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Featured Article

The impact of automated hippocampal volumetry on diagnostic confidence in patients with suspected Alzheimer's disease: A European Alzheimer's Disease Consortium study

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Abstract

Introduction: Hippocampal volume is a core biomarker of Alzheimer's disease (AD). However, its contribution over the standard diagnostic workup is unclear.

Methods: Three hundred fifty-six patients, under clinical evaluation for cognitive impairment, with suspected AD and Mini–Mental State Examination ≥20, were recruited across 17 European memory clinics. After the traditional diagnostic workup, diagnostic confidence of AD pathology (DCAD) was estimated by the physicians in charge. The latter were provided with the results of automated hippocampal volumetry in standardized format and DCAD was reassessed.

Results: An increment of one interquartile range in hippocampal volume was associated with a mean change of DCAD of −8.0% (95% credible interval: [−11.5, −5.0]). Automated hippocampal volumetry showed a statistically significant impact on DCAD beyond the contributions of neuropsychology, ^{18}F-fluorodeoxyglucose positron emission tomography/single-photon emission computed tomography, and cerebrospinal fluid markers (−8.5, CrI: [−11.5, −5.6]; −14.1, CrI: [−19.3, −8.8]; −10.6, CrI: [−14.6, −6.1], respectively).

Discussion: There is a measurable effect of hippocampal volume on DCAD even when used on top of the traditional diagnostic workup.

Keywords: Alzheimer's disease; Hippocampal volume; Biomarkers; Diagnostic confidence of AD; Medial temporal lobe atrophy

1. Introduction

Over the last decade, many steps have been performed to improve and update the diagnostic criteria of Alzheimer's disease (AD) [1–3]. The International Working Group [4,5] criteria stated that positivity of one or more biomarkers of brain amyloidosis and neuronal injury is associated with a high likelihood of AD.

Specifically, the core AD biomarkers are divided into (1) amyloidosis biomarkers (decreased levels of amyloid β 42 [Aβ42] in the cerebrospinal fluid [CSF] and increased binding of amyloid brain imaging ligands on positron emission tomography [PET]) and (2) neuronal injury biomarkers such as medial temporal atrophy (MTA), hippocampal volume reduction (both assessed on T1-weighted magnetic resonance images [MRIs] [6,7]), increased total tau or phosphotau CSF levels, cortical, temporoparietal, and posterior cingulate cortex hypometabolism on ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), and hypoperfusion on single-photon emission computed tomography (SPECT).

However, the authors of these revised criteria are extremely cautious on recommending the use of these biomarkers in a clinical setting [2]. Indeed, the clinical use of most, if not all, of the biomarkers mentioned previously is affected by the lack of standard operating procedures for their assessment [8,9]. Furthermore, to show that a proposed biomarker combination can significantly enhance the diagnostic accuracy over the pure clinical workup, a proper validation is needed [3]. Some longitudinal studies have been promoted to assess whether an extended range of biomarkers, added to the traditional clinical assessment, can improve the diagnostic accuracy, and their role is still under discussion [10]. Preliminary results suggest that a combination of imaging (in particular, the assessment of hippocampal volume and regional glucose metabolism by FDG-PET) and CSF biomarkers (in particular, Aβ42 levels) can improve prediction of progression from mild cognitive impairment (MCI) to AD dementia, compared to baseline clinical testing [11–16].

Among these core AD biomarkers, hippocampal volume is one of the most established and validated [17], and it is used in research studies to stage the progression of AD neurodegeneration across the entire spectrum of the disease [18]. Moreover, there is a widespread agreement on its clinical significance, even if its validation process in a clinical framework is still ongoing [19]. Recently, an important effort has been made to improve the accuracy and reproducibility of manual hippocampal volume measurements thanks to the Harmonized Protocol for Hippocampal Segmentation project [18,20]. However, manual segmentation is not feasible in routine clinical practice because it is a time-consuming task that requires highly trained operators. For this reason, fully automated hippocampal volumetry using