Journal of Clinical Neuroscience 44 (2017) 128–132

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical commentary

Agreement among neuropsychological and behavioral data and PiB findings in diagnosing Frontotemporal Dementia

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ARTICLE INFO

Article history:
Received 6 February 2017
Accepted 22 May 2017

Keywords:
Alzheimer's disease
Frontotemporal Dementia
[^{11}C]-PiB PET imaging
Neuropsychological assessment

ABSTRACT

Diagnostic inaccuracies have been reported in Alzheimer's disease (AD) and Frontotemporal Dementia (FTD) using clinical data alone. The [^{11}C]-PiB PET scan offers a new method of identifying AD based on the detection of amyloid deposits. Our study investigated whether there was an agreement between neuropsychological and behavioral data and PiB findings in the diagnosis of FTD. Participants were 32 patients diagnosed with suspected FTD by clinical consensus. All participants underwent neuropsychological testing and PiB imaging. In addition, caregivers completed behavioral ratings of participants' memory, frontal behaviors, and mood. Seventeen participants were classified as PiB positive (+). Results of MANOVA and subsequent ANOVA analyses showed a significant difference on memory performance between the PiB- and PiB + groups, with the PiB- group performing better than the PiB + group. There were no significant differences between the groups on cognitive or behavioral measures of executive/frontal impairment, mood. Both groups showed similar severity of dementia. These findings provide evidence for the utility of the [^{11}C]-PiB PET scan in distinguishing between AD and FTD, with evaluation of memory at clinical diagnosis serving as a valuable indicator of the absence of FTD and consideration for an AD diagnosis. Our results would support the concern that patients who may present with primary behavioral or executive dysfunction may not necessarily have FTD, particularly if memory deficits are evident.

1. Introduction

Frontotemporal Dementia (FTD) has a high rate of clinical misdiagnosis when later reviewed via autopsy studies, especially when patients present to clinic early in the disease process [1]. While the earliest states AD have been associated with primary memory deficits [2] and FTD has been associated with primary deficits in executive functioning and behavior (e.g., impaired planning and decision-making) [3], the manifestation of behavioral dysfunction in preclinical AD and FTD appear to typically follow similar patterns. For example, caregivers of AD and FTD patients tend to initially report prominent changes in personality and social behavior, such as changes in distractibility, impulsivity, poor judgment, and social disinhibition [4], resulting in diagnostic confusion at the early stages. The discovery of a frontal variant of AD further complicates the issue of accurate diagnosis. In addition to memory problems, a frontal-based manifestation of AD appears to share the cognitive deficits associated with FTD, including severe executive dysfunction and language impairment [5]. Furthermore, pathological evidence supports the existence of a frontal-AD subtype as a dense clustering of neurofibrillary tangles that can be found near the frontal lobes of patients with the frontal variant of AD [6], rather than the temporal parietal clustering found in typical AD. As such, it has been difficult to clinically identify the proper etiology leading to cognitive decline in patients with presentation of behavioral disturbance.

Over the past several years, research has focused on improving the early detection and clinical differentiation of AD and FTD using

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http://dx.doi.org/10.1016/j.jocn.2017.05.008
0967-5868/

various approaches. One method has incorporated the use of Positron Emission Tomography (PET) scans with the radiotracer [^{11}C] Pittsburgh Compound B (PiB [7]), which is known to bind with high specificity to amyloid-beta plaques. It has been proposed that by identifying the presence of amyloid plaques using a relatively non-invasive technique, PiB scanning offers a method of classifying AD based on physiological markers prior to autopsy [8]. While its efficacy as a diagnostic tool in detecting AD is still being evaluated, the presence of PiB pathology has been correlated well with neuropsychological and behavioral data in AD [9]. Similarly, PiB status has been identified as being related strongly to episodic memory in participants classified as healthy adults and individuals with Mild Cognitive Impairment (MCI [10]). Other research has reported the correlation of episodic memory and PiB retention in the posterior cingulum, frontal cortex, and temporal cortex, as well as conversion to a presence of amyloid pathology (PiB+) MCI cases (but absence of amyloid pathology, PiB-, MCI cases) to AD over a 2–16 month follow-up period (mean follow-up of 8 months) [11]. Alternatively, PiB binding in FTD is thought to occur in much lower rates relative to AD, based on the decreased involvement of amyloid pathology in FTD. Rowe and colleagues [12] reported no PiB binding present in a clinically diagnosed FTD population, whereas others have identified PiB + rates of 20–25% in clinically diagnosed FTD populations [8,9,13], although these higher rates were suggested to be a function of the population having mixed FTD/AD dementia or frontal variant AD [9].

