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PET amyloid imaging: state of the art and technical considerations

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ABSTRACT

INTRODUCTION

The development of PET radiopharmaceuticals suitable for the identification and in vivo quantification of β Amyloid plaques has been the focus of intense research, representing a useful means for the non-invasive detection of β Amyloid plaques in subjects affected by the Alzheimer's disease (AD). The purpose of this article is to provide a general overview of the application of PET radiopharmaceuticals currently available for in vivo imaging of β amyloid plaques. The aim is therefore to describe the chemical and synthetic characteristics of the main radiopharmaceuticals currently used in in vivo amyloid imaging and to provide a technical description of the acquisition protocols, always keeping the patient at the center of each step.

MATERIALS AND METHODS

Radiopharmaceuticals for PET imaging of amyloid β include two broad classes: planar hetero aromatic compounds and alkenes analogs. Among the former are 11C PiB and 18F Flutemetmol. While among the analogues of alkenes, the most used are the following two radiolabelled compounds: [18F] Florbetaben; [18F] AV-45, Florpyramine, [18F] Florbetapir.

A suitable and standardized protocol depending on the radiopharmaceutical used together with technical precautions and good communication with the client, contribute to the good quality of the service offered, both in terms of efficacy and safety of the treatments.

It is important to have a professional attitude aimed at active listening, to formulate short, precise sentences, composed of simple and clear words, to speak slowly and to give time to respond. The patient with demented syndrome needs a relaxed and non-judgmental environment.

Current PET / CT on the market are equipped with tools such as automatic exposure control and iterative algorithms, useful for reducing and optimizing the radiation exposure, the scan parameters may vary depending on the type of scanner. In clinical practice it is commonly used to use 120 KV and 60-100 mA, to obtain a suitable attenuation map and morphological localization. The PET scan is reconstructed using a 256 × 256 matrix using an iterative algorithm with a Gaussian low-pass filter. Both PET and CT data are constructed with a 25-30cm FOV.

CONCLUSIONS

The radiopharmaceuticals currently available must be known for their respective specifications by the technologist, in order to guarantee the correct acquisition and compliance with the exam timing. An adequate implementation of technical skills and soft communication skills makes an appropriate context for the delicate balance of AD patients, having the patients and their specific needs at the center of health care.

Keywords: Alzheimer's; β Amyloid plaques; 11C PiB; ^{18}F Flutemetamol; [^{18}F] Florbetaben; [^{18}F] AV-45, [^{18}F] Florbetapir; soft skills; enabling approach.

INTRODUCTION

Alzheimer's disease is the most common type of dementia, it occurs in subjects aged 65 or over, with a substantial cognitive decrease (1), such as to interfere in daily life by lowering the quality of life of the subjects concerned. This neurodegenerative disease causes progressive cognitive impairment by invalidating functions such as memory, understanding, language, attention, reasoning and judgment. 1Considered a typical senile disease, whose onset before the age of 65 is unusual and is observed in a small percentage of subjects, one of the first symptoms is the selective loss of short-term memory, to which is progressively added a worsening cognitive decline.

There are two main pathological signs contributing to the pathogenesis of AD which are the presence of extracellular amyloid plaques composed of amyloid-β (Aβ) and intracellular neurofibrillary tangles composed of hyper-phosphorylated tau. Despite extensive research on Aβ over the past two decades, Aβ-targeted therapies have not been very fruitful in treating AD as the efficacy of Aβ therapies observed in animal models is not reflected in human clinical studies. In light of the above, tau-directed therapies have received enormous attention as potential treatments for AD (2).

Tauopathies are closely related to dementia, immunotherapy has been shown to be effective in reducing tau pathology and improving cognitive deficits in animal models (3).

The development of PET radiopharmaceuticals suitable for the identification and in vivo quantification of β Amyloid plaques has been the focus of intense research efforts in recent years (4), representing a useful means for the non-invasive detection of β Amyloid plaques in subjects affected by Alzheimer's disease and can be used as an early diagnostic tool in individuals with no pathological signs of the disease.

The research field of PET radiopharmacology is tending towards innovative solutions not only in the diagnostic field, but also in the therapeutic field, in order to modify or reduce the quantity and extent of neuritic plaques in patients suffering from Alzheimer's disease.

The purpose of this work is to provide a general overview of the application of PET radiopharmaceuticals currently available for in vivo imaging of β amyloid plaques. The objective is therefore to illustrate the chemical and synthetic characteristics of the main radiopharmaceuticals currently used in in vivo amyloid imaging, finally providing a technical description of the acquisition protocols, always keeping the patient at the center of each step.

PET RADIOPHARMACEUTICALS FOR IN VIVO IMAGING OF AMYLOID β PLATES

General characteristics of PET radiopharmaceuticals for imaging amyloid β plates

The term radiopharmaceutical defines a radioactive preparation with particular chemical-physical-biological characteristics that comply with all the regulations of the Official Pharmacopoeia for administration to humans (5). Its diagnostic or therapeutic use must therefore be authorized

in advance, for each indication and method of administration, by the Health Authorities, like any other drug.

A radiopharmaceutical consists of a radionuclide, or a molecule linked to a radionuclide, appropriately chosen so that it concentrates in the organ under study or acts as a tracer of a particular biological function. The distribution in the body of each radiopharmaceutical depends on the chemical-physical constitution of the same, on the ability to cross biological barriers and be transported by the carriers and the patient's metabolic conditions.

The PET radiopharmaceuticals with broader clinical applications are those concerning diagnostics in the oncology, cardiology and neurology fields.

