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EDITORIAL COMMENTARY

Dual-phase amyloid PET: hitting two birds with one stone

Garibotto Valentina[1] · **Morbelli Silvia**[2] · **Pagani Marco**[3,4]

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One of the major breakthroughs in Alzheimer's disease (AD) clinical research over the past two decades has been the validation of diagnostic biomarkers able to demonstrate the presence of pathological mechanisms of AD and to predict further cognitive decline and dementia onset in mild cognitive impairment (MCI) patients by identifying the prodromal stage of AD [1, 2]. Among AD biomarkers, two main categories exist: (1) amyloidosis biomarkers, able to identify a molecular feature typical of AD: these include cerebrospinal fluid (CSF) amyloid-β42 reduction and PET imaging using radiotracers selectively binding to the fibrillar aggregates of amyloid-β plaques; (2) neurodegeneration biomarkers reflecting neuronal injury, such as the increase of tau and phosphorylated-tau levels in the CSF, regional atrophy as measured by MRI and demonstration of synaptic dysfunction/degeneration by means of 18F-fluorodeoxyglucose (FDG) PET. Neurodegeneration biomarkers are useful tools for further differential diagnosis among amyloid positive and amyloid negative forms of dementia, and also a prognostic tool in the MCI population.

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✉ Pagani Marco
marco.pagani@istc.cnr.it

[1] Division of Nuclear Medicine and Molecular imaging, Department of Medical Imaging, Geneva University and Geneva University Hospitals, Geneva, Switzerland

[2] Nuclear Medicine Unit, IRCCS San Martino – IST, Department of Health Sciences, University of Genoa, Genoa, Italy

[3] Institute of Cognitive Sciences and Technologies, CNR, Rome, Italy

[4] Department of Nuclear Medicine, Karolinska Hospital, Stockholm, Sweden

In this framework, different sets of criteria for diagnosis of AD at the stage of MCI have been proposed: the International Working Group (IWG)-1 [1, 3] and IWG-2 [4], and National Institute of Ageing Alzheimer Association (NIA-AA) criteria [2]. These criteria differ with respect to the definition of the biomarker abnormality needed to identify MCI at higher risk to convert to AD. The IWG2 criteria have been developed mainly for a research setting and propose to support clinical suspicion of AD only by means of amyloidosis biomarkers (defined as diagnostic biomarkers) [4]. By contrast, the NIA-AA criteria were designed for both clinical and research purposes and use the term 'MCI due to AD" for patients with cognitive impairment in any cognitive domain and abnormal amyloid markers or neuronal injury markers. In this frame, NIA-AA criteria relate the number of abnormal biomarkers to the likelihood that MCI is due to AD [2]. Although a prospective comparison between these two different approaches (IWG2 and NIA-AA) is still lacking, the validity of this NIA-AA model has been confirmed by a large retrospective multicenter study showing that, in the clinical setting, the combined use of both amyloid and neuronal injury markers offers the most accurate prognosis in MCI patients [5]. Similarly, in a recent survey, neurologists working in European Alzheimer's Disease Consortium Centres agreed that only a combination of amyloidosis and neuronal injury biomarkers is a strong indicator of an underlying AD [6].

The use of AD biomarkers in routine clinical practice should take into account not only the diagnostic performances of a test but also cost-effectiveness estimates [7].

In this respect, the possibility of acquiring information about amyloidosis and neurodegeneration with a single biomarker/procedure offered by CSF measures is a clear advantage. However, standardization of CSF biomarkers is still challenging (from handling of samples to identifying and interpreting cut-offs) and international collaborative efforts

are still ongoing to reduce the sources of their analytical variability and standardization [8].

A novel modality of amyloid PET data acquisition might also be able to evaluate both brain amyloidosis and neurodegeneration at the same time, namely the dual-phase amyloid PET scanning described and adopted in the paper by Lin et al. published in the present issue of the European Journal of Nuclear Medicine and Molecular Imaging [9].

Dual-phase amyloid PET refers to the acquisition of a short (usually 5 min) image immediately after injection, mirroring perfusion imaging, followed by an interval of variable length, depending on the kinetic properties of the specific tracer, and by the late "standard" acquisition at equilibrium to assess the specific binding to amyloid plaques.

