GUIDELINES FOR THE USE OF AMYLOID PET IN THE ASSESMENT OF COGNITIVE IMPAIRMENT

Catalan Society of Neurology and Catalan Society of Nuclear Medicine and Molecular Imaging
COGNITION AND BEHAVIOUR STUDY GROUP

Authors:

Dr. Alberto Lleó Bisa
Unitat de Memòria. Servei de Neurologia
Hospital de la Santa Creu i Sant Pau. Barcelona
CIBERNED (Centro de Investigación Biomédica en Red en enfermedades neurodegenerativas)

Dr. Albert Lladó Plarrumaní
Unitat d'Alzheimer i altres trastorns cognitius
Servei Neurologia. Institut Clínic de Neurociències
Hospital Clínic Barcelona

Dra. Valle Camacho
Servei de Medicina Nuclear
Hospital de la Santa Creu i Sant Pau. Barcelona

Dr. Francisco Lomeña
Servei de Medicina Nuclear
Centre de diagnòstic per la Imatge
Hospital Clínic de Barcelona

Dr. Carlos Lorenzo
Servei de Medicina Nuclear
Hospital Universitari Vall d'Hebron. Barcelona

February 2016

In the last recent years several PET tracers able to detect brain amyloid deposits have been developed. These tracers can be useful in the assessment of patients with cognitive disorders. The following amyloid PET tracers have been approved by the Ministry of Health: Amyvid® (^{18}F-Florbetapir, February 2014), Neuraceq® (^{18}F-Florbetaben, July 2014) and Vizamyl® (^{18}F-Flutemetamol, June 2015). Although there are no comparative studies between the different tracers, current published data suggest that all of them provide similar information.

The limited availability of these techniques and the associated costs make necessary the elaboration of guidelines to assist clinicians in their use.

The Alzheimer's Association together with the Society for Nuclear Medicine and Molecular Imaging recently published a document of appropriate use of amyloid PET (1,2). The Spanish Society of Neurology together with the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) published recommendations for the use of PET in patients with neurodegenerative disorders that cause dementia (3).

The structure and coverage of the health system in Catalonia differ in many aspects from the US and even from the Spanish health system. For this reason, this document aims at becoming a general and practical tool to summarize the current recommendations applied to the health system environment of Catalonia.

Preamble

When considering the use of amyloid PET it is important to consider the following aspects:

- A positive amyloid PET is not equal or sufficient to make a diagnosis of Alzheimer's disease (AD), since it cannot indicate whether the cognitive impairment of the patient is due to AD. For this reason, it is critical to characterize the clinical syndrome and to exclude other causes of cognitive impairment.
- Despite the fact that a number of studies have shown that amyloid PET can rule out AD pathology, the impact of the test on the clinical management and how the information affects the prognosis are not well established. However, the increase in the certainty in the diagnosis of a still incurable disease like AD may provide some benefits, such as a better therapeutic management in the early phases of the disease, a better prognostic delineation providing more accurate information to the patient and family which could allow better decisions and enhance autonomy about the future in phases in which the patient is still capable.
- Given the costs of the test and the implications of the results, it is recommended that an expert in cognitive and behavioural disorders orders the tests. An additional reason is that, as previously stated, the amyloid PET by itself is not sufficient to make a diagnosis of AD. In other words, the test can only detect the presence of β-amyloid deposits and is the combination of this result with a particular clinical syndrome that can aid the diagnosis increasing the certainty. The international recommendations (1,2) define a dementia expert as the physician with a specialized training in neurology, psychiatry or

geriatrics with clinical experience in the evaluation and management of patients with cognitive disorders.

- Amyloid PET should be performed in Nuclear Medicine centres and interpreted by a physician specialist in Nuclear Medicine with specific training in amyloid imaging. The reading should be performed in a standardised way according to the guidelines provided by the manufacturer of the tracer. The conclusion of the report should indicate whether the test is positive (presence of cortical amyloid plaques) or negative (absence of cortical amyloid plaques).
- These guidelines refer only to the clinical use of amyloid PET and not to the use in research.
- This document does not include other amyloid biomarkers, such as levels of Aβ42 in cerebrospinal fluid (CSF) that can be also useful in clinical practice in order to increase diagnostic certainty of AD. CSF biomarkers are the subject of an independent document elaborated by the Cognition and Behaviour Study Group from the Catalan Society of Neurology (4).
- The ^{18}F-fluorodeoxiglucose PET or the 99Tc-HMPAO - SPECT are considered markers of neurodegeneration and not markers of brain amyloidosis (5).

Evidence and specific recommendations:

The international document of appropriate use of amyloid PET (1,2) state that the utility of these techniques is limited to a reduced group of patients with cognitive impairment in whom there is suspicion of AD among other diagnostic possibilities and where the demonstration of presence or absence of amyloid deposits may change the clinical management.. This implies the need of a complete evaluation in order to show objective cognitive impairment and to rule out other causes that could explain the deficits.

Recommendation 1: Previous/initial evaluation

Before considering the request of an amyloid PET the clinical syndrome should be well characterized and other causes that could explain the symptoms should have been ruled out.

