Comparative insights into mild cognitive impairment: A clinical case study with ^{18}F-FDG and amyloid PET imaging

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Abstract

Early detection of mild cognitive impairment (MCI) is crucial for initiating therapeutic interventions that may slow or prevent further cognitive deterioration. Mild cognitive impairment represents a transitional phase between normal cognitive aging and more severe forms of dementia, such as Alzheimer's disease (AD). Positron emission tomography (PET) can provide insight into the pathophysiology and progression of neurodegenerative processes associated with dementia and MCI using either fluorine-18 (^{18}F)-florbetapir, which detects beta-amyloid plaque burden, or ^{18}F-fluorodeoxyglucose (^{18}F-FDG), which measures glucose metabolism. However, there are limited comparative studies using the two radiotracers to quantify cognitive decline. This case study presents an 83-year-old female with a clinical diagnosis of MCI and a mini-mental state examination (MMSE) score of 26, at the lower boundary for normal cognitive function; she was assessed with PET/computed tomography (CT) using both radiotracers. Although global assessments did not reveal significant abnormalities, localized findings showed hypometabolism in key brain regions, such as the posterior cingulate cortex, and beta-amyloid plaque accumulation in the anterior cingulate cortex. These results highlight the limitations of conventional cognitive assessments, like the MMSE, and underscore the potential value of PET imaging as a complementary diagnostic tool. The study supports the role of ^{18}F-FDG as a stronger indicator of cognitive impairment due to its correlation with cognitive scores, while recognizing the need for further research to evaluate the predictive value of both PET tracers in early MCI detection and their potential to improve diagnostic accuracy.

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Introduction

The identification of clinically significant cognitive decline in its early stages is increasingly recognized as vital. Simply distinguishing between dementia and the natural cognitive changes associated with aging is insufficient for detecting the onset of cognitive disorders. The clinical evaluation of patients with potential Alzheimer's disease (AD) now extends beyond dementia to include mild cognitive impairment (MCI), which represents a transitional phase from the expected cognitive decline of aging to severe forms of dementia. Mild cognitive impairment is particularly significant because it offers an opportunity for early intervention with therapeutic strategies that may slow or prevent further cognitive deterioration [1, 2]. Studies on MCI have highlighted specific brain regions with reduced metabolism, such as the frontal-medial areas, including the precentral gyrus and pars triangularis. This hypometabolism, especially in medial components, may be associated with progressive supranuclear palsy (PSP), making these regions focal points for understanding MCI pathology [3].

Molecular imaging with positron emission tomography (PET) has enabled the diagnosis and characterization of neurodegenerative processes associated with dementia and MCI. For instance, fluorine-18 (^{18}F)-florbetapir is a radiotracer used to detect beta-amyloid plaques [4]. Concurrently, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) measures glucose metabolism, reflecting functional activity in brain regions and thereby aiding in the assessment of neurodegenerative disorders like MCI. Although both tracers can provide insights into the pathophysiology and progression of MCI, there is a notable lack of literature comparing the two modalities. This gap highlights the need for thorough research to identify the best approach for evaluating and diagnosing MCI [5].

Regional brain changes are increasingly considered crucial biomarkers for cognitive impairment progression in MCI, pinpointing the specific neurological areas impacted by

the condition [3]. This case report details a patient whose ^{18}F-FDG PET scans show statistically significant hypometabolism in critical regions [6]. The patient's mini-mental state examination (MMSE) scores, which are essential for monitoring MCI progression, correlate with the observed regional metabolic variations [7]. The standardized uptake volume (SUV) values are notably higher than those typically predicted for someone within this MMSE score range. This discrepancy emphasizes the complexity of MCI and the necessity for more sophisticated diagnostic tools [8]. The present report provides a case that challenges traditional diagnostic parameters and underscores the potential of radiotracer imaging to improve our understanding of MCI and its clinical manifestations.

Case Report

An 83-year-old female with a clinical diagnosis of MCI and a MMSE score of 26 was selected from a trial approved by the Thomas Jefferson University Institutional Review Board. The MMSE scores range from 0 to 30, indicating severe dementia to normal cognitive function respectively [7]. This particular patient was included in the study because her risk factors for MCI, such as having a body mass index (BMI) of 27kg/m^2 - which classifies her as overweight - correlate with an increased risk of cognitive decline [9].

