Diagnostic utility of positron emission tomography-computed tomography and indications for 18F-Fluorodeoxyglucose and amyloid-tracers

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Abstract

Positron emission tomography-computed tomography (PET-CT) is a nuclear medicine imaging technique widely used in oncology, cardiology and neurology where it is becoming of great interest especially because of its role in the diagnosis and differential diagnosis between several pathological conditions involving the nervous system. In neurodegenerative diseases, the most used PET-CT radiopharmaceuticals are 18F-Fluorodeoxyglucose (18F-FDG), a glucose analogue that is able to identify abnormalities of cerebral glucose metabolism, and amyloid-tracers (11C-PiB, 18F-Florbetapir, 18F-Flutemetamol, 18F-Florbetaben) that are able to detect presence of amyloid plaques. Depending on the specific characteristic of tracers and patient’s disease, the examination has dedicated appropriate indications that are illustrated in this article. PET-CT, with its several tracers, is an accurate tool in evaluating neurodegenerative diseases. 18F-FDG is considered a hallmark of the stage of the disease. Glucose hypometabolism in specific cerebral areas allows distinguishing different degenerative diseases. Amyloid tracers are considered the hallmark of the state of the disease. The uptake of PET-amyloid tracers reflects the cortical regional density of amyloid plaques.

Introduction

Positron emission tomography-computed tomography (PET-CT) is a nuclear technique of functional diagnostic imaging that finds its application especially in the oncological field, but it is also very employed in the neurological and cardiological fields and in cases of infections/inflammations. PET-CT employs several radiopharmaceuticals: 18F-Fluorodeoxyglucose (18F-FDG) (the most used one), 18F-Choline, 68Gallium- Peptides and many more, each one with their own specific indications depending on the metabolic/receptorial characteristics of the pathology that needs to be studied. All radiotracers are equal or similar to the main constituents of the organism and, for this reason: i) do not have any side effects or contraindications (except for ongoing pregnancy); ii) allow to obtain quantitative information on body consumption and use of a specific substance; iii) allow to gain earlier information compared to morphological imaging because functional alterations often precede morphological ones.

In the neurological field there is an always greater interest in the performance of cerebral exams through PET-CT with 18F-FDG and/or amyloid tracers to support the diagnosis of neurodegenerative disorders (which consist of loss of cognitive abilities such as memory, attention, speech, progressive and irreversible worsening of neuronal function), as well as with other radiopharmaceuticals such as 18F-DOPA, 11C-methionine, etc. in movement disorders and brain tumours.

Another nuclear medicine technique that can be used to evaluate neurological diseases is single positron emission tomography (SPET) imaging, but its power of resolution is only 8 mm vs 4 mm of PET-CT, its quantitative measurements are more complicated and some tracers are less physiologic (99mTc–hexamethylpropyleneamine oxime, etc.) compared to PET tracers. However, SPET remains helpful for the assessment of regional differences in cerebral blood flow and for the evaluation of brain metabolism especially in neurodegenerative disorders.

Materials and Methods

18F-Fluorodeoxyglucose-positron emission tomography-computed tomography

18F-FDG is a glucose analogue widely used for the evaluation of cerebral glucose metabolism. It is well known that glucose oxidation produces the necessary energy for an adequate cerebral activity and >95% of adenosine triphosphate molecules derive from glucidic catabolism. Global and regional consumption of glucose (cerebral metabolic rate of glucose, CMRglu, mL/min/100 g) is related to neuronal activity,7 and more specifically to metabolic variations at a synaptic connection level: they vary depending on the functional status of the patients (synaptic and cognitive integrity) and their age. The major peak of CMRglu (about 60 µmol/min/100 g in rest conditions) is reached at around 20 years of age; in a healthy geriatric population, grey matter’s CMRglu is about 40 µmoles/min/100 g (Figure 1). In a healthy geriatric population, global CMRglu inversely correlates with patients’ age, fac- ing a reduction of 12%-13% between 20 and >70 years old.3,5 CMRglu’s reduction in specific cerebral regions (especially fronto-basal and peri-silvian ones) correlates with cognitive age-related decline.6 CMRglu, as such, results as being a measurement of synaptic functionality density. In a healthy geriatric population, eventual loss of memory depends on frontal-cortex integrity and insufficient coding and recovery of episodic memory processes that involves the temporo-parietal lobes.7 In fact, studies have demonstrated that CMRglu experiences reduction in cerebral regions that are phylogenetically and ontogenetically younger.
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Amyloid deposits in different neurodegenerative disorders.