The general characteristics of an imaging agent intended for in vivo neurological applications are as follows (4):

(a) the compound's ability to quickly cross the brain's blood-brain barrier (BEE) in quantities suitable for non-invasive imaging;

(b) the selective and high affinity link with the target audience;

(c) rapid clearance from non-target brain regions.

In general, a compound suitable for neurological imaging must have a molecular weight of less than 600 (4), must be neutral and must have a lipophilicity between 1.0 and 3.5 log P in order to cross the BEE by passive diffusion (6). The target should have high initial brain absorption (> 4% dose/g 2 min from injection in mice), while normal brain tissue should have a rapid wash out (<1% dose/g 30 min after injection in mice) (7-8). The ideal drug radio should not be metabolized in the brain and must be resistant to peripheral metabolism in plasma. Radio-drug metabolites must be polar enough to prevent their accumulation in the brain (4).

A generic model has been proposed based on the interaction of a planar aromatic structure with negatively charged functional groups interacting with specific amino acid residues present in the β conformation of fibrillary amyloid aggregates (9). This generic model has been used to explain Congo red bond interaction to amyloid aggregates. The development of PET imaging agents for the identification of βA plaques in AD is mainly based on structural changes in dyes, such as Congo red and tioflavin-T, used for post-mortem histopathological staining of βA plaques and NFTs in brain tissue sections, as confirmation of AD diagnosis. The structural changes consist mainly of the elimination of charged species which represent a limit to the crossing of the BEE and modifications that allow increase of clearance from normal brain tissue and increase of the affinity of binding to the target, in particular to fibrillary plates of βA (4).

Amyloid β PET imaging radiopharmaceuticals comprise two large classes (4):

1) Hetero aromatic planar compounds (benzothiazoli, benzoxazole analogues and benzofurans);

2) Alkene analogues.

Aromatic straight analogues

^{11}C PiB

Tioflavin-T has been used as an imaging agent for βA plaques. [^{11}C] PiB is an analogue of theoflavin-T, able to cross the BEE and maintain or improve the ability of tyoflavin-T in the identification of βA plaques. [^{11}C] PiB is among the most widely used PET drug radios for the delineation of βA plaques in the brain. It is used in neuroimaging studies for early detection of AD and as a non-invasive imaging marker in experimental studies to evaluate the effectiveness of two potential AD therapies.

The initial radiochemical approach uses aniline derivative metossmethyl ether (MOM) (6-MOMOBTA-0) as a precursor. With the use of a strong base (KOH) in dimethylsulphoxide and the [^{11}C] CH^{3}I at high temperature, the desired intermediate molecule is obtained. The MOM protection group is removed in acid solution (MeOH / HCl) at 125 ° C for 5 minutes (Figure 1). The obtained [^{11}C] PiB is purified in the reverse semi-preparation phase with HPLC to produce a final product with average yields of 12.1%. Applying this synthesis method, radiochemical purity and chemical purity are > 95% and the average specific activity is about 85 GBq/mmol (Figure 2).

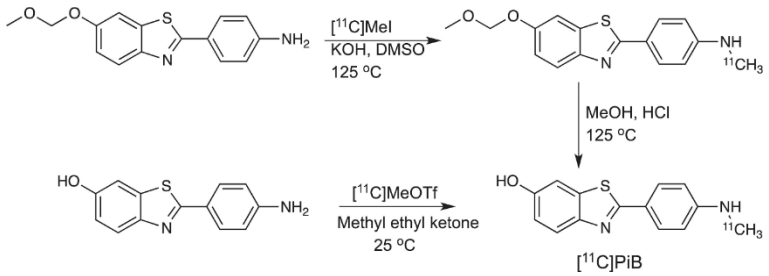

Fig.1– [^{11}C]PiB radiosynthesis (N. Scott Mason, Chester A. Mathis, and William E. Klunk. Positron emission tomography radioligands for in vivo imaging of Aβplaques 2013)

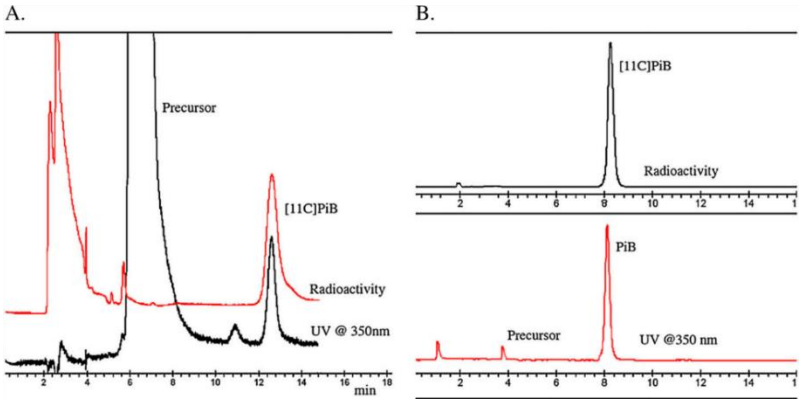

Fig.2 – A. Diagram of semi-preparative HPLC for radio synthesis of [11C] PiB. B. Corresponding diagram for HPLC analytical quality control. (N. Scott Mason, Chester A. Mathis, and William E. Klunk. Positron emission tomography radioligands for in vivo imaging of Aβplaques 2013)

The use of the most reactive synton, [^{11}C] methyl triflate, under neutral conditions with the free phenolic precursor, 2- (4-aminophenyl) benzo [d] tiazol-6-olo, provided a direct radiosynthesis approach in a single step for the production of [^{11}C] PiB (10).This approach has been used at the University of Pittsburgh in recent years for over 1000 productions of [^{11}C] PiB, has proven to be reliable and provides [^{11}C] PiB compliant with the requirements of the U.S. Pharmacopoea. This process of radio synthesis results in average yields of 19-28.5% for a total synthesis time of 40-45min (including quality control). Chemical and radiochemical purity must be more than 95% with specific activity of 120 ± 45 GBq/mmol (3.23 ± 1.31 Ci/mmol). Recently, a fully automated production process was built for the [^{11}C] PiB. The automated process produces [^{11}C] PiB with a yield of 1.6% (4).

