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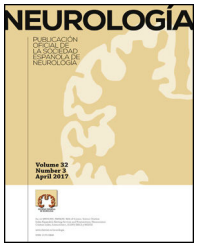

EDITORIAL

PET biomarkers: Use of imaging techniques in Alzheimer disease and neurodegeneration clinical diagnosis☆

Biomarcadores por tomografia por emisión de positrones (PET): imagen de la patología de Alzheimer y la neurodegeneración al servicio del diagnóstico clínico

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Professionals have new tools that complement and support clinical diagnosis of Alzheimer disease (AD) thanks to the introduction of positron emission tomography (PET) with fluorine-18-fluorodeoxyglucose (FDG), a biomarker for synaptic dysfunction, and the recent approval by the Spanish Agency for Medicines and Medical Devices (AEMPS) of commercial PET radiotracers which bind to cortical amyloid deposits.

There is now considerable cumulative experience with using PET-FDG to identify AD by differential diagnosis, and to estimate risk of progression from predementia stages to established AD. Additionally, available amyloid radioligands have been observed to bind to amyloid deposits with high specificity and sensitivity; also, the correlation between amyloid plaque density in histological studies and uptake in PET images is excellent. Although interobserver reliability for these images is high, regulatory agencies have issued requirements for specific nuclear medicine training programmes, considering the significance of how results are interpreted.

A variety of modern PET-CT equipment is currently available in Spain, which was the first country in Europe to market amyloid radiotracers with a reimbursement price. All this has provided further incentives for analysing the usefulness and promoting correct implementation of brain PET techniques, which has sparked collaborative efforts between the medical societies of those professionals involved in the diagnosis and treatment of dementing diseases. During the 65th Annual Meeting of the Spanish Society of Neurology (SEN), a scientific session organised jointly by the SEN study group for behavioural neurology and dementia and the

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neuroimaging study group of the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) was attended by more than 200 neurologists and experts in nuclear medicine. This session gave rise to a peer-to-peer working group that conducted a systematic review of clinical studies of PET-FDG and amyloid-PET with the aim of drafting clinical recommendations. The resulting consensus statement has been approved by the SEN Study Group for behavioural neurology and dementia, with scientific backing from SEMNIM, the Spanish Society of Geriatrics and Gerontology (SEGG), the Spanish Society of Psychiatry (SEP), and the Spanish Psychogeriatric Society (SEPG). This document has been published in the official journal of the SEMNIM.[1]

Similarly to the report by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging,[2] the SEN-SEMNIM consensus statement lists a series of recommendations for appropriate use of amyloid-PET. Additionally, it includes guidelines for using PET-FDG, given that both have demonstrated their usefulness as supplementary techniques for the diagnosis of AD through multimodal neuroimaging studies.[3]

In order for PET biomarker findings to have a significant impact on diagnosis, they should only be used in those patients with an adequately defined clinical and cognitive profile accompanied by a high degree of suspicion of AD without meeting criteria for dementia due to probable AD (NIA-AA criteria).[4] PET images are biomarkers of a pathophysiological process (amyloid deposition) or synaptic dysfunction (cortical hypometabolism). However, only the correct assessment of clinical and neuropsychological symptoms can link a nosological diagnosis to this finding. Therefore, PET studies should be requested whenever these images might support or rule out the clinically suspected aetiology and thus result in modifications to the therapeutic approach. Correct use of PET studies may help avoid costly, inadequately prescribed, and potentially harmful treatments on the one hand; on the other, it may eliminate diagnostic delays and shorten the experience, common to many patients and family members, of trying one specialist clinic after another. Timely and accurate diagnoses have important therapeutic consequences, in addition to their personal, family, and social impact.

Recommendations and consensus criteria on the use of amyloid PET studies and/or FDG are aimed at 2 clinical situations. First, these techniques are to be applied in cases of persistent or progressive cognitive impairment in the absence of criteria for dementia due to probable AD; here, confirming the presence of fibrillar amyloid deposits or hypometabolism with a characteristic pattern may result in a different therapeutic approach and affect the patient personally and socially. Second, PET studies should be considered in cases in which cognitive impairment has an atypical phenotype meeting criteria for possible AD (consensus criteria of the National Institute of Ageing-Alzheimer's Association [NIA-AA]),[4] or for atypical or mixed AD (criteria of the Second International Working Group [IWG-2]).[5] The cases referred to above fall into two different categories: those displaying early-onset cognitive impairment and those in which differential diagnosis is used to rule out other neurodegenerative entities progressing with dementia.

Several articles have shown that the information provided by brain PET studies may modify the initial clinical diagnosis, increase the degree of diagnostic certainty, or change the therapeutic approach. It may be too soon to establish whether incorporating PET studies into the diagnostic routine (under the conditions listed for appropriate use) will affect such other healthcare indicators as survival, quality of life, and degree of response to pharmacological treatment, or potentially modify progression of the disease. However, in the context of dementing diseases, establishing an accurate and timely diagnosis may not depend exclusively on the presence of a curative treatment or an effective means of modifying disease progression. As in many other diseases, a diagnosis of dementia will have implications on the personal, family, and social levels, in addition to any changes in drug treatment. We also believe that in order to develop a drug able to effectively modify AD progression, we will first have to learn how to diagnose the disease in earlier stages. In any case, using new diagnostic techniques appropriately in the clinical context of translational research will deliver that knowledge if we all promote systematic recording of information in well-structured shared-access databases. To this end, neurologists, nuclear medicine specialists, and biomarker researchers must collaborate closely.

Research has provided physicians with reliable, sensitive, and accessible diagnostic tools to complement clinical observations with data indicating presence or absence of the pathophysiological findings typical of AD, amyloidosis, or topographically compatible neurodegeneration. If patients are to benefit from these new methods, their doctors must face a twofold task: persuading healthcare authorities to approve use of these resources while ensuring appropriate and rational use of the same.

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