Clinical diagnosis of FTD has not proven to be as reliable as the diagnosis of clinical AD or other related disorders when confirmation is undertaken using post-mortem autopsy. Because advancements in treatment options and the need for adequate family/patient counseling make early diagnosis imperative, it is important to evaluate the accuracy of the clinical diagnosis of FTD. The accurate differentiation of AD and FTD requires a collection of information from neuroimaging results, neuropsychological performance, and behavioral data. Although the nature of caregivers' reports tend to be similar between preclinical AD and FTD, frontal-related atrophy and the hallmark executive dysfunction associated with FTD [3] suggest that caregivers should report relatively greater displays of inappropriate social behavior and poor judgment in rating FTD patients. Our group has previously shown that patients with a clinical consensus diagnosis of FTD but a molecular imaging (11C-dihydrotetrabenazine PET imaging of striatal vesicular monoamine transporters and PIB imaging) diagnosis of AD, patients exhibited better memory functioning, more frequent behavioral complaints and a trend toward more impaired frontal lobe functioning as compared to those with a clinical consensus diagnosis of AD and concordant molecular imaging consistent with AD [14]. There were no differences between PiB + and PiB- molecularly diagnosed FTD patients in neuropsychological performance when examining a brief battery of tests, though there were some significant behavioral differences. The lack of neuropsychological differentiation may have been due to the small sample size and reduced number of executive functioning tasks included in the battery, as well only limited behavioral/memory ratings. The clinician's ability to interpret behavioral data and to form a diagnostic opinion based on the presentation of clinical symptoms is a critical factor which influences the patient's course of treatment and, therefore, outcome. The current study examines the concordance between measures of behavior and neuropsychological performance with [^{11}C]-PiB-PET scanning in a larger subset of patients clinically diagnosed with FTD than we have previously reported and using a more extensive neuropsychological test battery and observer ratings scales.

In this current study, we examined patients who received a clinical diagnosis of FTD or MCI-executive type with suspicion of having a bvFTD and who underwent [^{11}C]-PiB PET scanning as part of a larger longitudinal project. Patients with FTD or probable FTD were identified as being either PiB positive or PiB negative (see Methods section), and the groups were compared on neuropsychological and behavioral profiles. We hypothesized that the presence of amyloid pathology would be associated with greater memory impairment and fewer frontal-related behavioral features as compared to the [^{11}C]-PiB negative group.

2. Methods

32 individuals clinically diagnosed with FTD (n = 20) using Neary criteria [3] or with MCI-executive type (n = 12) [15] and suspected to be early in the clinical course of FTD. Participants were not suspected to have Primary Progressive Aphasia, but rather the bvFTD. There were no differences between the bvFTD and MCI-executive type groups in terms of PIB status, χ^2 (1, n = 32) = 3.69, p = 0.08, Cramer's V = 0.34, suggesting that they may be adequate to combine into one group. Participants were enrolled as part of the longitudinal study of memory and aging (University of Michigan-Memory and Aging Project; UM-MAP) at the University of Michigan Alzheimer's Disease Center (MADC). Individuals were recruited from the Cognitive Disorders Clinic in the Department of Neurology, the Neuropsychology Section, or through MADC community outreach programs. Following screening for a history of stroke, Traumatic Brain Injury, and other medical conditions including intellectual disability, participants were enrolled in the MADC as part of the UM-MAP. Participants were evaluated by a neurologist and underwent neuropsychological testing with a trained technician and neuroimaging with [^{11}C]-PiB PET scans; the majority of participants underwent neuropsychological testing and neuroimaging either on the same day or within 48 h of each other (68.8%, with 93.8% within three months of each other; 1 had a testing/scanning 6 months apart and another had them 19 months apart), and they completed a measure of current mood symptoms. Diagnosis of the participants was done at a consensus meeting consisting of at least one neuropsychologist and two neurologists. A study partners/caregiver for each participant completed measures relating to the patient's neurobehavioral symptoms. Caregivers were identified as a spouse, family member, or close friend who knew the participant well, could rate the participant's functioning, and "who provided care to the participant." UM-MAP is approved by the Institutional Human Use Review Board of the UMHS (IRBMED).

2.1. Caregiver measures

2.1.1. Neuropsychiatric inventory questionnaire (NPI-Q [16])

The NPI-Q assesses psychopathology commonly found in dementia patients through a semi-structured interview of a caregiver by a trained staff member. The version used evaluates delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities. Higher scores reflect increased severity.

2.1.2. Frontal behavioral inventory (FBI [1])

The FBI is a rating scale of patients' frontal-behavioral functioning designed to help diagnose FTD. Caregivers are asked to rate changes in personality and behavior, such as apathy, judgment, and inflexibility. Higher scores reflect greater disturbance in negative behaviors and disinhibition.

2.1.3. Memory complaint questionnaire (MAC-Q [17])

The MAC-Q is a measure of age-related memory decline, requiring caregivers to rate the participant's memory functioning in