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LETTER TO THE EDITOR

In the era of FDG PET, is it time for brain perfusion SPECT to gain a place in Alzheimer's disease imaging biomarkers?

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Dear Sir,

We read with great interest the recent paper by Coutinho et al., entitled "Brain PET amyloid and neurodegeneration biomarkers in the context of the 2018 NIA-AA research framework: an individual approach exploring clinical-biomarker mismatches and sociodemographic parameters" published in EJNMMI [1]. The authors aimed to investigate the proportion of beta amyloid and the presence of glucose metabolism abnormalities across three groups, demented or MCI subjects and cognitively intact older individuals, using [11C]PIB and [18F]FDG PET imaging. In cases of clinical-biomarker mismatches, they used the "A(N)" staging system proposed by the 2018 NIA-AA research framework, in order to achieve an individual classification and explore any relation to sociodemographic characteristics. Main findings of this study were the correlation of beta amyloid positivity with a glucose hypometabolism pattern typical of AD, the higher proportion of A+(N)+ in probable AD compared with aMCI or healthy subjects, and the significant role of [18F]FDG-PET in the classification of subjects with clinical-biomarker mismatch.

The use of [18F]FDG-PET has been recommended as an imaging biomarker of neurodegeneration or neuronal damage by the NIA-AA since 2011 for the diagnosis of AD, MCI due to AD, and the preclinical stage of AD [2–4]. PET molecular neuroimaging with [18F]-FDG detects the alterations in brain glucose metabolism, reflecting the underlying neurodegenerative processes and synaptic dysfunction in vivo. There exist a great number of published studies in AD which have shown characteristic patterns of [18F]FDG reduced uptake in specific brain regions including the temporoparietal, precuneus, and posterior cingulate cortices, usually bilaterally and asymmetric, as well as the frontal cortex to a variable degree [5–7]. These patterns are considered typical of AD and may be helpful to distinguish AD from other forms of dementia.

However, a large amount of information has also been collected the last decades on the use of brain perfusion SPECT in dementia. SPECT perfusion studies have revealed alterations associated with neurodegeneration in AD, in the same cortex areas as those seen in [18F]FDG-PET [7, 8]. By virtue of coupling of neural activity and brain glucose metabolism with cerebral blood flow, perfusion SPECT allows functional imaging of neurodegenerative disorders. In that sense, perfusion SPECT was considered by the European Federation of the Neurological Societies (EFNS) that could be useful in the investigation of dementia, increasing the confidence of diagnosis [9], while the NIA criteria for MCI due to AD recommend both [18F]FDG-PET and perfusion SPECT, as equivalent biomarkers [3]. Clinical-pathological studies have shown a higher specificity of perfusion SPECT compared with clinical diagnostic criteria for the diagnosis and differential diagnosis of AD. Especially in cases of possible AD, the technique provided useful information, increasing the likelihood of 67% for AD without SPECT to 84% with a positive SPECT and 52% with a negative SPECT [10, 11].

The preferential use of [18F]FDG-PET as an imaging dementia biomarker is supported by the advantageous characteristics of the method and mainly the higher spatial resolution, the quantitative assessments of data, and the more physiological features of radiolabeled glucose as a tracer [12]. However, PET is an expensive and not widely available method, while in many countries, healthcare systems do not approve [18F]FDG-PET imaging for dementia investigation. On the other hand, SPECT is a cheaper and worldwide available technique, and brain perfusion SPECT studies can be performed easily in daily clinical practice without any specific

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preparation. Additionally, the last decades, significant advances have been made in SPECT technology with the development of hybrid SPECT/CT systems, imaging reconstruction hard- and software, and quantitative analysis software. These innovations improved spatial resolution and quantification of SPECT, providing a voxel-by-voxel analysis of the whole brain with a reference in the stereotactic space and comparison with databases of normal subjects and led to more reliable assessments and better discrimination of AD [13, 14]. Moreover, the limited number of head-to-head studies comparing [18F]FDG-PET and perfusion SPECT has shown that the diagnostic accuracy is nearly equal [15, 16].

Another potential limitation of [18F]FDG-PET imaging in dementia, which may be relatively underlooked, is the application of the technique in diabetic patients with poorly controlled blood glucose levels. Glucose is transported into the brain by glucose transporters (GLUT 1–4) and mainly the GLUT1 and GLUT3 [17]. Different types of GLUT are expressed in different brain areas and neuron cells. High blood glucose levels compete with [18F]-FDG and reduce radiotracer's uptake in both normal and pathologic brain tissues [18]. Additionally, the increase of endogenous insulin levels in response to high blood glucose causes higher [18F]-FDG uptake in insulin-sensitive normal tissues, resulting in further decrease of brain [18F]-FDG uptake in normal, as well as in pathologic states. It has been supposed that chronic hyperglycemia down-regulates GLUT1 and GLUT3 expression in an effort to prevent cell damage from excessive glucose entering the cell [19]. As a result, hyperglycemia-induced decrease of 18F-FDG uptake in the brain may complicate the optimal detection of hypometabolic regions in dementia and overestimate the extent and/or the severity of hypometabolism. More interestingly, it has been reported that hyperglycemia-induced hypometabolism may result in patterns mimicking those seen in AD, possibly due to regional differences of Glut-1 or 3 receptor/hexokinase expression [20].

In conclusion, since both methods have different advantages and disadvantages, perfusion SPECT should not be disregarded from the diagnostic work-up of dementia, and the selection of the modality used should be based on its availability and the individual characteristics of the investigated demented subject.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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