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COMMENTARY

Amyloid imaging in prodromal Alzheimer's disease

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Abstract

Patients with mild cognitive impairment are at an increased risk of progression to Alzheimer's disease. However, not all patients with mild cognitive impairment progress, and it is difficult to accurately identify those patients who are in the prodromal stage of Alzheimer's disease. In a recent paper, Koivunen and colleagues report that Pittsburgh compound-B, an amyloid-beta positron emission tomography ligand, predicts the progression of patients with mild cognitive impairment to Alzheimer's disease. Of 29 subjects with mild cognitive impairment, 21 (72%) had a positive Pittsburgh compound-B positron emission tomography baseline scan. In their study, 15 of these 21 (71%) patients progressed to Alzheimer's disease, whilst only 1 out of 8 (12.5%) Pittsburgh compound-B-negative patients with mild cognitive impairment did so. Moreover, in these mild cognitive impairment patients, the overall amyloid burden increased approximately 2.5% during the follow-up period. This is consistent with other longitudinal amyloid imaging studies that found a similar increase in amyloid deposition over time in patients with mild cognitive impairment. These studies together challenge current theories that propose a flattening of the increase of brain amyloid deposition already in the preclinical stage of Alzheimer's disease. These findings may have important implications for the design of future clinical trials aimed at preventing progression to Alzheimer's disease by lowering the brain amyloid-beta burden in patients with mild cognitive impairment.

Introduction

Mild cognitive impairment (MCI) is considered a transitional stage between normal aging and dementia, in particular Alzheimer's disease (AD) [1]. The rate of conversion from MCI to AD is approximately 15% per year [2]. However, a substantial number of MCI patients have cognitive complaints caused by other conditions, such as depression, stress, or sleeping disorders. It is important, therefore, for clinicians to identify individuals who are in the prodromal stage of AD, in particular because these patients may be a target for future disease-modifying treatments. Advanced neuroimaging techniques may improve diagnostic accuracy in this patient group. The positron emission tomography (PET) ligand ^{11}C labeled Pittsburgh compound-B ([^{11}C]PIB) [3] detects fibrillary amyloid-beta (Aβ) *in vivo*, and may be used for this purpose. [^{11}C]PIB PET discriminates well between AD and controls [3,4] and between AD and other types of dementia [5], with the exception of dementia with Lewy bodies [6]. In patients with MCI, little is known about the predictive value of [^{11}C]PIB PET for progression to AD, or about temporal changes in [^{11}C]PIB binding.

Recently, Koivunen and colleagues [7] reported the results of a prospective 2-year follow-up study in which they assessed the predictive value of [^{11}C]PIB PET for progression to AD as well as the temporal changes in amyloid deposition in MCI patients. In the present commentary, we discuss the findings of this study and its potential implications for future clinical trials with disease-modifying agents in prodromal AD.

Identifying prodromal AD with [^{11}C]PIB PET

Koivunen and colleagues [7] performed amyloid imaging with [^{11}C]PIB PET at baseline and after 2 years of follow-up in a sample of 29 MCI patients. They divided MCI patients into converters and non-converters, based on clinical diagnosis at follow-up. At baseline, MCI converters had substantially higher mean [^{11}C]PIB levels compared to MCI non-converters in the posterior cingulate, lateral frontal and temporal cortices and in putamen and caudate nucleus. After classifying [^{11}C]PIB PET scans into either positive or negative, using a cut-off point of 1.5 standardized uptake value ratio (SUVr), 21 of 29 (72%) subjects with MCI had a positive [^{11}C]PIB PET scan. In their study, 15 of the 21 (71%) [^{11}C]PIB-positive MCI patients progressed to AD while only 1 out of 8 (12.5%) [^{11}C]PIB-negative MCI patients did so. These results are in accordance with several previous studies [8,9] and indicate that [^{11}C]PIB PET predicts progression to AD in MCI patients.

