BRAIN PET SCAN: STUDY PROTOCOL OF DEMENTIA

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KEYWORDS: Medicina Nucleare, PET cerebrale, demenza, malattia di Alzheimer, amiloide, Pet amiloide, protocollo di studio, florbetaben, Neuraceq,

ABSTRACT

In questo lavoro viene presentato lo studio Pet cerebrale con Neuraceq che ha come obiettivo l'individuazione delle placche di β amiloide. Questo risulta molto importante nello studio delle demenze e in particolar modo della malattia di Alzheimer in cui si ha l'accumulo delle placche ancor prima del sopravvento dei primi sintomi. Riuscire a dimostrare l'esistenza delle placche di β amiloide è fondamentale per effettuare un'accurata diagnosi e un'identificazione precoce del deterioramento cognitivo e funzionale.

INTRODUCTION

Positron Emission Tomography ("PET") is a method of nuclear medical expertise that is based on the highlighting by images (qualitative evaluation) and numerical parameters (quantitative evaluation) of the spatial temporal distribution of radioactive substances called tracers. These molecules are administered intravenously and are real drugs that have the ability to track, or mimic the behavior of the molecules of the body, giving information on the functioning of the organs.

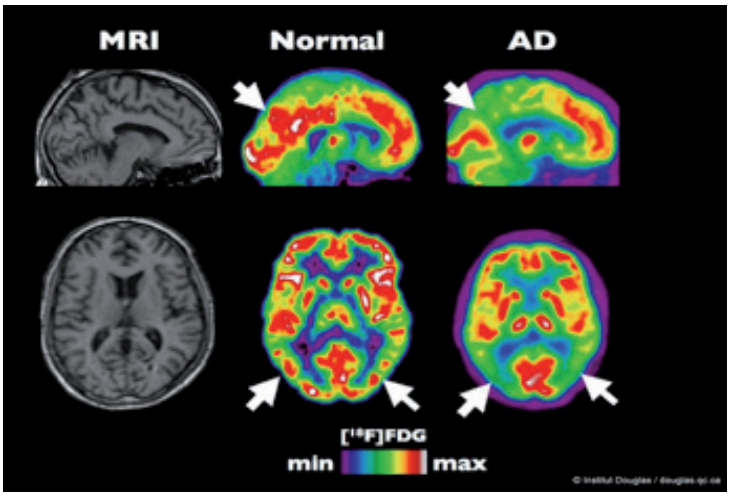
Thanks to PET we can measure real functional and biochemical parameters such as blood flow, metabolism (glucidic, lipidic and oxygen), protein synthesis, distribution and receptor density, distribution and activity of certain enzymes. The possibility to study in a non-invasive way in vivo the biochemical and biological processes that are the basis of the functions of organs and apparatuses has made this method of great interest both in the field of medical research and in the clinical field. The measurement of glucose metabolism with 18F-FDG was among the first to be used in the neurological field where information extractable from functional images consists in the detection of district variations in the distribution of the radiopharmaceutical in different brain structures. These studies were the first to measure the increase in synaptic activity induced by sensory processes such as vision, but it is above all in the study of dementias, epilepsy and tumors that the measurement of glucose metabolism has allowed us to provide information of pathophysiological and diagnostic interest.

In this paper we will discuss the protocols of study of cerebral PET regarding primary degenerative dementias, i.e. Alzheimer's disease, frontotemporal dementia (FTD) and Lewy's body disease (LBD), in particular we will present the PET studies with 18F-FDG and with the most recent NeuraCeq.

CEREBRAL PET IN THE STUDY OF DEMENTIA

Dementia can be defined as a cognitive deterioration, i.e. a decline, a loss, compared to the performance prior to the known or presumed onset of disease, global, i.e. involving all cognitive functions, and chronic, i.e. that it continues uninterrupted over time. The need for early diagnosis is particularly evident from the perspective of pharmacological treatment, which, however, still does not allow for substantial changes in the course of the disease.