^{11}CPiB radiolabeled with carbon tends to decay rapidly (20 min), making it unsuitable for routine use in most centers. For this reason, new fluorine-labeled tracers have been introduced on the market which guarantee longer stability for few hours post production (11).

^{18}F Flutemetamol

The use of ^{11}CPiB for imaging βA plates in vivo has led to intense research efforts with the aim of developing a similar label with F-18. A wide variety of structural analogues have been studied in vitro, in preclinical models, and later in humans. One of these compounds, 2- (3- [^{18}F] fluoro-4-(methylamino) phenyl) benzo [d] tyazole-6-olo ([^{18}F] 3'F-PIB or [^{18}F] GE067 or [^{18}F] Flutemetamol) has passed clinical trials and is currently on the market.

Radiosynthesis of [^{18}F] Flutemetamol occurs through the nucleophilic reaction. The precursor (N-methyl-N- [4- (6- ethyl-2-metoxy benzo [d] thyazolyl) -2-nitrophenyl] formammide) reacts with Kryptofix K222/potassium bicarbonate/K[18F]F in DMSO at high temperatures (Figure3).

Then acid hydrolysis occurs followed by HPLC purification in the reverse phase of [18F] Flutemetamol. Average yields of 15% with specific activity of more than 74 GBq/mmol (> 2.0 Ci/mmol) are obtained (12). Thanks to the use of an automatic synthesizer[^{18}F] Flutemetamol is obtained with a radiochemical yield of 15-25% (4).

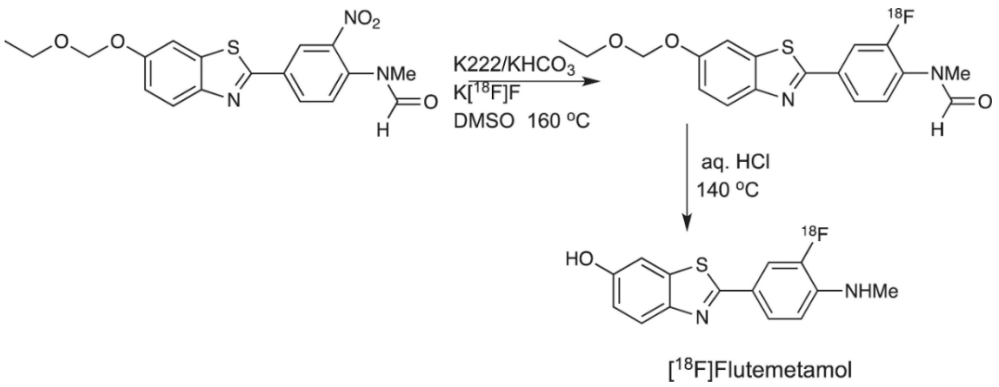

***Fig.3** – Radiosintesi del [^{18}F] Flutemetamol (N. Scott Mason, Chester A. Mathis, and William E. Klunk. Positron emission tomography radioligands for in vivo imaging of Aβplaques 2013)*

The distribution of the radiopharmaceutical takes place in single-dose bottle. The mean reference dose is 185 MBq. This dose varies according to the instrumentation and possibly the patient's weight (13) even if the pharmaceutical company does not recommend weight adjustments. The route of administration is intravenous. A cannula is used and the radiopharmaceutical is administered with a slow bolus (about 20 sec), then the administration of the radiopharmaceutical is followed by a flush of physiological solution. The drug is in an alcoholic solution and easily adheres to the plastic walls (13) so it is advisable to prepare the dose immediately before administration. Images are captured after 90 minutes (13) (reference data: 20 minutes for standard dose of 185 MBq) (13).

Aalkene analogues

Among the analogues of alkenes, the most used are the following two radiolabelled compounds:

- [^{18}F] Florbetaben;
- [^{18}F] AV-45, Florpiramina, [^{18}F] Florbetapir.

These two radiolabeled compounds are diaryl alkenes (stilbenes and styrylpyridines) engaged by a rigid and conjugated aromatic structural core (4).

^{18}F Florbetaben

^{18}F Florbetaben is a derivative of stilbene, a diariletene (14), a hydrocarbon composed of an etene replaced with a phenyl group on both carbon atoms of the double bond (12). Another derivative of stilbene is ^{18}F Florbetapir. The main difference with ^{18}F Florbetaben is the modification of the nucleus of stilbene present in ^{18}F Florbetaben with a molecule of styilpyridine. This structural change reduces the molecule's lipophilia and leads to faster brain kinetics than ^{18}F Florbetaben (15). As a result, PET image capture can be done 30 to 50 minutes after injection (13). Like all radiolabelled compounds used in the common clinical routine, it is also extremely important for 18F Florbetaben to establish reliable automated synthesis for clinical use.