The diagnosis of MCI in this patient was based upon the following criteria [10]:

1. A self-reported complaint of memory or cognitive decline, which was corroborated by an informant.
2. A clinical dementia rating (CDR) global score of 0.5, indicating a level of decline not categorizable as dementia [11].
3. Objective evidence of cognitive impairment or marginally normal cognition with a documented history of higher cognitive performance.
4. Absence of any obvious neurological or medical cause for the cognitive impairment, such as encephalopathy, nephropathy, head trauma, or stroke.
5. Normal activities of daily living.

Upon enrollment, the patient underwent a thorough evaluation that included brain computed tomography (CT) scans and PET scans with both ^{18}F-florbetapir and ^{18}F-FDG. All imaging procedures were performed after the patient had fasted overnight for at least eight hours, ensuring that blood glucose concentrations were below 8mmol/L.

Low-dose CT imaging was conducted to provide attenuation correction and anatomical context. The parameters for the CT scan were 140kV, with a current of 30-110mA, a noise index of 25, a rotation time of 0.8 seconds, and a slice thickness of 3.75mm. The reliability and accuracy of the neuroimaging data were verified by correcting the scans for scatter, attenuation, and dead time.

The ^{18}F-FDG PET scan protocol was aligned with the Alzheimer's disease neuroimaging initiative [12]. Participants received an injection of approximately 185MBq (5mCi) of ^{18}F-FDG. Imaging commenced around 30 minutes post-administration, with a total acquisition time of 30 minutes. A subsequent transmission scan was conducted for attenuation correction.

The ^{18}F-florbetapir PET scans adhered to established protocols [13]. A dose of approximately 370MBq (10mCi) of ^{18}F-florbetapir was administered to the subjects, with the scan starting around 50 minutes after injection. The acquisition time for the ^{18}F-florbetapir PET scan was 10 minutes, which was also followed by a transmission scan for attenuation correction.

Analysis

Analysis of the regional brain uptake of both ^{18}F-florbetapir and ^{18}F-FDG was performed using MIMneuro version 7.1.5 (MIM Software, Inc., Cleveland, Ohio). The analysis utilized validated methods. Positron emission tomography data were mapped on a voxel-by-voxel basis to a standardized brain template designed for comparison against an integrated anatomical brain atlas, which includes predefined regions of interest (ROI). For the ^{18}F-FDG workflow, MIMneuro analyzed 70 predefined regions (Figure 1), and for the florbetapir analysis, 16 predefined regions were assessed (Figure 2). Following this mapping, the software exported cross-sectional z-scores for each predefined ROI. These z-scores represent the number of standard deviations a patient's ^{18}F-FDG uptake or amyloid burden is from the control group's mean value, utilizing age-matched normal controls as a benchmark. Additionally, the mean standardized uptake value (SUVmean) was calculated by the software to quantify the overall metabolic activity and global amyloid burden. The employment of MIMneuro for this rigorous analytical process facilitated the precise quantification of regional metabolic uptake in the brain.

Results and Discussion

This case report presents an 83-year-old female clinically diagnosed with MCI who was included in our study due to pre-existing risk factors for cognitive decline. The global brain assessment with ^{18}F-florbetapir (SUVmean=0.59) and ^{18}F-FDG PET/CT (SUVmean=3.83) did not reveal a significant presence of beta-amyloid plaques or global hypometabolism, respectively. However, localized imaging identified several brain regions with a substantial presence of either beta-amyloid plaques or hypometabolism. Moreover, the patient's MMSE score of 26 places her at the lower boundary of the normal cognition range (26-30). The disparity between the imaging findings, the clinical diagnosis of MCI, and the MMSE score underscores the limitations of the MMSE and the necessity for more sophisticated diagnostic tools to complement the existing techniques for evaluating MCI.

