Added value of $^{18}$F-florbetaben amyloid PET in the diagnostic workup of most complex patients with dementia in France: A naturalistic study

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Abstract

Introduction: Although some studies have previously addressed the clinical impact of amyloid positron emission tomography (PET), none has specifically addressed its selective and hierarchical implementation in relation to cerebrospinal fluid analysis in a naturalistic setting.

Methods: This multicenter study was performed at French tertiary memory clinics in patients presenting with most complex clinical situations (i.e., early-onset, atypical clinical profiles, suspected mixed etiological conditions, unexpected rate of progression), for whom cerebrospinal fluid analysis was indicated but either not feasible or considered as noncontributory (ClinicalTrials.gov: NCT02681172).

Results: Two hundred five patients were enrolled with evaluable florbetaben PET scans; 64.4% of scans were amyloid positive. PET results led to changed diagnosis and improved confidence in 66.8% and 81.5% of patients, respectively, and altered management in 80.0% of cases.

Discussion: High-level improvement of diagnostic certainty and management is provided by selective and hierarchical implementation of florbetaben PET into current standard practices for the most complex dementia cases.

Keywords: Alzheimer’s disease; Clinical practice; Diagnosis; Patient management; Florbetaben; Amyloid imaging

1. Introduction

Alzheimer’s disease (AD) is the most common cause of cognitive impairment, accounting for over 60% of all dementia cases [1]. Dementia experts can diagnose “probable AD” with a sensitivity and specificity of only 71% compared with brain histopathology [2]. As many as 39% of patients diagnosed with non-AD dementia show histopathological features of AD on postmortem examination, while up to 25% of patients with a clinical diagnosis of AD have no amyloid pathology at autopsy [2]. Diagnosis of AD thus remains challenging, especially in younger patients (early-onset dementia), patients with complex clinical presentations (i.e., atypical nonamnestic clinical profiles such as predominant language, visuospatial, or behavioral symptoms), patients with mixed conditions [3], as well as in those presenting with an unexpected rate of progression (see Supplementary Material) [4,5]. Although disease-modifying medications do not exist yet for AD, timely introduction of an improved diagnostic pathway has the potential to provide actual health benefits to patients presenting with cognitive decline and may also be cost-effective [6]. Uncertainty of diagnosis, especially when it lasts a long time, may have devastating effects on quality of life and health of patients with dementia [7].

AD-specific biomarkers, such as amyloid beta (Aβ), are now detectable in vivo and can be measured directly through positron emission tomography (PET) using amyloid-specific ligands [8] or indirectly by assessing Aβ42 levels in cerebrospinal fluid (CSF) [9]. Amyloid imaging for detection of neuritic plaques has high sensitivity and specificity compared with histopathology as standard of truth [10–12]. It has been demonstrated that a reduced CSF level of Aβ42 in patients with AD is due to Aβ deposition and, thus, reflects plaque (or fibrillar Aβ) load in the brain [9]. An inverse relation has been described between CSF Aβ42 levels and binding of amyloid PET tracers in cortical brain regions [13], and the high concordance between CSF Aβ42 and amyloid PET imaging (see Supplementary Material and [9,14]) suggests that they may be used interchangeably to aid clinical diagnosis workup. Although in many countries analysis of CSF AD biomarkers has been accepted as standard practice to improve diagnostic certainty in patients with atypical neurocognitive decline [15], the use of amyloid PET remains restricted to the research setting.

Several past and present studies investigate the cumulative utility of amyloid imaging on the routine clinical diagnostic assessment of large sets of patients evaluated for cognitive impairment in memory clinics (see Table 1). Population of patients and inclusion criteria of course vary, with respect to the use of appropriate use criteria (AUC) recommendations. Nevertheless, only a few studies have been implemented in natural settings, and specifically in tertiary memory clinics. Finally and above all, none of them selectively used CSF biomarker information to improve diagnostic dilemmas before PET assessment. For example, Zwan et al. [16] included patients with early-onset or mild dementia, who benefited of a lumbar puncture (LP), but CSF results were not disclosed before PET data were available and were not taken into account for the initial diagnosis, thereby altering the natural setting. In daily practice, LP cannot be performed in all patients for whom CSF analysis would otherwise be recommended because of medical reasons such as use of oral anticoagulants or spinal problems or because of patient refusal. Moreover, variability of CSF analyses is common between and within laboratories, in particular for Aβ1–42 and phosphorylated tau, which may have a large impact on CSF-based AD diagnosis in clinical settings [32]. Clinicians interpret profiles of CSF biomarkers within a clinical context [33], which, in case of limit values, or partial abnormalities associated with complex clinical...
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