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Temporal changes in amyloid burden in MCI

Recently, Jack and colleagues [10] proposed a hypothetical model that positioned established and novel biomarkers in the continuum of AD. This model elaborates on the amyloid-cascade hypothesis [11], which states that accumulation of Aβ initiates a cascade of neuropathological events, such as the formation of neurofibrillary tangles and neuroinflammation. This may in turn lead to neurodegeneration that presumably is followed by cognitive deterioration and finally results in dementia. Accumulation of Aβ is thought to set in decades before the first cognitive complaints arise, starts to accelerate already in the preclinical stage of AD, and reaches a relative plateau at the time symptoms emerge [12].

In the study by Koivunen and colleagues, the overall amyloid burden in MCI patients increased approximately 2.5% in 2 years. This increase was most prominent for those patients who did not convert to AD. However, the overall increase in amyloid deposition was only modest, whilst hippocampal volumes decreased more strongly. This is in line with the idea that Aβ starts off the cascade and may uncouple at a later time point from neurodegenerative processes. Previous studies that related the presence of amyloid plaques with the course of brain atrophy [13] and glucose hypometabolism [14] also found this dissociation between amyloid deposition and structural and functional changes. The findings of Koivunen and colleagues suggest that the time span between deposition of amyloid and actual neurodegeneration may perhaps be shorter than previously assumed, given the dynamic Aβ changes in MCI patients in this study.

The finding of increased amyloid burden over time in MCI patients is consistent with other recent longitudinal amyloid imaging studies. Villemagne and colleagues [15] reported that 65 MCI patients had a mean increase in [^{11}C]PIB retention of 2.1% over a 20-month follow-up period (annual increase of 1.3%). A study by Jack and colleagues [16] showed an annual increase of 1.7% in 32 MCI patients. Moreover, in an unpublished study from our group in 12 MCI patients, [^{11}C]PIB binding increased by 5.0% over a 30-month period (annual increase 2%). These results are in accordance with the 2.5% increase over 24 months (annual increase 1.25%) reported by Koivunen and colleagues. In all these longitudinal studies, the increased amyloid burden was primarily driven by MCI patients that displayed high [^{11}C]PIB retention at baseline. Taken together, amyloid deposition seems to increase in both MCI converters and non-converters, thereby challenging the theory that amyloid plaque load is stable in the prodromal stage of AD.

A limitation of the study by Koivunen and colleagues, especially given its longitudinal design, is the use of SUVr, which overestimates [^{11}C]PIB binding in comparison with fully quantitative kinetic models [17]. Furthermore, SUVr does not correct for factors that are inherently associated with disease progression, such as heterogeneous flow effects in the region of interest compared to the reference region. We therefore argue that quantitative modeling, and thus dynamic PET scanning, is essential for longitudinal amyloid imaging studies.

Amyloid imaging in clinical trials

The finding that [^{11}C]PIB PET can help identify prodromal AD patients and that most MCI patients show an increased amyloid burden over time may have implications for the design of future clinical trials. First of all, amyloid imaging may be used as an enrichment strategy by enabling the selection of subjects at risk for AD, in order to administer disease-modifying agents to the right patients. Secondly, Aβ PET ligands may be used as a secondary outcome measure to provide biological insight into cognitive primary outcome measures. Finally, amyloid imaging can be applied as a surrogate outcome measure to test whether anti-amyloid therapies are efficacious by measuring the amount of fibrillary Aβ prior to and after the time window of the intervention. In this respect one should note that patients with prodromal AD may still show an increase in amyloid plaque formation, instead of the previously assumed plateau due to an equilibrium between production and clearance of Aβ. This will affect power calculations for such trials. Current development of several fluor-18-labeled amyloid PET tracers (which have a longer half-life time compared to carbon-11) will further increase the availability and applicability of amyloid imaging in both clinical practice and for scientific purposes.

Conclusion

Koivunen and colleagues showed that amyloid imaging may be used to predict clinical progression to AD in patients with MCI and that, contrary to current hypothetical biomarker models, amyloid deposition increases over time in patients with MCI. These findings are relevant for the design of future clinical trials aimed at the prevention of progression to AD by lowering the Aβ burden in the brains of patients with MCI.

Abbreviations

[^{11}C]PIB, ^{11}C labeled Pittsburgh compound-B; Aβ, amyloid-beta; AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography; SUVr, standardized uptake value ratio.

Competing interests

The authors declare that they have no competing interests.

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