Cerebral PET finds among the main clinical indications the diagnosis of dementia on a degenerative basis, especially AD or Alzheimer's disease which is the most widespread, followed by dementia with Lewy bodies and Fronto-Temporal dementia. In fact, PET-FDG can be used to assess glucose metabolism at the level of the brain that correlates with brain function and, more specifically, with synaptic activity and function. Consequently, the hypocaptation of a specific brain area can be indicative of an altered glucose metabolism and therefore of a neuronal loss. The PET image can be reconstructed on maps also three-dimensional able to show specific patterns of hypocaptation that correlate with the different forms of dementia. Since the functional alterations are earlier than the morphological ones, PET is able to show a brain malfunction already in early stages of disease. In Alzheimer's dementia it is considered a very useful method from a diagnostic and prognostic point of view, in fact already in 1981 Alavi and collaborators observed a reduction in the regional cerebral consumption of glucose in 20-30% of the affected patients compared to normal subjects of the same age. Further experience has shown that AD patients frequently present at PET with FDG a picture of biparietal hypometabolism that is considered almost typical of the condition and is present months before



Img. 1 Cerebral PET with 18F-FDG of a patient with Alzheimer's disease, it shows the reduction of metabolic activity mainly in the posterior temporal and parietal areas.

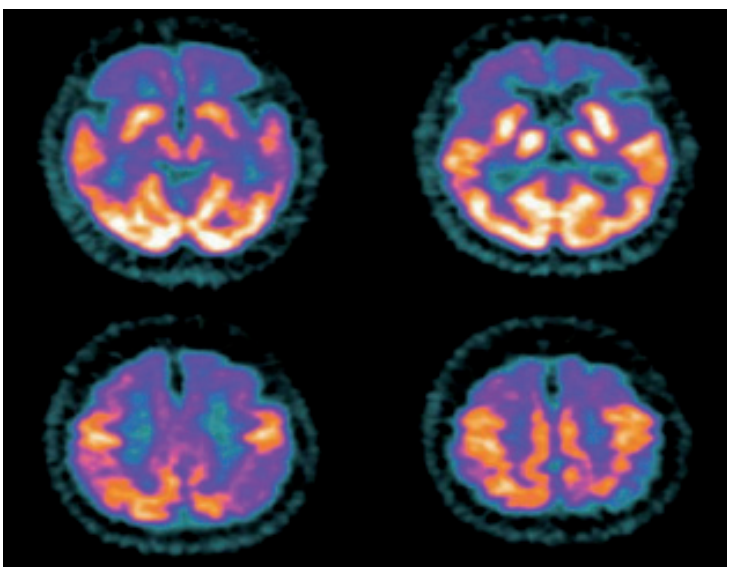
the clinical diagnosis. Progressively hypometabolism involves other associative brain regions, including frontal areas, while sensory-motor regions are the last to be affected. Through the study of glucose metabolism by PET-FDG, a hypocaptation of the radiopharmaceutical at the cortical temporal, parietal and posterior cingulate levels is observed (img.1).

In Fronto-Temporal dementia the pattern of hypometabolism is different because the regions first involved are the frontal ones (fig.2) while in dementia with Lewy bodies we have a pattern similar to AD with involvement of the occipital lobe. Therefore, through these differences one can already orient oneself towards a type of dementia and for this reason PET with FDG has been for years the basis of functional imaging in the study of dementias.