Pittsburgh compound B (11C-PIB), a neuroimaging (MRI) and PET (18F-FDG, used in clinical practice are: magnetic resonance imaging, amyloid imaging (11C-PIB, amyloid tracers). Nowadays, dosage of cerebro-spinal fluid proteins such as Aß40, Aß42, and tau-protein is the most employed biomarker in the research field.

Regarding 18F-FDG PET-CT, its diagnostic accuracy is very high (>85%) and it is particularly useful for differential diagnosis between dementia in AD patients, the scintigraphic pattern shows severe hypometabolism in temporo-parietal lobes, involving the frontal lobe in an advanced stage; in MCI, the scintigraphic pattern shows mild hypometabolism in temporo-parietal lobes; in fronto-temporal dementia, hypometabolism involves frontal and temporal lobes; in vascular dementia, the scintigraphic pattern is characterized by scattered areas of focal cortical and subcortical hypometabolism; in Lewy bodies dementia hypometabolism involves the occipital, temporal and parietal lobes. Figure 2 shows some scintigraphic patterns in different neurodegenerative disorders.

Amyloid tracers
The first approved tracer to study amyloid plaques’ deposits was 11C-labeled Pittsburgh compound B (11C-PIB), a tioflavine-analogue that specifically binds fibrillar deposits of beta-amyloid proteins with high affinity. Recent studies demonstrated that a regional uptake of this tracer reflects plaques’ density. A limit to its use is represented by its high quality, which rapidly decays. Since 2012, Food and Drug Administration and European Medicine Agency approved three more radiotracers for cerebral amyloid protein detection, all labelled with 3Fluorine, all lipophilic and all competing with the same binding sites on amyloid deposits: i) Florbetapir (Amyvid™); ii) Flutemetamol (Vizamyl™); iii) Florbetaben (Neuraceq™). Binding of one of these tracers to the plaques allows to count regional amyloid density and realize a quantitative analysis. In AD, amyloid deposits are considered the primum movens of the subsequent abnormalities, according to the cascade hypothesis: synaptic and neuronal degeneration, atrophy, neuronal symptoms. All AD patients have deposits of amyloid plaques in cortical brain regions: they show amyloid-tracer uptake in cortical brain regions. Figure 3 shows two representative cases of: i) healthy geriatric subjects with no amyloid-tracer uptake in grey-matter cortical regions; and ii) an AD patient with intense and diffuse amyloid-tracer uptake in all grey-matter cortical regions. Moreover, these tracers do not significantly bind tangles, Pick bodies, Lewy bodies and cytoplasmic glial inclusions, cells of the cerebral cortex of patients with fronto-temporal dementia, tauopathies or sinucleopathies. Amyloid PET-CT’s negative predictive value is very high, reaching 100% and consents to exclude AD diagnosis. It is positive predictive value, instead, appears variable because it is not still clear whether plaques represent a sign of AD/disease or if they are responsible for the clinical symptoms. Studies in literature demonstrated that around 40% of asymptomatic subjects that are amyloid-PET-positive, have higher probability to develop cognitive decline and to progress towards MCI or AD. These patients would be ideal to test new anti-amyloid therapies. Another 25% of asymptomatic patients, instead, do not show amyloid deposits but positivity to another biomarker of cognitive impairment, such as MRI or 18F-FDG. These patients are defined as suspected non-alzheimer pathology and this picture could be explained by other causes, such as vascular diseases, tauopathies, sinucleopathies, etc.

In healthy individuals with neuropsychological negative tests, positive functional imaging with amyloid tracers is predictive of a short-term progression. Therefore, in non-symptomatic patients, selected on behalf of their risk factors (strong familiarity and/or positive APOE), an amyloid PET-CT investigation could be useful for them to be enrolled in clinical trials testing new anti-amyloid drugs or drugs against progression of the disease (preventive role). This, provided that medical science will successfully further elucidate the link between the pathological cascade of AD/AD-related diseases and the appearance of clinical symptoms. The exact aetiology and pathogenesis of these cognitive disorders are still not clear. What is certainly known is that the pathological aspect comprehends amyloid plaques, (Aß40 proteins), neurofibrillary deposits (with hyperphosphorilate tau proteins), neurotransmission system alterations and loss of neurons. Up to now, amyloid-PET-CT would normally not be recommended in asymptomatic patients, even if with familiarity for cognitive impairment disorders but with negativity of APOE.

