanska L, De Santi S, Rusinek H, de Leon MJ. Early detection of Alzheimer's disease using neuroimaging. *Exp Gerontol*. 2007;42(1-2):129-138.
9. Silverman DH, Cummings JL, Small GW, et al. Added clinical benefit of incorporating 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography into the clinical evaluation of patients with cognitive impairment. *Mol Imaging Biol*. 2002;4(4):283-293.
10. Jagust W, Reed B, Mungas D, et al. What does FDG PET imaging add to a clinical diagnosis of dementia? *Neurology*. 2007;69(9):871-877.
11. Silverman DH, Truong CT, Kim SK, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. *Mol Genet Metab*. 2003;80(3):350-355.
12. Ibach B, Poljansky S, Marienhagen J, et al. Contrasting metabolic impairment in frontotemporal degeneration and early onset Alzheimer's disease. *Neuroimage*. 2004;23(2):739-743.
13. Jeong Y, Cho SS, Park JM, et al. 18F-FDG PET findings in frontotemporal dementia: an SPM analysis of 29 patients. *J Nucl Med*. 2005;46(2):233-239.
14. Salmon E, Garraux G, Delbeuck X, et al. Predominant ventromedial frontopolar metabolic impairment in frontotemporal dementia. *Neuroimage*. 2003;20(1):435-440.
15. Varma AR, Adams W, Lloyd JJ, et al. Diagnostic patterns of regional atrophy on MRI and regional cerebral blood flow change on SPECT in young onset patients with Alzheimer's disease, frontotemporal dementia and vascular dementia. *Acta Neurol Scand*. 2002;105(4):261-269.
16. Gilman S, Koeppe RA, Little R, et al. Differentiation of Alzheimer's disease from dementia with Lewy bodies utilizing positron emission tomography with [18F]fluorodeoxyglucose and neuropsychological testing. *Exp Neurol*. 2005;191(suppl 1):S95-S103.
17. Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol*. 2001;50(3):358-365.
18. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1143-1153.
19. Moulin-Romsee G, Maes A, Silverman D, Mortelmans L, Van Laere K. Cost-effectiveness of 18F-fluorodeoxyglucose positron emission tomography in the assessment of early dementia from a Belgian and European perspective. *Eur J Neurol*. 2005;12(4):254-263.
20. Silverman DH, Gambhir SS, Huang HW, et al. Evaluating early dementia with and without assessment of regional cerebral metabolism by PET: a comparison of predicted costs and benefits. *J Nucl Med*. 2002;43(2):253-266.

21. Gill SS, Rochon PA, Guttman M, Laupacis A. The value of positron emission tomography in the clinical evaluation of dementia. *J Am Geriatr Soc*. 2003;51(2):258-264.
22. Galasko D, Hansen LA, Katzman R, et al. Clinical-neuropathological correlations in Alzheimer's disease and related dementias. *Arch Neurol*. 1994;51(9):888-895.
23. Feldman HH, Jacova C, Robillard A, et al. Diagnosis and treatment of dementia. *CMAJ*. 2008;178(7):825-836.
24. DeCarli C. The role of neuroimaging in dementia. *Clin Geriatr Med*. 2001;17(2):255-279.
25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4th ed. Washington, D.C.: American Psychiatric Association; 1994.
26. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.
27. McKhann GM, Albert MS, Grossman M, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol*. 2001;58(11):1803-1809.
28. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology*. 1992;42(3 pt 1):473-480.
29. McKeith IG, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*. 1996;47(5):1113-1124.
30. Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Förstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging*. 2004;25(8):1051-1056.
31. Drzezga A, Grimmer T, Siebner H, Minoshima S, Schwaiger M, Kurz A. Prominent hypometabolism of the right temporoparietal and frontal cortex in two left-handed patients with primary progressive aphasia. *J Neurol*. 2002;249(9):1263-1267.
32. Camargo EE. Brain SPECT in neurology and psychiatry. *J Nucl Med*. 2001;42(4):611-623.
33. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol*. 2001;58(12):1985-1992.
34. Drzezga A, Lautenschlager N, Siebner H, et al. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. *Eur J Nucl Med Mol Imaging*. 2003;30(8):1104-1113.
35. Huang C, Wahlund LO, Svensson L, Winblad B, Julin P. Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. *BMC Neurol*. 2002;2:9.