While the MMSE is known for its specificity in diagnosing dementia, it lacks the sensitivity to effectively distinguish between normal cognition, MCI, and dementia [14]. Mini-mental state examination scores can be influenced by confounding variables such as the patient's age or educational level; for instance, a study reported that individuals with a me-

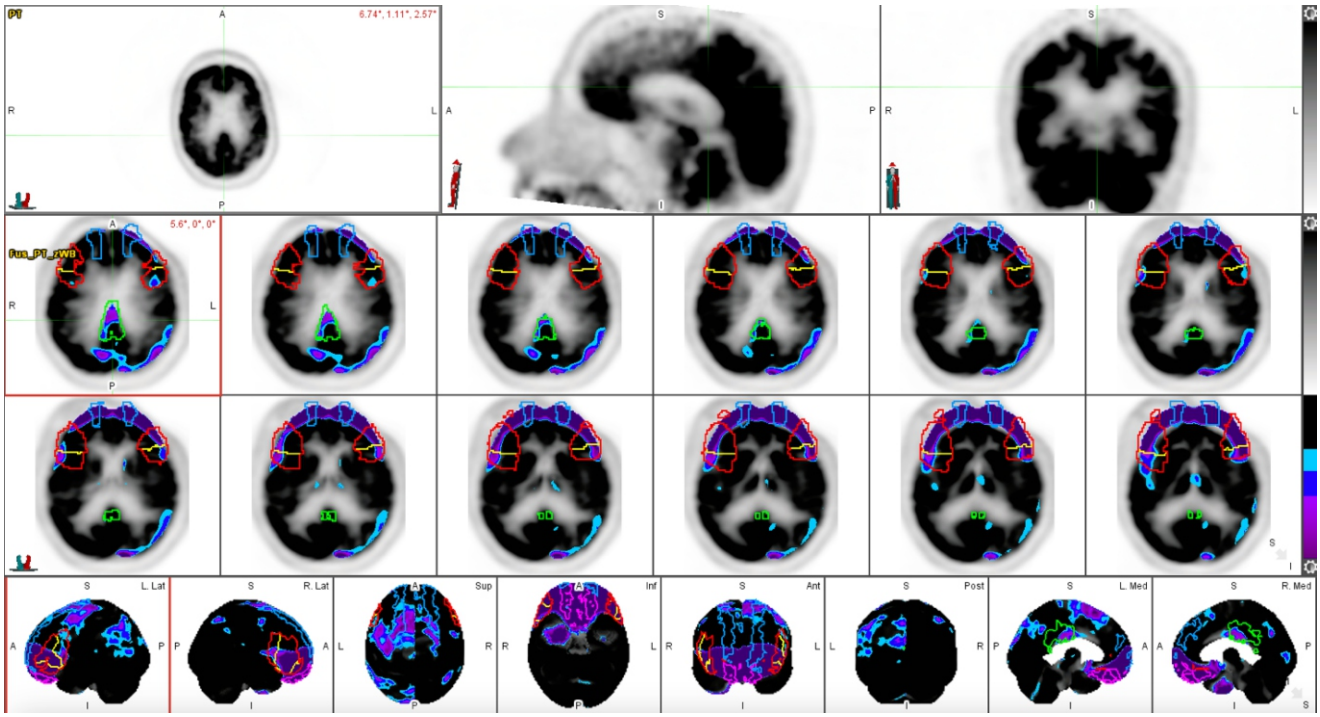

Figure 4. Evaluation of ^{18}F-FDG PET through quantitative analysis using MIMneuro version 7.1.5 (MIM Software, Inc., Cleveland, OH, USA). Low ^{18}F-FDG uptake is represented by purple and blue contours. The medial orbital gyrus (pink), and inferior frontal gyrus (red), inferior frontal gyrus, pars orbitalis (light blue), inferior frontal gyrus, pars triangularis (yellow), superior frontal gyrus (blue), and posterior cingulate gyrus (green) have been delineated as regions of interest in this patient.