The automated synthesis of 18F Florbetaben consists of a two-step reaction, consisting of the nucleophilic displacement of the metansulfonic acid group in the precursor, metansulfonic acid 2- {2- [2- (4- {2- [4- (terzbutoxycarbonyl-methyl-amino) phenyl] -vinyl} -phenoxy) -ethoxy] -ethoxy} -etilester (Boc-Stilbene-PEG-Ms), with 18F fluoride, followed by acid hydrolysis. Total synthesis takes 90 minutes. The radiochemical purity of the final product > 99%. 18F Florbetaben can also be produced through automated synthesis in a single phase, in which metansulfonic acid 2- [2- (2- {4- [2- (4-methyl-mino-phenyl) -vinyl] -phenoxy} -ethoxy) -ethoxy] ethoxy ethyl ethyl as a precursor is used. This process is characterized by a synthesis time of 50 min and a lower radiochemical purity (~95%). On February 24, 2014, has been announcedto the European Union the approval of ^{18}F Florbetaben for PET imaging of the density and extent of beta-amyloid neuritic plaques in humans' brains.

The radiopharmaceutical is distributed in single-dose bottles. The average reference dose is 300 MBq (Max 360 Min. 260), which can be varied according to the instrumentation and patient's weight, even if the pharmaceutical company does not recommend weight adjustments. It is administered intravenously, by slow bolus (about 20 sec.) using a cannula. Immediately after the administration of the radiopharmaceutical, a flush of physiological solution must be injected. The drug is in an alcoholic solution and easily adheres to the plastic walls so it is advisable to prepare the dose immediately before administration (14). The images are acquired 90 minutes after the injection of the radiopharmaceutical (reference data: 20 minutes for a standard dose of 300 MBq) (13).

^{18}F Florbetapir

The modification of the nucleus present in [^{18}F] Florbetaben with a residue of styridine pyridine provides the molecular nucleus of the [^{18}F] Florbetapir(17). This structural change reduces the lipophilicity of the molecule and leads to faster brain kinetics than [^{18}F] Florbetaben. The process of radiosynthesis reported by Choi, et al. it is very similar to the synthesis process used for [^{18}F] Florbetaben. The main difference is the use of the protected N-BOC toxin precursor. Radio synthesis is divided into two phases: nucleophilic displacement reaction with Kryptofix K222 and potassium carbonate in DMSO at high temperatures followed by hydrolysis mediated by aqueous hydrogen chloride (Figure 4).

After the synthesis reaction, semi-preparational purification is performed in reverse phase with HPLC. The [18F] Florbetapir obtained from the reaction has a radiochemical yield of 10-30%. The radiochemical purity of the final product is > 99% and the specific activity measured is 37-185 GBq / mmol (1-5 Ci / mmol). Recently, a radiosynthesis process for [18F] Florbetapir was introduced in GMP, based on automated multipurpose fluoridation using synthesis modules (F121R). The automated process provided radiochemical returns of 25.4 ± 7.7% over a total synthesis time of about 104 min. The radiochemical purity of the radiolabeled product is 95.3 ± 2.2% and the specific activity is 470 ± 135GBq/μmol. Using this GMP method in the formulation of the final product of [18F] Florbetapir there is the presence of a precursor of acetonitrile as chemical impurity.

The labeling indication states that [18F] Florbetapir is a radioactive diagnostic agent for PET imaging of the brain capable of estimating the neuritic plaque density of β-amyloid in adult patients with cognitive impairment who are being evaluated for AD or other causes of cognitive decline (18).

The radiopharmaceutical is distributed in a multi-dose bottle. The images are acquired 30-50 minutes after the injection of the radiopharmaceutical (reference data: 10 minutes for a standard dose of 370 MBq) (13).

The table below illustrates the main radiopharmaceutilcals for amyloid imaging and their characteristics (13).