However, today it is possible, through specific tracers, to study the concentration of amyloid plaques at the level of the cerebral cortex. This is important because a correlation has been found between the onset of dementia, especially Alzheimer's dementia, and the accumulation of β-amyloid plaques. The β-amyloid is the product of catabolism of a protein, precursor of the amyloid (APP), by some proteases (β- and γ-secretase) that cause its accumulation at the level of neurons that progressively undergo degeneration. They are mainly distributed in the frontal cortex, posterior cingulate, temporo- lateral regions and in the parietal region. Amyloid plaques have also been found in patients with dementia with Lewy bodies and in healthy elderly subjects while they are not present in frontotemporal and secondary dementia. β-amyloid deposition is considered as a distinctive sign in the pathognesis of AD, and most likely begins years before the onset of detectable cognitive symptoms. Clinical tests using neuropsychology or memory tests are the standard tool to diagnose AD as clinically possible or probable but confirmation of the clinical diagnosis requires the identification of β-amyloid plaques which until recently was only possible after death by autopsy. Today, on the other hand, using the bases of immunohistochemistry for the histological study of amyloid pathology, starting from thioflavin capable of marking the amyloid, PET tracers have been developed to provide a mapping of the amyloid load in patients during their lifetime. The first tracer to be developed was the Pittsburgh Compound (PIB) which, being radiolabelled with carbon, decayed too quickly (20 min), making it unsuitable for routine use in most centres. For this reason, new fluorine-labeled tracers have been introduced on the market that guarantee use times within a few hours of production (img.3).

The first fluorinated radiopharmaceutical to be introduced was 18F-florbetapyr, followed by 18F-flutemetamol and the more recent 18F-florbetaben or NeuraCeq. All have a high binding affinity for the fibrillar amyloid, similar to that of [11C]PIB, and a high initial uptake in the brain followed by a tracer wash-out that did not bind in cortical areas without fibrillar amyloid.

PET imaging with florbetaben has proven to be useful not only for the clinical diagnosis of AD, but also for identifying patients with mild cognitive impairment (MCI) who will progress towards AD, resulting in a much more specific and reliable method.



Img. 2 Cerebral PET with 18F-FDG of a patient with fronto-temporal dementia. The reduction of metabolic activity is shown mainly in the frontal, insular, and anterior temporal areas.

NEURACEQ

The florbetaben (C21H26FNO3) is a derivative of the stilbene marked with fluorine-18. Its trade name is NeuraCeq. NeuraCeq is a radiopharmaceutical indicated for viewing by positron emission tomography (PET) of the density of β-amyloid neuritic plaques in the brains of adult patients with cognitive impairment who are evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. NeuraCeq should be used in conjunction with a clinical evaluation.

18F-florbetaben binds to neuritic β-amyloid plaques of the brain. In vitro, florbetaben shows an affinity for nanomolar binding to β-amyloid fibrils and brain homogenates with AD. In addition, the binding of

florbetaben to β-amyloid plaques in post-mortem sections of the brain with AD has been demonstrated by autoradiography and supported by results obtained by immunohistochemistry or Bielschowsky staining. The recommended activity for an adult is 300 MBq and the maximum dose should not exceed 360 MBq and should not be less than 240 MBq at the time of administration.

Neuraceq is not intended for use by children and adolescents under 18 years of age.

Most of the injected tracer is eliminated by hepatobiliary conjugation, followed by excretion in the gastrointestinal tract; the rest is eliminated by renal excretion. Since hepatobiliary excretion is the predominant clearance mechanism, the wall of the gallbladder is the radio-dosimetrically critical organ and attention must be paid to patients with liver and kidney problems.

Florbetaben is removed from the plasma of AD patients with an average biological half-life of about 1 hour. About 4 hours after the injection there is no longer measurable radioactivity in the blood.

Twelve hours after injection, up to about 30% of the injected radioactivity is excreted in the urine. Times beyond that interval do not allow further quantification of activity in the urine. Twelve hours after injection 98.93% of activity declined, 24 hours after injection 99.99% of activity declined.

This medication contains up to 1.5 mmol of sodium (i.e. 33 mg) per dose. This should be considered in patients on a low sodium diet.