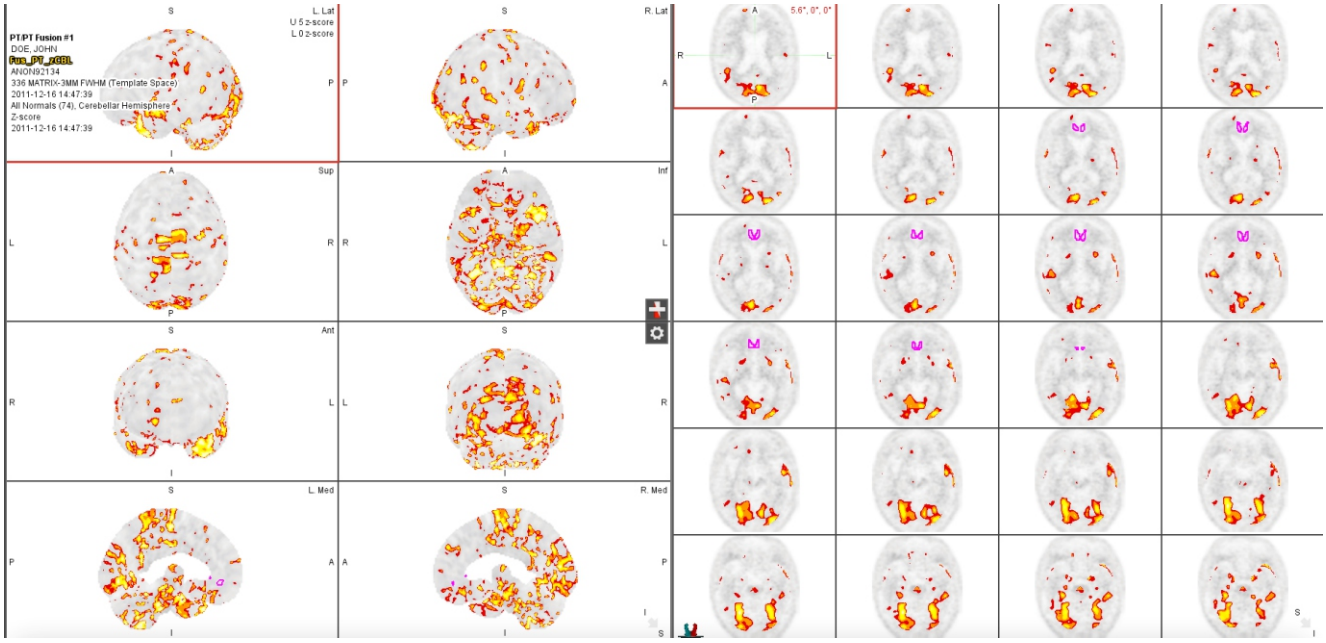

Figure 5. Evaluation of ^{18}F-florbetapir through quantitative analysis using MIMneuro version 7.1.5 (MIM Software, Inc., Cleveland, OH, USA). Increased ^{18}F-florbetapir uptake is represented by yellow and red contours. The anterior cingulate gyrus (pink) has been delineated as a region of interest in this patient.

dian age of 70 and over seven years of education had a median MMSE score of 29, in contrast to a median score of 23 among those with the same median age but only three years of education [14]. This study also indicated that the AB cognitive screen (ABCS) was less affected by patient-related factors and offered better clinical utility [14]. Jia et al. (2021) found that the Montreal cognitive assessment (MoCA) was more sensitive for detecting MCI than the MMSE, suggesting that MoCA is a superior measure of cognitive function [15]. Zhuang et al. (2021) recommend employing a combination of sensitive cognitive assessment tools for initial MCI screening and highly specific tools for secondary screening, excluding the MMSE from their recommendations [16]. However, these cognitive assessments rely on subjective interpretation and can be influenced by various external factors within the healthcare delivery process. Our patient's normal MMSE score, despite imaging and clinical evidence of cognitive decline, accentuates the potential value of objective data from PET imaging to aid in the evaluation and diagnosis of MCI.

A key area of interest showing hypometabolism is the posterior cingulate gyrus (z= -3.17) within the posterior cingulate cortex (PCC), which is crucial for early AD identification [17]. The PCC is involved in episodic memory tasks, including autobiographical memory, future imagination, spatial navigation, and scene processing [17]. Impairment in these areas is a hallmark of AD and can indicate MCI depending on the severity. Posterior cingulate cortex hypometabolism is one of the earliest markers in AD and serves as an indicator of the progression from MCI to AD [18-23]. Fluorine-18-FDG PET studies suggest that hypometabolism in the PCC is highly prevalent among amnestic MCI cases [3, 23, 24].