The concept of dual-phase scanning is not new; it has been tested both with 11C-PIB and with 18F-Florbetapir and is mainly linked to the fact that amyloid tracers have high lipophilicity, which makes them good perfusion surrogates [10, 11].

The data available so far show that early phase images have strong similarities with FDG PET images in AD and frontotemporal lobar degeneration [10, 12–14], can distinguish MCI from healthy controls [15], and recent evidence suggests a potential diagnostic advantage also in patients with cerebral amyloid angiopathy [16].

The perfusion imaging measured by the early acquisition, is, according to the recent diagnostic criteria for AD, a topographical/functional biomarker reflecting disease progression, in analogy with perfusion imaging measured by SPECT or MRI techniques and brain glucose metabolism, measured by FDG PET, while the late-phase amyloid PET acquisition represents a pathophysiological marker, indicating the presence of a disease-related molecular process.

The dual-phase approach, providing the possibility to investigate at once neuronal injury and molecular pathology, has obvious advantages, as compared with two separate scans.

First, the radiation dose would be reduced at least by half, as compared with a standard assessment with serial FDG and amyloid PET.

Second, in a time in which economic hardship heavily impacts clinical setup, the accurate evaluation of the cost-effectiveness for diagnostic procedures is becoming of vital importance in the diagnostic work-up [17]. Preliminary studies have shown that the use of biomarkers might be cost-effective, but larger validation studies are still required [18–20]. In this respect, dual-phase amyloid PET allows to obtain pooled clinical information with substantial sparing of direct medical costs as scanning time and radiopharmaceutical expenses. In fact, this approach would be economically challenging for routine clinical use, reducing the total cost by 1000 Euros, avoiding additional FDG or other functional evaluations. Furthermore, this "one-stop-shop" approach would reduce non-medical costs as transportation fees and losses of productivity due to sick leave.

The proposed methodology minimizes not only radiation exposure but also patient and caregivers burden, avoiding for patients to undergo a second examination with the associated stress. Moreover, theinvestigation of multiple biomarkers at once will reduce the time necessary to come to an early and accurate diagnosis, accelerating case management, treatment initiation, and ultimately increasing the efficacy of theavailable therapies.

There are three main open issues to be addressed before translating this approach into daily clinical practice. The first regards the validation of the scanning and assessment methods to be used for single-subject analysis of the early phase amyloid PET. All studies on this topic have so far shown that at the group level, the distribution of perfusion, as measured by the early phase of amyloid PET, is comparable (with some regional differences) to the distribution of metabolism shown by FDG PET. However, none of these studies has assessed the sensitivity and the reproducibility of this measure in individual cases.

The second concerns the sensitivity of this tool for a specific population, namely MCI subjects, to predict clinical progression. Indeed, we know that while amyloid negativity has an excellent negative predictive value for conversion [21, 22], among amyloid-positive MCI subjects, the interval to progression can be variable, and functional measures can predict more accurately the time to conversion [23, 24]. Although the value of FDG PET in this setting is well established, perfusion measures should be validated for this specific and highly interesting indication [25–28].

A third issue, strongly linked with the previous ones, is the need for a deeper investigation of the differences, and not only the analogies, between perfusion surrogates, such as measured by early phase PET scanning, and glucose metabolism imaging in degenerative disorders. The interrelationship between perfusion and metabolism might change along with the disease progression and might be different in the early disease stage, when changes are subtle and due to a combination of local neuronal dysfunction and disconnection mechanisms [29]. This aspect concerns not only early phase amyloid scanning but also other measures of perfusion, which are increasingly investigated in this field, such as arterial-spin-labeling, as measured by MRI. Perfusion and metabolism are indeed strongly coupled in the brain, and a large body of literature has evaluated perfusion changes in dementia and degenerative disorders, mainly by perfusion SPECT, showing patterns of hypoactivity similar to the patterns classically described for FDG PET. It is also known that perfusion SPECT has lower sensitivity and specificity, and this has been mainly explained by the difference in spatial resolution between the two methods [30]. However, detailed comparative analysis in the same

individuals is still limited, and some recent data show that a mismatch can be observed in various regions [12, 31].

In conclusion, the assessment of functional (e.g., perfusion) changes is a validated and well-established biomarker for early and differential diagnosis and prognostic evaluation in patients with MCI or dementia. The possibility of combining this information to each amyloid PET scan at no additional costs is very promising, and deserves larger testing in the nuclear medicine community.

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