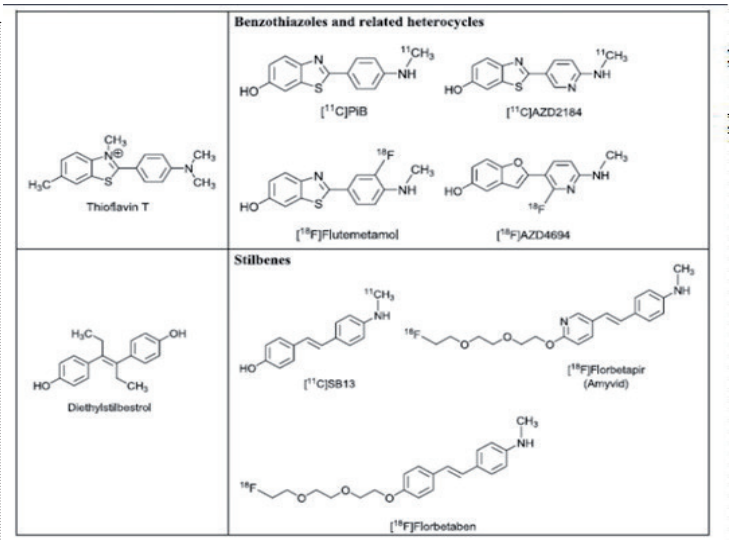
It also contains 15% by volume of ethanol (alcohol), i.e. up to 1.2 g per dose equivalent to 30 mL of beer or 12.5 mL of wine. This can be dangerous for those suffering from alcoholism, and should also be taken into account in pregnant or nursing women and in high-risk groups such as patients with liver disease or epilepsy.

CEREBRAL PET: STUDY PROTOCOL WITH FDG

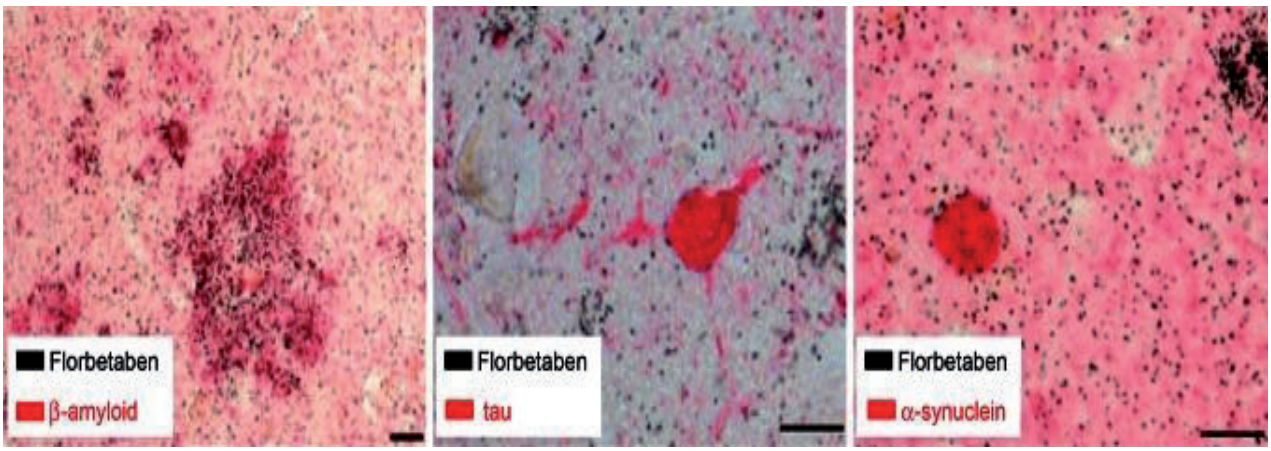
Before performing the examination, the patient must be prepared and instructed, first of all he must respect a fast of at least 6 hours, during this period sweetened drinks are not allowed and no glucose intake is allowed in the six hours before the examination. This is essential to decrease blood sugar levels because high levels can result in a reduction in the fixation of 18F-FDG by competitive inhibition between glucose and D-glucose. It is advisable for the health care professional to keep an accurate history of the patient's medical history, acquiring information on possible interventions, inflammations, pathologies, if he is a diabetic person, if he takes drugs such as antidepressants, benzodiazepines that can modify the values of glucose metabolism. After the anamnesis, the blood glucose is analyzed. In order to be optimal, it must be around 140 mg/dL, otherwise the patient cannot perform the examination.