The correct characterization includes at least (see also CSN clinical guidelines for cognitive impairment) (6):

o Complete clinical evaluation
o Blood analyses to exclude treatable causes
o Cognitive evaluation to asses adequately the different cognitive domains
o Structural brain imaging studies (CT o MRI).

Recommendation 2: Early-onset dementia

The use of amyloid PET can be useful in the evaluation of subjects with cognitive impairment/dementia with early age of onset (onset of symptoms before 65 years). In general, the diagnosis in these cases has additional personal, familial, legal, work, and

social implications compared to cases with late-onset (onset of symptoms at or after 65). Amyloid PET can be useful to increase the certainly of AD or to exclude it in those cases in whom the uncertainly persists after the completion of the tests previously mentioned. It is recommended to limit the amyloid PET to those cases in whom the previous evaluation is not sufficient to make a diagnosis.

Recommendation 3: Mild cognitive impairment (MCI)

Amyloid PET can be also useful in the evaluation of patients with MCI, although their use should be limited to a reduced subgroup due to the high prevalence of this clinical entity. In order to define the group of patients with MCI who could benefit from this technique, the following aspects should be considered:

1) The presence of amyloid pathology in the brain is frequent in subjects older than 75 years and these deposits might not be related to symptoms.
2) The presence of amnestic MCI, with deficits in episodic memory defined with proper tests, represents often the prodromal phase of AD.. In this group of patients, different tests are often ordered to establish or to exclude whether the symptoms of the patient are the first manifestation of an underlying AD. These tests include brain MRI to demonstrate hippocampal atrophy, ^{18}F-FDG PET to detect temporoparietal hypometabolism or CSF biomarkers to measure levels of $A\beta_{42}$, tau and p-tau. Amyloid PET can be useful in patients with MCI, especially in cases where it is not possible to perform such tests, the tests are not informative or other causes coexists (vascular o brain trauma). In this last situation, a negative amyloid PET has been associated with a lower risk of progression to dementia.

In conclusion, the recommendation of the current guidelines is to restrict the use of amyloid PET to patients with amnestic MCI with less than 75 years in whom other tests could not exclude or confirm with enough certainty AD.

Recommendation 4: Atypical forms

The use of amyloid PET can increase the diagnostic certainty in some patients with primary progressive aphasia and posterior cortical atrophy in whom there is suspicion of AD and the remaining evaluation is not sufficient to make a diagnosis.

Recommendation 5: Non-appropriate use

The use of amyloid PET is not recommended in the following situations:

- Patients with typical AD
- To determine the stage of the disease
- Patients with subjective memory complaints or without objective cognitive deficit.
- Asymptomatic individuals (usually with family history of AD or concerned about having the disease).
- Non-medical indications (for example, work, legal or financial reasons).

Conclusions

Amyloid PET can have utility in the evaluation of subjects with cognitive impairment/dementia with early age of onset, cases with amnestic MCI with onset before 75 years in whom other tests could not exclude or confirm with sufficient certainly AD, and in the evaluation of some patients with atypical presentations of AD. Before considering the request of an amyloid PET the clinical syndrome should be well characterized and other causes that could explain the symptoms should have been ruled out.

References

1. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Hedrick S, Pappas V, Carrillo MC, Hartley DM; Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Update on appropriate use criteria for amyloid PET imaging: dementia experts, mild cognitive impairment, and education. Alzheimers Dement. 2013 Jul;9(4):e106-9.

2. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Carrillo MC, Hartley DM, Hedrick S, Pappas V, Thies WH; Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement. 2013 Jan;9(1):e-1-16.

3. Arbizu J, García-Ribas G, Carrió I, Garrastachu P, Martínez-Lage P, Molinuevo JL. Recommendations for the use of PET imaging biomarkers in the diagnosis of neurodegenerative conditions associated with dementia: SEMNIM and SEN consensus. Rev Esp Med Nucl Imagen Mol. 2015 Sep-Oct;34(5):303-313.

4. Balasa M, Piñol G, Molinuevo JL, Lleó A, Lladó A. Guies clíniques d'ús de biomarcadors d'Alzheimer en el líquid cefaloraquidi en l'avaluació de pacients amb deteriorament cognitiu, (2015) http://www.scn.cat/docs/grups_treball/

5. Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D, Bateman R, Cappa S, Crutch S, Engelborghs S, Frisoni GB, Fox NC, Galasko D, Habert MO, Jicha GA, Nordberg A, Pasquier F, Rabinovici G, Robert P, Rowe C, Salloway S, Sarazin M, Epelbaum S, de Souza LC, Vellas B, Visser PJ, Schneider L, Stern Y, Scheltens P, Cummings JL. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014 Jun;13(6):614-29.

6.Bello J., Piñol-Ripoll G., Lleó A., Lladó A. Guía diagnòstica i terapèutica de la Malaltia. d'Alzheimer. (2015). http://www.scn.cat/docs/grups_treball/2_Diagnostic_tractament_Alzheimer_2015.pdf