Indications and appropriateness of amyloid PET-CT scans have been published in 2015 by the Italian Interdisciplinary Working Group (AIMN, AIP, SINDEM), and request the contemporary presence of the following three conditions: i) the patient must have a cognitive impairment objectively confirmed through a battery of standardized neuropsychological examinations.
(validated on Italian people); ii) the cause of cognitive impairment must remain uncertain despite extensive clinical evaluation performed by an expert in dementia (working in a Cognitive Disorders and Dementia Center (CDCD)); iii) the demonstration of the presence or absence of cerebral amyloidosis could increase the diagnostic accuracy and change the patient’s clinical management. PET-CT should be recommended in following cases: i) subject with MCI who have an atypical or uncertain clinical onset without a diagnosis clear; ii) patients diagnosed with possible Alzheimer’s disease, defined according to the National Institute on Aging (NIA) - Alzheimer’s Association (AA) criteria when the definitive diagnosis is still uncertain despite the patient being subjected diagnostic procedures including morphological neuroimaging and possibly functional impairment; iii) person with cognitive decline or progressive dementia associated with onset at a young age (≤65 years), when the diagnosis of the experts is still uncertain; iv) Patients suffering from focal syndromes (e.g. progressive aphasia, agnosia and apraxia, cortico-basal syndrome) when the expert diagnosis is not clear with the purpose of excluding the Alzheimer’s disease.

Figure 2. Transversal slices of brain 18F-Fluorodeoxyglucose positron emission tomography-computed tomography in various neurodegenerative conditions: A) mild cognitive impairment; B) Alzheimer’s disease; C) fronto-temporal dementia; D) Lewy-bodies dementia.

Figure 3. Examples of amyloid positron emission tomography-computed tomography in a healthy geriatric subject (A) and in a patient with Alzheimer’s disease (B).
Results and Discussion

Despite those clear indications, some relevant issues often rise during daily routine in clinical practice.

Regarding the first needed condition for appropriateness, objective evaluations by clinicians are not always carried out using the same tests in every region of the country, and cut-offs and results are not always read in the same way. Regarding the second condition, for a correct identification of the cognitive impairment, an accurate clinical expert evaluation has to be supported by basic blood tests (associated to the specific neuropsychological pattern) and a first-level neuroimaging, the MRI. The MRI helps excluding non-degenerative causes such as expansive lesions, encephalitis, vascular malformations, etc. Unfortunately, in clinical practice patients usually undergo CT scans. When MRI (and/or CT) is performed, in a minority of patients it is positive for expansive lesions, encephalitis, vascular malformations, etc. while in most cases it is negative or undiagnostic. In these latter cases, amyloid PET-CT has its role allowing evaluating the presence/absence of amyloid plaques. Regarding the third condition, in case of high clinical-neuropsychological probability of AD, likelihood of amyloid PET-CT being positive is high and therefore of little utility for patients’ management. Instead, if patients’ symptoms are not expressive of the specific cause of the cognitive impairment and there is an atypical standardized neuropsychological battery, amyloid PET could be of substantial help in evaluating the presence/absence of amyloid plaques.

Conclusions

PET-CT is a technologically advanced diagnostic tool and it represents quite an innovation in the neurological field. 18F-FDG PET-CT has a very high diagnostic accuracy and is considered a marker of the stage of the disease. Amyloid-tracers are markers of the state of the disease because its uptake reflects deposition of amyloid plaques: when amyloid-PET/CT is negative, AD diagnosis can be certainly excluded. In fact, the indications for the use of amyloid-tracers clearly assert that they are indicated to exclude AD and not to confirm it. However, in patients with MCI or AD clearly defined on the basis of clinical-neuropsychological criteria, positivity of amyloid PET-CT could be considered as definitely diagnostic and as a brain biopsy.

References