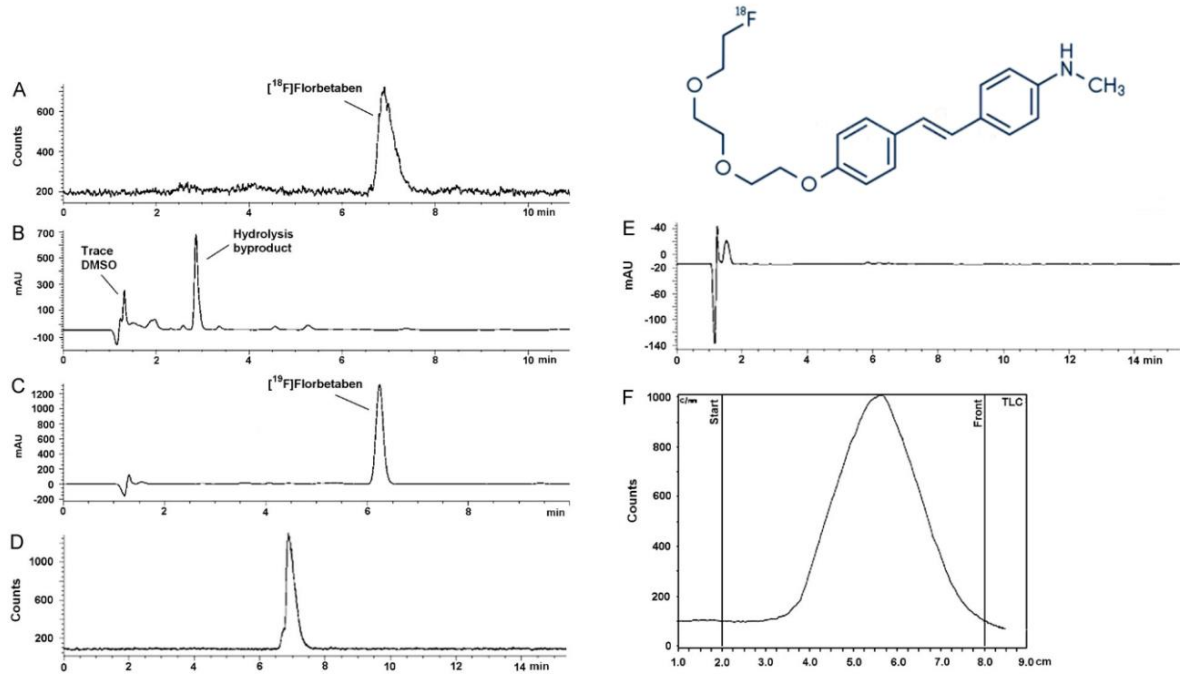

Fig. 4 Chemical formula of [^{18}F] Florbetaben, below left analytical HPLC chromatograms of [^{18}F] Florbetaben (Stilbene-PEG-OM as precursor) purified with Sep-Pak cartridges. (A) The radioactive chromatogram for [^{18}F] Florbetaben. (B) The UV chromatogram. (C) The UV chromatogram for [^{18}F] Florbetaben. Bottom right analytical HPLC and radio-TLC chromatograms of [^{18}F] Florbetaben (Stilbene-PEG-OM as precursor) purified with semi-preparative HPLC. (D) The radioactive chromatogram for [^{18}F] Florbetaben injection. (E) The UV chromatogram for [^{18}F] Florbetaben injection. (F) Theradio-TLC for [^{18}F] Florbetaben injection

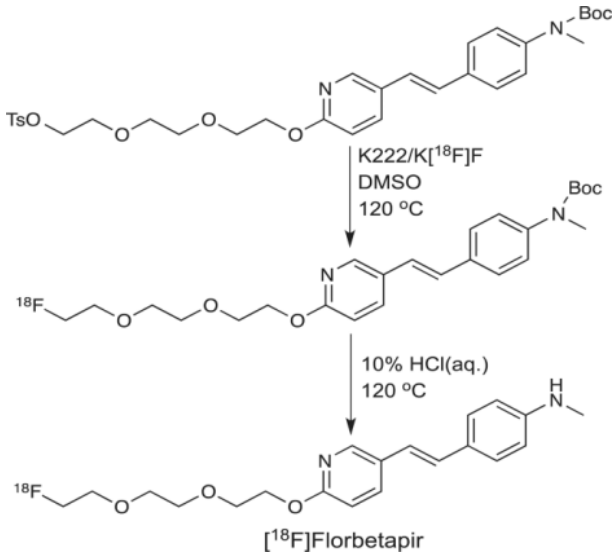

Fig. 5– *Radiosynthesis of [^{18}F] Florbetapir (N. Scott Mason, Chester A. Mathis, and William E. Klunk. Positron emission tomography radioligands for in vivo imaging of Aβplaques 2013)*

Acquisition data	Heteroaromaticanalogs		Analogues of alkenes	
TC 120 Kv 60-100 mA Scan time 10s				
PET				
FOV 30 cm Matrix 256x256 (pixel 1-2 mm) Iterative method OSEM (80 iterazions o subset) Gaussian filter FWHM 1-2 mm	**^{18}F Flutemetamol** **Image Acquisitioni:** 90 min from injection of radiopharmaceutical **Acquisition time:** 20 minutes for standard dose of 185 MBq.	**^{11}CPIB** Analogue of thioflavin-T	**^{18}F Florbetaben** derivative of stilbene **Image Acquisitioni:** 90 min from injection of radiopharmaceutical **Tempo acquisizione:** 20 minutes for a standard dose of 300 MBq.	**^{18}F Florbetapir** residue of styryl pyridine in the nucleus of [^{18}F] Florbetaben **Image Acquisitioni:** 30-50 minutes from the injection of the radiopharmaceutical **Tempo acquisizione:** 10 minutes for a standard dose of 370 MBq.

Tabella 1: main radiopharmaceuticals for amyloid imaging and their characteristics.

Methods of effective communication with the patient

The synergy of hybrid imaging makes it possible to obtain functional images thanks to the contribution of PET, while the morphological contribution is derived from CT images. The fusion of the two components allows not only to exploit the best aspects of both methods, but to obtain an attenuation correction quickly and with the lowest possible noise contribution, and also the accuracy, provided by the CT side, in the localization of certain pathological uptake detected by the other component (19).

The set of technical and clinical precautions, together with informed consent and good communication with the client, contribute to the good quality of the service offered, both in terms of efficacy and safety of the treatments (20). Considering that fasting or particular procedures are not required in the case of diabetic patients, no suspension of therapeutic plans of a pharmacological type, not even particular injection methods, such as low illumination in the case of investigations with fluorinated tracers (13), these represent advantages for patient preparation.

Good hydration during the preliminary phase of the investigation is necessary, in order to maintain a good standard of iconographic quality, this will be communicated to the patient during the medical history. This foresight will make it possible to achieve a good signal-to-noise ratio

(21), lowering the activity belonging to the bottom. The intake of liquids is also important for radioprotection purposes as the administered dose is disposed of electively via the urine.

After the useful time, which varies depending on the pharmacokinetics of the tracer used, the patient is welcomed by the medical radiology technician inside the PET-TC rooms.

In the literature it has been highlighted that communication plays a fundamental role in the patient with AD (22). It is important to have a professional attitude aimed at active listening, to formulate short, precise sentences, composed of simple and clear words, to speak slowly and to give time to respond. The patient with demented syndrome needs a relaxed and non-judgmental environment (22).

This specific approach is consistent with the enabling attitude (23), a communication strategy that undoubtedly facilitates assistance to the patient with AD, avoid contradicting even just to correct, avoid using the adverb "not", respect the expressive slowness, the silence and finally the pauses, allows to favor the communication compliance between the healthcare professional and the patient.