Once it has been established that the patient is not taking contraindicated drugs and that blood sugar levels are optimal, the patient is placed in a room that is as quiet as possible and with soft light for the administration and accumulation of FDG. Here, the patient will be incanulated at least ten minutes before the injection of the radiopharmaceutical and will be asked to stay with their eyes closed, not to speak or read to maintain sensory rest. This is necessary to avoid over-activating areas of the brain and staggering the accumulation of the radiopharmaceutical.

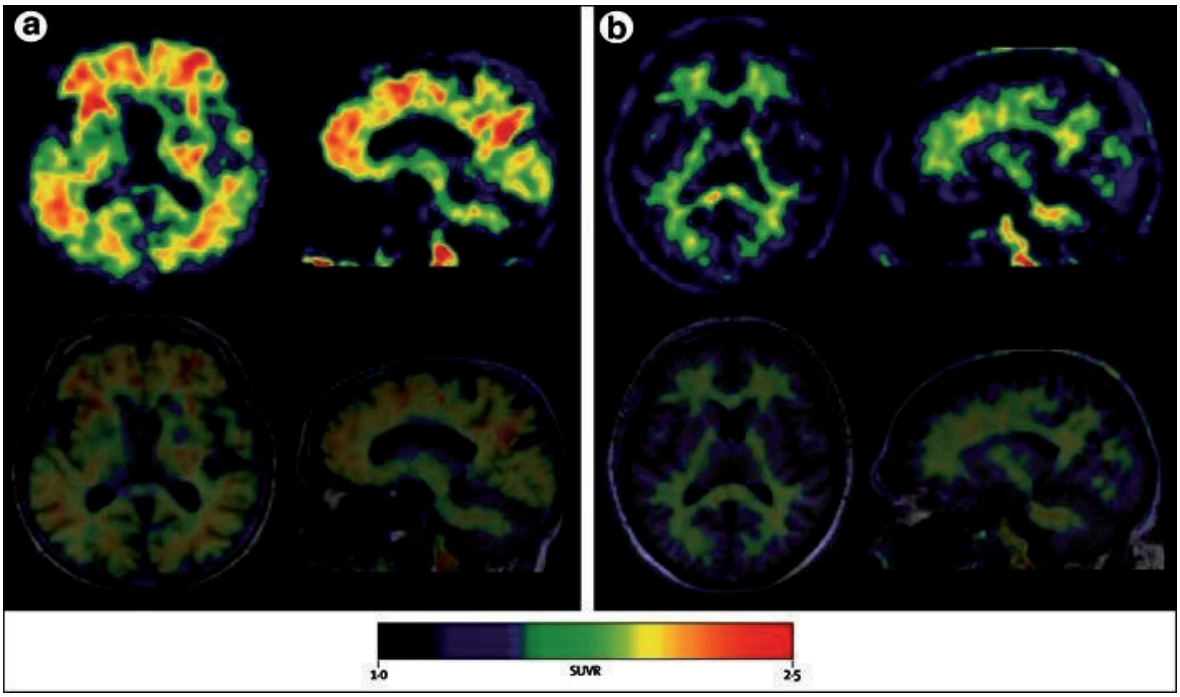
After 10 minutes, the injection of 18F-FDG will be



Img 3. F18 marked PET-amyloid tracers.



Img 4. Specificity of the bond with the florbetaben.



Img 5. PET with 18F-florbetaben. a) Alzheimer's patient; b) control of a healthy patient.

carried out, which must be done with the patient's eyes closed, relaxed and relaxed. The injected dose is about 4 MBq per kilo of body weight. After administration, the patient should maintain sensory rest for at least 45 minutes, which is the time required for sufficient cerebral metabolisation of the tracer.