Other regions exhibiting hypometabolism are the superior frontal gyrus (SFG) (z= -3.95), middle frontal gyrus (MiFG) (z= -2), and inferior frontal gyrus (IFG) (z= -5.56). The SFG is associated with working memory and higher cognitive functions, while the MiFG is believed to play a significant role in numeracy and literacy. The IFG is implicated in speech processing and response inhibition [25]. Hypometabolism in the IFG sub-regions, pars orbitalis (z= -9.87), and pars triangularis (z= -5.73), can contribute to the symptoms of MCI, such as memory loss and word-finding difficulties. These findings align with various studies identifying these regions as susceptible to metabolic changes in MCI [26-28]. Specifically, the IFG was highlighted as a strong predictor for AD development in MCI patients carrying the APOE genotype [29]. Notably, hypometabolism in the anterior cingulate cortex (ACC) is commonly observed in MCI cases but was not present in this patient (z= 0.34) [26-28, 30, 31]. However, ^{18}F-florbetapir PET imaging indicated a significant accumulation of beta-amyloid plaques in the ACC (z=2.14), a finding aligned with studies differentiating healthy controls from AD subjects using ^{18}F-florbetapir SUV which were significantly higher in the AD group (P= 0.003) with respect to the ACC [30].

Despite existing studies on how ^{18}F-FDG and amyloid PET tracers evaluate MCI, research comparing the two types of radiotracers remains scarce. A recent study [32] demonstrated that both ^{18}F-florbetapir and ^{18}F-FDG could effectively distinguish MCI and AD subjects from normal controls but were less effective at differentiating between MCI and AD subjects. Fluorine-18-FDG was found to be a more potent indicator of cognitive impairment due to its stronger correlation with MMSE scores compared to ^{18}F-florbetapir. Although limited, our case findings support these observations. As indicated by prior research [17-28], regions of interest in cognitive impairment include the precuneus, ACC, PCC, inferior parietal lobe, superior/middle temporal gyrus, SFG, MiFG, and IFG. Hypometabolism measured by ^{18}F-FDG was identified in four of the nine regions. Fluorine-18-florbetapir imaging analyzed only five of the nine regions of interest, with a significant presence of beta-amyloid plaques observed in only one. It is noteworthy that no regions showed overlap in significant hypometabolism or beta-amyloid plaque presence. Amyloid PET tracers have higher sensitivity but relatively lower specificity compared to ^{18}F-FDG PET [32]. However, the presence of amyloid plaques in healthy individuals [33] has been reported, indicating that amyloid presence alone is insufficient for an AD diagnosis.

There is a wealth of literature on the predictive value of ^{18}F-FDG PET for dementia development and the transition from MCI to AD. However, research on ^{18}F-FDG PET ability to predict the progression from normal cognition to MCI is limited. Early detection of MCI is critical as it is associated with an increased risk of progressing to dementia. Early identification allows for timely support, monitoring of disease progression, and an earlier diagnosis of dementia. In the future, this could facilitate the initiation of preventive treatments to slow the progression to dementia. In the case of the MCI patient observed, hypometabolic regions such as the PCC, SFG, MiFG, and IFG were noted, mirroring patterns seen in other MCI and dementia cases. The ACC, another region of interest, showed high levels of beta-amyloid plaques. Further research is needed to determine whether the metabolic patterns observed and the presence of amyloid plaques in these regions are reliable indicators of the transition from normal cognition to MCI.

The study is limited by the small number of regions assessed with ^{18}F-florbetapir and the lack of baseline brain region observations from when the patient had normal cognitive function before developing MCI. Future studies, particularly longitudinal studies, should compare the diagnostic and prognostic utility of ^{18}F-FDG and ^{18}F-florbetapir PET to evaluate their effectiveness in assessing disease severity and progression.

In conclusion, global and regional analysis of ^{18}F-FDG PET uptake in the brain reveals distinct patterns of hypometabolism indicative of MCI. Understanding these changes may improve clinical diagnosis and prediction of disease progression. Areas of ^{18}F-florbetapir uptake did not overlap with regions of hypometabolism, indicating that the two radiotracers detect distinct pathologies occurring in MCI. Further research is warranted to determine the clinical efficacy of ^{18}F-FDG and ^{18}F-florbetapir PET in the early detection and management of MCI.

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