In order to facilitate the interaction with the patient, the healthcare professional can use a short list or written instructions as a reminder (if the reading has not already been compromised), this can help to maintain a state of calm and control of the patient. context on the part of the patient (23).

Even if for a limited period of time, thanks to the foregoing, a relationship of trust is created during the diagnostic service with the patient who thus becomes predisposed to greater collaboration, facilitating the effectiveness and efficiency of the technical-diagnostic process. Soft skills are fundamental skills on a par with technical ones (24), precisely in the case of the patient suffering from AD, good communication and optimal situational awareness are able to guarantee an adequate technical diagnostic performance both in terms of goodness of process plus safety and well-being of the patient. Elements such as rhythm, such as the cadence given by the distribution of accents in the conversation and the emphasis of emphasizing a word or part of a word to give it more importance, can also contribute to better patient care. affected by AD, as the capacitating attitude suggests (25).

To achieve physical and mental relaxation of the client, music can be used as a non-pharmacological tool (26), Gallego et al described an improvement in orientation, depression and anxiety, in mild and moderate cases of AD; this clarifies how well structured the environment can influence the patient's degree of collaboration.

Specifications of the technical acquisition process

Any type of removable metal object must be removed to avoid metal artifacts, as undesirable effects could lead to defects inherent in the attenuation correction map, but also in the dose administered to the patient (27).

Current PET / CT on the market are equipped with tools such as automatic exposure control (AEC) and iterative algorithms, useful for reducing and optimizing radiation exposure (28), sometimes guaranteeing a significant lowering of the patient dose.

It will be the responsibility of the healthcare staff to verify the removal of acoustic, dental, earrings or any object that may involve the introduction of metal artifacts.

Above the tomography table, absorbent paper crosspieces will be placed at the height of the patient's pelvis, in order to absorb urine that the patient may not be able to hold during the investigation.

While inviting the patient to go to the toilet before the exam, it is good practice to take into account that the demented syndromes in the advanced stages induce a progressive loss of self-control from a physiological point of view, if this event occurs on the PET tomography bed. CT could lead to major contamination issues (29).

Through a suitable communicative relationship, the patient receives the instructions relating to the positioning useful for the investigation, supine with the skull welcomed by the specific support.

The radiographer determines whether the communication strategy can be preferred to traditional restraint systems such as bands, in order not to alter the patient's emotional-psychological state and to encourage collaboration. Should the situation require it, in technical opinion, the synergy between the restraint devices and a communication calibrated on the subject can be exploited.

A position that is as functional as possible to the investigation time is useful for increasing the patient's collaboration and immobility. If necessary, it is recommended to use a support for the lower limbs in order to promote the comfort of the patient and to use a band to favor the position along the body of the upper limbs. Possibly also containment systems can contribute to maintaining the imposed position.

Once the correct positioning has been visually confirmed through the laser centering devices, we will begin the scout setting phase relating to the selection of the acquisition volume. A scout should be preferred both in an antero-posterior and a lateral-lateral view, in order to improve the accuracy of the positioning of the volume to be acquired.

The radiographer will take care to position the patient including the entire cranial structure in a single field of view, to obtain this orientation the skull will be tilted in a way that the canthus-meatal plane is perpendicular to the axis of the tomograph tunnel (z axis). The shims supplied with the tomograph can support the maintenance of the imposed position avoiding rotations and thus reducing possible movement artifacts (30).

The correct positioning of the skull also plays a fundamental role in order to reduce the number of interpolations during the reconstruction and multiplane analysis phase (31).

If for the execution of the investigation it is necessary to sedate the patient, to maintain immobility during the image acquisition phase, it is advisable to do this in the post-injection phase, just before the acquisition procedure on the PET bed (13).

After the injection of the radiopharmaceutical the radiographer proceeds with the acquisition of the PET starting from the following stages:

- the patient is positioned, using a containment pad, in the gantry.
- the canthus-meatal line is used to standardize the position of the head.
- the patient is informed of the need to avoid moving the head.

For hybrid PET / CT systems, CT is used for the correction for attenuation.

Scanning parameters may vary depending on the type of scanner. In clinical practice it is commonly used to use 120 Kv (11) and 60-100 mA, to obtain a good map for correcting the attenuation and morphological localization. Scanning parameters may vary depending on the type of scanner. Typically 140 kV, 60-100 mA are used for CT (13).

The AIMN Guidelines published in 2017 suggest the use of 140 Kv, in clinical practice it is commonly used to use 120 Kv (11), in order to reduce the patient dose and obtain a good attenuation correction map. The scan time is approximately 10 sec.

The PET scan is acquired at the end of the CT with 3D mode, a single segment or table (axial dimension of 15 cm) is sufficient to include the patient's skull from the vertex to the base in the visual field. The acquisition can be static or dynamic: in the first mode a frame of 15 minutes is acquired, in the second mode 3 frames of 5 minutes each are acquired. Dynamic mode is useful for detecting motion artifacts (11).

The PET scan is reconstructed on a 128 × 128 or 256 × 256 matrix using an iterative algorithm with a Gaussian low-pass filter. Both PET and CT data are constructed with a 25-30cm FOV (11).

An example of PET acquisition with a radiopharmaceutical for amyloid imaging is shown in Figure 6.

Conclusions

The radiopharmaceuticals currently available must be known for their respective specifications by the radiographer, in order to guarantee their correct acquisition and compliance with the timing.

An adequate implementation of technical skills and soft communication skills creates an appropriate context for the delicate balance of patients with AD, having the patients and their specific needs at the center of the procedure.

