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General review

Molecular imaging in the diagnosis of Alzheimer's disease and related disorders☆

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ABSTRACT

Introduction. – The diagnosis of Alzheimer's disease (AD) and its related disorders rely on clinical criteria. There is, however, a large clinical overlap between the different neurodegenerative diseases affecting cognition and, frequently, there are diagnostic uncertainties with atypical clinical presentations. Current clinical practices can now regularly use positron emission tomography (PET) and single-photon emission computed tomography (SPECT) molecular imaging to help resolve such uncertainties. The Neurology Group of the French Society of Nuclear Medicine and Federations of Memory, Resources and Research Centers have collaborated to establish clinical guidelines to determine which molecular imaging techniques to use when seeking a differential diagnosis between AD and other neurodegenerative disorders affecting cognition.

State of knowledge. – According to the current medical literature, the potential usefulness of molecular imaging to address the typical clinical criteria in common forms of AD remains modest, as typical AD presentations rarely raise questions of differential diagnoses with other neurodegenerative disorders. However, molecular imaging could be of significant value in the diagnosis of atypical neurodegenerative disorders, including early onset, rapid

☆ Recommendations for clinical practice from a collaboration of the Federations of Memory, Resources and Research Centers [Centres de Mémoire, de Ressources et de Recherche (CMMR)] and Neurology Group of the French Society of Nuclear Medicine and Molecular Imaging [Groupe Neurologie de la Société Française de Médecine Nucléaire (SFMN)].

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cognitive decline, prominent non-amnestic presentations involving language, visuospatial, behavioral/executive and/or non-cognitive symptoms in AD, or prominent amnestic presentations in other non-AD dementias.

Conclusion and perspective. – The clinical use of molecular imaging should be recommended for assessing cognitive disturbances particularly in patients with early clinical onset (before age 65) and atypical presentations. However, diagnostic tools should always be part of the global clinical approach, as an isolated positive result cannot adequately establish a diagnosis of any neurodegenerative disorder.

1. Introduction

Magnetic resonance imaging (MRI), molecular positron emission tomography (PET) and single-photon emission computed tomography (SPECT) brain scans can confirm or reinforce the diagnosis of neurodegenerative diseases, and are often performed to establish a positive differential diagnosis, regardless of whether it is early- or late-stage disease. Functional disorders associated with neurodegenerative diseases most often precede brain atrophy [1]. Functional abnormalities may appear in cortical and/or subcortical structures before any cognitive and/or motor symptoms appear. Molecular PET and SPECT imaging is therefore a useful tool for the diagnosis of Alzheimer's disease (AD) and related disorders.

Depending on the type of radiotracer used, PET and SPECT imaging can provide information on distinct processes: (i) global synaptic activity, evaluated through neurovascular coupling by glucose metabolism consumption using PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and cerebral perfusion using SPECT with technetium-99m-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) or -ethyl cysteinate diethylester (^{99m}Tc-ECD); (ii) neurotransmission, by objectifying abnormalities of either dopaminergic or noradrenergic synapse for Parkinson syndromes, using ^{123}I-2β-carbometoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT; DaTscan™, GE Healthcare, Wauwatosa, WI, USA) with SPECT imaging for assessment of dopamine transporters and, therefore, the integrity of the presynaptic nigrostriatal pathway; cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is also a sensitive tool for detecting cardiac sympathetic denervation; and (iii) direct imaging of neuropathological lesions, using amyloid/tau PET imaging.

While some techniques such as amyloid imaging are promising, others already play an important role in the diagnostic approach of neurodegenerative disorders. Their use, however, should be properly established and integrated in the current diagnostic criteria together with other preexisting imaging and/or biological tools as part of a hierarchical diagnostic approach. With such an approach, evaluating the benefit/risk ratio, accessibility and cost of these investigations can be integral parts of good clinical practice recommendations (Haute Autorité de Santé [HAS; French National Healthcare Authority], 2011) [2].

The present report describes the current value of molecular imaging in diagnosing AD and related disorders, and its role with respect to other diagnostic modalities. To this end, our Working Group briefly reviewed each molecular imaging method to recommend its clinical use in the differential diagnosis of AD from other neurodegenerative disorders affecting cognition (related or associated disorders), such as: frontotemporal lobar degeneration (FTLD); primary tauopathies such as corticobasal degeneration/supranuclear palsy (CBD/SNP), particularly when the initial presentation is a non-motor type; Lewy body dementia (LBD); and mixed conditions (degenerative with a vascular component).

These differential diagnostic issues are of particular importance, given the near-future emergence of disease-modifying therapies for several neurodegenerative diseases, especially AD.

2. Brain metabolism and perfusion studies

Regional cerebral blood flow (rCBF) measurements using SPECT and the consumption of glucose using PET are two methods for assessing brain function. As global synaptic activity is based on glucose metabolism, ^{18}F-FDG, with a half-life of 110 min, is a good marker of such activity [3]. Under physiological conditions, changes in metabolism and rCBF seem to correlate, although the amplitude of rCBF variation is greater than that of glucose consumption and, thus, overestimates actual energy requirements [4].

PET–computed tomography (CT) cameras are 10 to 20 times more sensitive than SPECT at its highest resolution and have higher spatial resolution (3–5 mm for PET and 7–8 mm for SPECT) [5]. Also, as ^{18}F-FDG PET can detect damage to structures smaller than 5 mm, such as the hippocampus, and has a more favorable exposure dosimeter with a shorter half-life, its use is preferable to SPECT. The exceptions are patients with unbalanced diabetes and/or patients at centers with no access to brain PET imaging. While there are no studies directly comparing the performances of ^{18}F-FDG PET *vs* SPECT in diagnosing neurodegenerative diseases, recent meta-analyses evaluating the diagnostic accuracy of ^{18}FDG PET and SPECT in separating AD from healthy controls found better sensitivity with ^{18}F-FDG PET (86%) *vs* SPECT (76%), with each having the same specificity (86%). The prognostic accuracy of ^{18}F-FDG PET in predicting progression in mild cognitive impairment (MCI) also showed better specificity (74%) *vs* SPECT (64%), but comparable sensitivity with both methods (78% *vs* 76%, respectively) [6].

2.1. *In Alzheimer's disease*

In AD patients, alterations of brain metabolism are found at the temporoparietal junction, and in the posterior cingulate cortex and precuneus, and are often asymmetrical in early stages of the disease [7]. The progression to hypometabolism follows the