When the patient is ready for the start of the image acquisition, he will be placed in the normal supine decubitus with the arms along the body on the bed of the PET/CT system with the head inserted in the appropriate headrest and gently immobilized by a band to promote immobility. Immobilization is necessary to reduce motion artifacts and in particular to avoid problems related to misalignment of CT and PET. Patient movement may lead to incorrect alignment of the attenuation correction map and make the images uninterpretable.

The gantry lasers will align the patient with the transverse, coronal and sagittal median planes (fig.6). The patient will be instructed not to move and to breathe regularly. At this point a scanogram will be carried out in the LL projection (side-to-side) and the packet will be set on it. We will start with a low-dose TC for attenuation correction (120 KV; 40 mAs).

The PET is acquired at the end of the CT with 3D mode, a single segment or bed (axial dimension of 15cm) is sufficient to include in the field of view the skull of the patient from the vertex to the base. The acquisition can be static where you acquire a 15-minute frame or dynamic where you acquire 3 frames of 5 minutes each. Dynamic mode is useful for reducing motion artifacts.

The PET scan is reconstructed on a 128x128 or 256x256 matrix using filtered rear projection or preferably an iterative algorithm with Gaussian low-pass filter. Both PET and TC data are back-built with a 25-30 cm FOV.

CERERBRAL PET: STUDY PROTOCOL WITH NEURACEQ

In this case, unlike PET with FDG, no special patient preparation is required, no fasting or established blood glucose values must be respected because this tracer binds to protein complexes and there is no problem of competition with glucose. However, as it is a blood-dependent drug, it is recommended to have a quiet environment before, during and after administration so that the patient is relaxed. In fact, in some cases, an uptake has also been identified in extracerebral structures such as the face, scalp and bones. The reason for this accumulation is not known but it could be due to the accumulation of 18F-florbetaben, or to the radioactivity of the blood.

The dose (200-350 MBq) is administered by slow intravenous bolus injection (6 sec/mL) followed by washing with approximately 10 mL of an injectable solution of sodium chloride 9 mg/mL (0.9%) to ensure complete dose delivery.

Patients with a cognitive disorder may have difficulty standing still during the acquisition of the PET scan. Therefore, it is not uncommon to observe movements in the images of PET scans for amyloid capture so in clinical practice a dynamic acquisition of 4 frames of 5 minutes allows you to exclude images that have motion. Image acquisition starts later (90 minutes) than with the FDG protocol because the longer the time for the tracer to distribute and bind to the amyloid.

CONCLUSION

The information extractable from functional images consists in the detection of district variations in the distribution of the radiopharmaceutical in different brain structures. The diagnostic criteria are not only represented by the extent of variation of this distri-

bution, but also by their location, specific to each disease. PET is the most widely used method in the study of dementia because it has, compared to other methods, a greater diagnostic accuracy.

More than 44 million people worldwide have been diagnosed with a type of dementia, with two thirds of this population probably suffering from a mild, moderate or even severe form of AD. This number is expected to double by 2030 and triple by 2050. Accurate diagnosis and early identification of cognitive and functional impairment due to AD and other aetiologies are essential for the optimization of patient care and the initiation of appropriate therapies. When used in combination with other clinical trials, florbetaben may help in the diagnosis of AD by detecting the presence or absence of β-amyloid plaques. This is particularly relevant in the prodromal phase of mild cognitive impairment AD (MCI) and in the dementia phase of this disease, where clinical trials lack precision to establish a reliable diagnosis of AD. In recent years, PET-amyloid has made great progress in diagnosing dementias, highlighting brain deposits of beta-amyloid once detectable only by autopsy studies. In addition, the possibility of having neuropathological data on large numbers compared to autopsy studies, has made it clearer how cerebral amyloidosis can be found, albeit in lower percentages, even in healthy elderly subjects and other forms of degenerative dementia.

Amyloid imaging is at the beginning of its clinical use and it is necessary that everyone, within the scope of their knowledge, from the physician to the technician to the physicist, gives their contribution to implement the method in all its aspects.

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