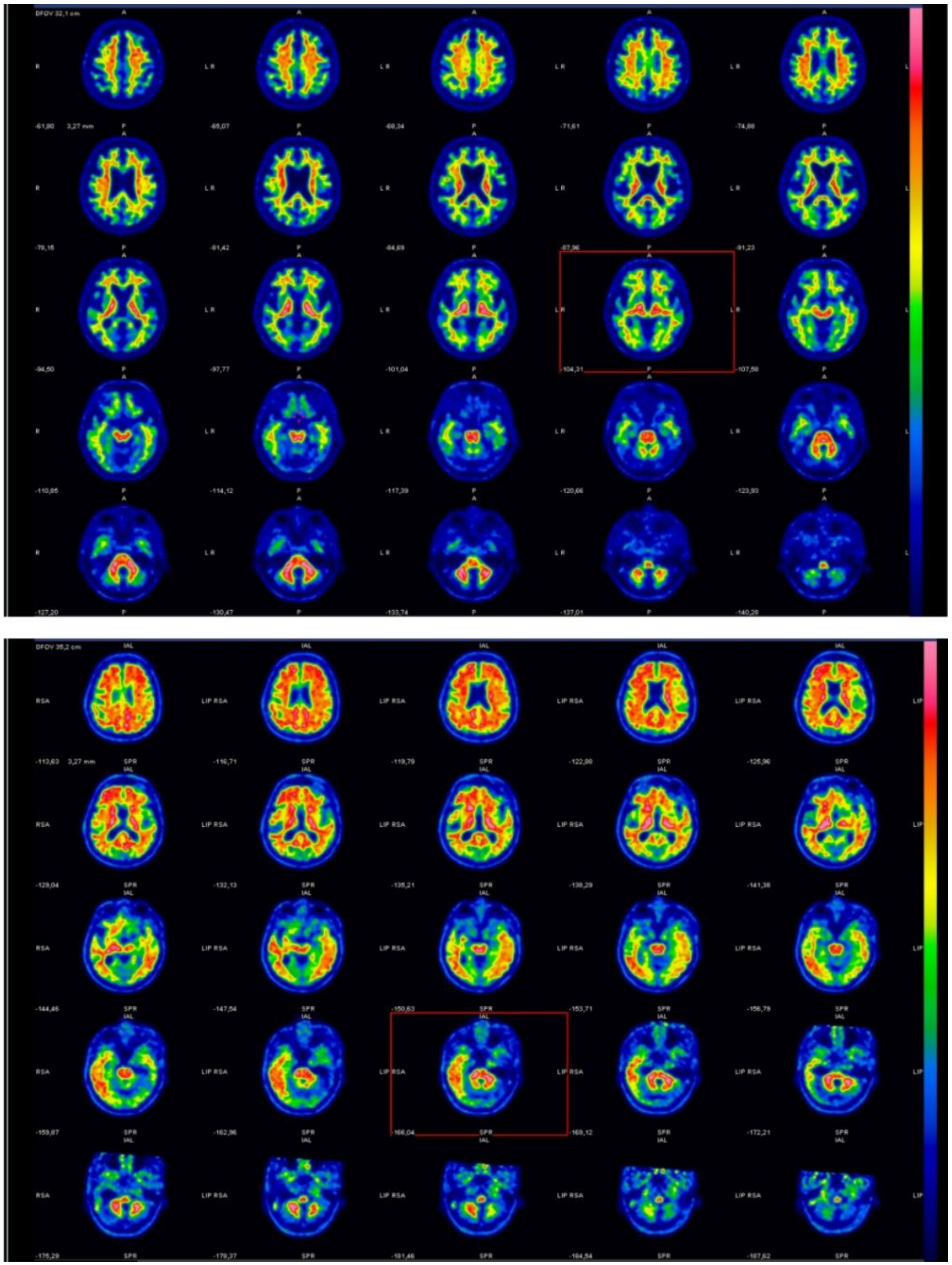

Fig. 6 - PET acquisition with a radiopharmaceutical for amyloid imaging: above, a negative case, below a positive case (Nuclear Medicine and Molecular Imaging Dpt ASST Spedali Civili di Brescia)

REFERENCES

[1] Anil K., Jaskirat S., Amandeep G., Jack W. T. Alzheimer Disease. Treasure Island (FL): StatPearls Publishing; 2022 Jan

[2] Ashford JW, Salehi A, Furst A, Bayley P, Frisoni GB, Jack CR, Jr., et al. *Imaging the Alzheimer brain*. J Alzheimers Dis 3: 1-27. (2011)

[3] Fong P. C., Khuen Y. N., RhunY.K. ,Soi M. C. Tau Proteins and Tauopathies in Alzheimer's Disease. Cellular and molecularneurobiology. 2018 Jul; 38(5):965-980

[4] N. Scott Mason, Chester A. Mathis, and William E. Klunk. Positron emission tomography radioligands for *in vivo* imaging of Aβplaques . (2013)

[5] Fondamenti di medicina nucleare. Tecniche e applicazioni. D. Volterrani, P. A. Erba, G. Mariani. (2010)

[6] Braak H, Braak E. *Frequency of stages of Alzheimer-related lesions in different age categories*. NeurobiolAging 18(4): 351-7.(1997)

[7] Riassunto delle raccomandazioni del Gruppo di Lavoro Intersocietario Italiano per l'Utilizzo dell'Imaging di Amiloide nella Pratica Cinica. A cura del GdS di Neurologia dell'AIMN. *Libera traduzione di Ambra Buschiazzo e Silvia Morbelli dall'originale Guerra UP, Nobili FM, Padovani A, Perani D, Pupi A, Sorbi S, Trabucchi M. Recommendations from the ItalianInterdisciplinary Working Group (AIMN, AIP, SINDEM) for the utilizationofa-myloidimaging in clinical practice. Neurol Sci. 2015 Jan 24. [Epub ahead of print]; PMID:25616445)

