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Impact of molecular imaging on the diagnostic process in a memory clinic

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Abstract

Background: [^{11}C]Pittsburgh compound B ([^{11}C]PIB) and [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) PET measure fibrillar amyloid-β load and glucose metabolism, respectively. We evaluated the impact of these tracers on the diagnostic process in a memory clinic population.

Methods: One hundred fifty-four patients underwent paired dynamic [^{11}C]PIB and static [^{18}F]FDG PET scans shortly after completing a standard dementia screening. Two-year clinical follow-up data were available for 39 patients. Parametric PET images were assessed visually and results were reported to the neurologists responsible for the initial diagnosis. Outcome measures were (change in) clinical diagnosis and confidence in that diagnosis before and after disclosing PET results.

Results: [^{11}C]PIB scans were positive in 40 of 66 (61%) patients with a clinical diagnosis of Alzheimer's disease (AD), 5 of 18 (28%) patients with frontotemporal dementia (FTD), 4 of 5 (80%) patients with Lewy body dementia, and 3 of 10 (30%) patients with other dementias. [^{18}F]FDG uptake patterns matched the clinical diagnosis in 38 of 66 (58%) of AD patients, and in 6 of 18 (33%) FTD patients. PET results led to a change in diagnosis in 35 (23%) patients. This only occurred when prior diagnostic certainty was <90%. Diagnostic confidence increased from 71 ± 17% before to 87 ± 16% after PET ($p < .001$). Two-year clinical follow-up ($n = 39$) showed that [^{11}C]PIB and [^{18}F]FDG predicted progression to AD for patients with mild cognitive impairment, and that the diagnosis of dementia established after PET remained unchanged in 96% of patients.

Conclusions: In a memory clinic setting, combined [^{11}C]PIB and [^{18}F]FDG PET are of additional value on top of the standard diagnostic work-up, especially when prior diagnostic confidence is low.

Keywords: PET; [^{11}C]PIB; [^{18}F]FDG; Memory clinic; Alzheimer's disease; FTD; Lewy body dementia; MCI; SMC

1. Introduction

The diagnosis of patients with cognitive and/or behavioral symptoms can be complicated as different types of neurodegenerative disorders show overlap in clinical presentation, particularly in patients with an early onset of disease (<65 years) [1]. Furthermore, it is difficult to identify patients in a prodromal stage of Alzheimer's disease (AD) or other forms of dementia based on clinical symptoms alone. Improvement of early and differential

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diagnosis is desirable, especially in view of emerging disease-modifying agents. Over the past decades, several biomarkers have been developed to increase diagnostic accuracy in neurodegenerative diseases. These biomarkers have caused a major paradigm shift and have been incorporated in recently revised criteria that aim for more accurate and earlier diagnosis of AD, frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) [2–6].

Molecular imaging biomarkers most frequently used in the diagnosis of dementia are [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) and [^{11}C]Pittsburgh compound B ([^{11}C]PIB), which can be imaged using positron emission tomography (PET). [^{18}F]FDG is the more established tracer and provides a measure of metabolic activity of the brain. [^{18}F]FDG does not directly measure pathology, but rather the extent of metabolic impairment predicts cognitive decline, and is closely related to disease severity [7–9]. Mapping the pattern of glucose hypometabolism has high sensitivity (94%) for diagnosing AD, but specificity is lower (73%), as other neurodegenerative diseases can induce a decrease in glucose metabolism resembling the pattern seen in AD [10–12]. Reading [^{18}F]FDG images requires a well-trained eye, and even then only moderate interrater reliability is accomplished [13,14].

More recently, [^{11}C]PIB [15] became available for in vivo detection of fibrillary amyloid plaques, a neuropathologic hallmark of AD. Probing the underlying neuropathologic substrate may be helpful in identifying the correct type of dementia, particularly in patients with an atypical presentation [16]. [^{11}C]PIB discriminates AD patients from cognitively normal elderly [15,17,18], is a strong predictor of progression of mild cognitive impairment (MCI) to AD [19–21], and distinguishes AD reasonably well from other forms of dementia such as FTD [16,22] and vascular dementia (VaD) [23]. Patients with DLB, however, show positive [^{11}C]PIB scans in up to 89% of cases [24], which corresponds to increased amyloid burden found at postmortem examination in the majority of DLB patients [25]. Visual assessment of parametric [^{11}C]PIB images is straightforward and shows a high level of agreement between readers [14].

The current literature on [^{18}F]FDG and especially [^{11}C]PIB PET typically consists of comparisons of highly selected diagnostic groups. In general, these studies show good correspondence between clinical diagnosis and neuroimaging results. The potential lack of variation in pretest diagnostic certainty, however, may overestimate this concordance and may actually be lower in a more representative sample of a memory clinic population. The aim of the present study was therefore to assess the impact of [^{11}C]PIB and [^{18}F]FDG PET on the diagnostic process in a large sample of patients from a memory clinic, encompassing a wide spectrum of cognitive and/or behavioral symptoms.

2. Methods

2.1. Subjects and diagnostic procedure

Between March 2009 and September 2011, 154 patients were included from the outpatient memory clinic of the VU University Medical Center. All patients underwent standard diagnostic work-up for dementia consisting of medical history, informant based history, physical and neurologic examinations, screening laboratory tests, brain magnetic resonance imaging (MRI), and neuropsychologic testing [26]. This was followed by paired [^{11}C]PIB and [^{18}F]FDG PET scans. To ensure substantial variation in pretest diagnostic certainty, patients were recruited from two cohorts. One hundred nine patients were enrolled in the Center for Translational Molecular Medicine (CTMM) Leiden Alzheimer Research Netherlands (LeARN) project. The aim of this project is to evaluate the cost-effectiveness of ancillary investigations in a memory clinic setting, encompassing a wide spectrum of cognitive and/or behavioral symptoms. Patients with a Mini-Mental State Examination (MMSE) score of $\geq$20 and a maximum clinical dementia rating (CDR) of 1, without major neurologic and psychiatric disorders, recent vascular events, and excessive substance abuse, could participate in LeARN. In a second group of 45 patients, [^{11}C]PIB and [^{18}F]FDG PET scans were performed in case of substantial uncertainty about the diagnosis after the standard diagnostic work-up. The aforementioned inclusion criteria did not apply to the latter group of patients. A clinical diagnosis was made by consensus of a multidisciplinary team using established clinical criteria [27–31]. Diagnostic categories were AD, FTD, VaD, DLB, dementia-other (i.e., corticobasal degeneration [CBD] and progressive supranuclear palsy [PSP]), MCI, subjective memory complaints (SMC), psychiatry, and neurology-other (i.e., normal pressure hydrocephalus). In December 2011, 2-year clinical follow-up data (consisting of neurologic and neuropsychologic reevaluation, without neuroimaging) were available for 39 patients. All patients gave written informed consent after they had received a complete written and verbal description of the study. The medical ethics review committee of the VU University Medical Center approved the study.

2.2. PET imaging and analysis

PET procedures have been reported elsewhere [26]. Briefly, PET scanning was performed on an ECAT Exact HR+ scanner (Siemens/CTI, Knoxville, TN). After a 10-minute transmission scan, a dynamic 90-minute emission scan was started simultaneously with an intravenous injection of 367 $\pm$ 43 MBq [^{11}C]PIB. After coregistration of the MRIs to the corresponding PET images, the data were further analyzed using PVELab [32]. Regions of interest (ROIs) were projected onto nondisplaceable binding