[8] Wang H, Guo X, Jiang S, Tang G. *Automated synthesis of [^{18}F] Florbetaben as Alzheimer's disease imaging agent based on a synthesis module system*. ApplRadiatIsot 71(1): 41-6. (2013)

[9] Hiltunen M, van Groen T, Jolkkonen J. Functional *roles of amyloid-beta protein precursor and amyloid-beta peptides: evidence from experimental studies*. J Alzheimers Dis 18(2): 401-12. (2009)

[10] Buccino P., Savio E., Williams P.Fully -automated radiosynthesis of the amyloid tracer [11C] PiB via direct [11C]CO2 fixation-reduction. EJNMMI Radiopharmacy and Chemistry volume 4, Article number: 14 (2019)

[11] Brain PET Scan: study protocol of dementia De Rosa Salvatore, Beneduce Carmela, Cuocolo Alberto, Gallo Giada. (2020)

[12] Lide D. CRC Handbook of Chemistry and Physics. 76th edition ed. USA: CRC Press, Inc. (1995)

[13] https://www.aimn.it/documenti/lineeguida/16_RP_AIMN_neuro.pdf consultato il 18/03/2022

[14] Patt M, Schildan A, Barthel H, Becker G, Schultze-Mosgau MH, Rohde B, et al. *Metabolite analysis of [18F]Florbetaben (BAY 94-9172) in human subjects: a substudy within a proof of mechanism clinical trial*. J Radioanal-NuclChem 284: 557–62. (2010)

[15] Mason NS, Mathis CA, Klunk WE. *Positron emission tomography radioligands for in vivo imaging of Abeta plaques*. Journal of labelled compounds & radiopharmaceuticals 56(3-4): 89-95. (2013)

[16] Zhang W, Oya S, Kung MP, Hou C, Maier DL, Kung HF. *F-18 Polyethyleneglycol stilbenes as PET imaging agents targeting Abeta aggregates in the brain*. Nucl Med Biol 32(8): 799-809. (2005)

[17] http://www.piramal.com/imaging/pdf/Final-U-Approval-pr.pdf. (2014) consultato il 18/03/2022

[18] Radiotracers for Amyloid Imaging in Neurodegenerative Disease: State-of-the-Art and Novel Concepts Angelina Cistaro, Pierpaolo Alongi, Federico Caobelli and Laura Cassalia Current Medicinal Chemistry, 2018, 25, 3131-3140

[19] N. Belcari, A. Del Guerra, Il tomografo PET e PET/TC. In: Volterrani D, Erba P. A., Mariani G. a cura di. Fondamenti di medicina nucleare, Springer; 2010. p. 274-275

[20] https://www.nurse24.it/specializzazioni/management-universita-area-forense/migliorare-qualita-comunicazione-sanita.html consultato il 18/03/2022

[21] Ceriani L., Suriano S., RubertoT., Giovanella L.Could Different Hydration Protocols Affect the Quality of 18F-FDG PET/CT Images. Journal of Nuclear Medicine Technology. June 2011, 39 (2) 77-82

[22] Pragmatica della comunicazione umana. Studio dei modelli interattivi, delle patologie e dei paradossi. Paul Watzlawick (Autore), J. H. Beavin (Autore), D. D. Jackson (Autore), M. Ferretti (Traduttore). Casa Edittrice Astrolabio 1978

[23] Vigorelli P. Alzheimer, Come favorire la comunicazione nella vita quotidiana. Milano: Edizioni Franco Angeli; 2015

[24] Flin R., O'Connor P., Crichton M., Safety at the Sharp End - A guide to Non-Technical Skills. Burlington (USA): Ashgate Publishing Company; 2008

[25] Vigorelli P. (2007): Dalla Riabilitazione alla Capacitazione: un cambiamento di obiettivo e di metodo nella cura dell'anziano con deficit cognitivi. Geriatria, 4, 31-37.)

[26] Garcia-CasaresN., Moreno-Leiva M.R., Garcia-Arnes A. J. Music therapyas a non-pharmacological treatment in Alzheimer'sdisease. A systematic review. Rev Neurol. 2017 Dec 16;65(12):529-538.

[27] Sureshbabu W., Mawlawi O. PET/CT imaging artifacts. J NuclMedTechnol. 2005 Sep;33(3):156-61

[28] Gould S.M., Mackewn J., Chicklore S, Cook J.R.G., Mallia A., Pike L. Optimisation of CT protocols in PET-CT across different scanner models using different automatic exposure control methods and iterative reconstruction algorithms. EJNMMI Phys. 2021 Jul 31;8(1):58.

[29] A Burger I., A ScheinerD., W Crook D, Treyer V., F Hany T.,K von Schulthess G. FDG uptake in vaginal tamponsis caused by urinary contamination and related to tampon position. Eur J Nucl Med Mol Imaging. 2011 Jan;38(1):90-6.)

[30] Camoni L, PesteanC, Testanera G, Costa PF. Basics for nuclear medicine image reconstruction, Reference Module in Biomedical Sciences, Elsevier, 2022, ISBN 9780128012383

[31] Cooke, C.D., Faber, T.L., Galt, J.R., 2011. Fundamentals of image processing in nuclear medicine. In: Khalil, M.M. (Ed.), Basic Sciences of NuclearMedicine. Springer Berlin Heidelberg, Berlin,Heidelberg, pp. 217–257.