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Use of radiopharmaceuticals in the diagnosis of neurodegenerative diseases

Anna Tempesta [a,b], Anna Tolomeo [a], Azzurra Stefanucci [b,*], Lorenza Marinaccio [b], Adriano Mollica [b]

[a] ITEL Telecomunicazioni S.r.l - Radiopharmaceutical Division, Italy
[b] Department of Pharmacy, Università degli Studi "G. d'Annunzio" Chieti, Pescara, Italy

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ABSTRACT

Neurodegenerative diseases are illnesses that affect the central nervous system (CNS) characterized by a series of symptoms such as dementia, motor disturbances, behavioural and psychological disorders, and cognitive impairments. The most common neurodegenerative disorders are Alzheimer's disease and Parkinson's disease, for which radiopharmaceuticals have been developed and approved for the purpose of PET investigation. Biomarkers are molecules that can be studied and used for diagnostic purposes, to monitor diseases, and to identify potential risk factors early.

1. Alzheimer's disease: an overview

Alzheimer's disease (AD) is one of the most common form of dementia worldwide [1]. It is the only one of the top 10 causes of dementia that continues to see a significant increase. The cause of the AD remains under investigation and is not yet fully understood. Unfortunately, symptoms are often not diagnosed early and can be mistakenly attributed to other conditions or even ignored, with damaging consequences for the patient. Some of the first symptoms appear years before a proper diagnosis of dementia is made. Early diagnosis is crucial in order to address these diseases [2–4].

So, understanding the pathophysiology of Alzheimer's is important to deal with this disease. It is characterized by two main alterations in the brain: amyloid plaques and neurofibrillary tangles. Amyloid plaques are accumulations of a protein called beta amyloid. These plaques are formed extracellularly and are found in the brain, hippocampus, girdle gyrus and associative cortices of the frontal and temporo-parietal regions. Specifically, amyloid plaques are characterized by a central part in which amyloid protein accumulates and a peripheral part in which neuronal debris accumulates.

The B-amyloid peptide is the main component of amyloid plaques, which generates the Amyloid Precursor Protein (APP) (Fig. 1). This membrane protein is encoded by a gene on chromosome 21 and normally promotes cell growth. Usually, APP produces a harmless cleavage product, called P3, which is derived from the cleavage of two proteases. However, if the B-secretase protein intervenes inappropriately during the cleavage process, which promotes cleavage at the level of the N-terminal extracellular domain, it produces an amyloidogenic fragment. Beta amyloid monomers can aggregate into various types of groups, including oligomers, protofibrils and amyloid fibrils. Amyloid fibrils are large and insoluble and can assemble into amyloid plaques, while amyloid oligomers are so soluble that they can spread throughout the brain [5–7].

Neurofibrillary tangles are formed primarily by the hyper phosphorylated tau protein that normally plays the role of stabilizing microtubules [2]. Due to the formation and accumulation of amyloid plaques and neurofibrillary tangles, a series of processes occur, such as neuronal damage and therefore alteration of nerve cell function, activation of the immune system and changes at the vascular level. In addition, synaptic receptors, which are essential for neuronal communication, are also damaged, and there is a reduction in the production of neurotransmitters by reducing the transmission of signals [4]. Early Alzheimer's disease can manifest as a preclinical stage in which the patient's ability shows a slight decrease, or as mild cognitive impairment (MCI). MCI represents an intermediate state between normal cognition and dementia. Follow-up studies have shown that even after 10 years, not all MCI patients have progressed to AD. Some patients may maintain their stable condition or even return to normal cognitive condition. In order to be treated early and to promote an increase in life expectancy, it is essential to identify patients with MCI [8].

* Corresponding author.
E-mail addresses: a.tempesta@itelte.it (A. Tempesta), a.stefanucci@unich.it (A. Stefanucci).

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1.1. Diagnosis and treatment of Alzheimer's disease

For the treatment of Alzheimer's disease, most studies are focused on the deposition of beta-amyloid plaques, which induce the formation of toxic substances, for which the level is to be reduced. In fact, many studies have shown that the reduction of beta-amyloid plaque linked to the use of drugs, promotes a slow decline in cognitive and functional measures. This research is then followed by the study of the abnormal and hyperphosphorylated form of the tau protein (p-tau). Both are pathogenic factors of the disease, resulting in extensive neuronal damage and synaptic dysfunction.

There are several drugs that have passed the different stages of clinical trials, but, despite this, current therapies (*e.g.* rivastigmine and donazepil) appear to be of secondary importance. First of all, there could be other pathological pathways, such as neuroinflammation, that could promote the disease. In addition, many drugs developed have chemical-physical problems, for which they are unable to cross the blood-brain barrier and consequently have a completely reduced bioavailability. These drugs may also be unstable and toxic to tissues [9,10].

Considering the above, nuclear doctors are encouraged to detect Alzheimer's early, to greatly improve life expectancy and therefore patient management. In fact, early identification could reduce the costs that characterize patients with this disease [11].

Early diagnosis is important, as one study reports that identifying and treating patients with AD at an early stage could reduce costs and promote increased patient health benefits. Currently, beta-amyloid peptide is believed to be an important component of the disease process, and amyloid plaques are considered a hallmark of AD. In fact, amyloid plaques have become a key part of neuropathological diagnostic criteria through current imaging techniques that use radiolabelled tracers that bind to the amyloid peptides in the plaques, allowing clinicians to directly measure the pathology through diagnostic imaging.

The most widely used techniques to identify disease features include magnetic resonance imaging (MRI), single photon emission tomography (SPECT), and positron emission tomography (PET). PET uses radionuclides that emit positrons, which interact with the electrons present within the brain tissue, producing photons, signals that can be identified by suitable detection systems and which then produce tomographic images [12].

PET has been a game-changer in identifying amyloid deposits in picomolar concentrations for Alzheimer's patients. As a result, it was possible to quantify the development of amyloid deposits and thus predict the staging of AD. The amyloid burden seen with PET is related to disease progression. In addition, this imaging technique makes it possible to detect variants related to Alzheimer's disease, such as posterior cortical atrophy, the executive frontal variant or in the logopoeic variant.

Initially, the radiotracers used were based on 11C. In particular, the tracer PiB which has a good affinity for fibrillar amyloid species. In general, however, these radiotracers, despite having a high signal-to-noise ratio, have a short half-life, such that they require an on-site cyclotron. In fact, to date, the major radiotracers used are 18F-based, characterized by a half-life of about 109 min and therefore with a value twice as high as 11C-based radiotracers [13,14].

In addition, researchers are further attracted to novel radioligands that allow to identify pathological tau in vivo and thus to obtain information on toxicological processes when amyloid and tau interact [13].

Among the main fluoro-18-based radioligands, fluorodeoxyglucose (18F-FDG) is the most widely used to identify various types of diseases. These include Alzheimer's, as patients suffering from this neurodegenerative disease are found to have reduced glucose metabolism due to reduced cellular activity and for this reason, the radiotracer accumulates in these areas, allowing the measurement of changes in glucose metabolism in the brain. This radiotracer is injected intravenously, phosphorylated into the cells where there is a greater consumption of glucose, and then retained in the brain.

The radiotracers used for AD belong to a variety of chemical classes. It has been hypothesized that the difference is related to how they bind to amyloid beta plaques [12].

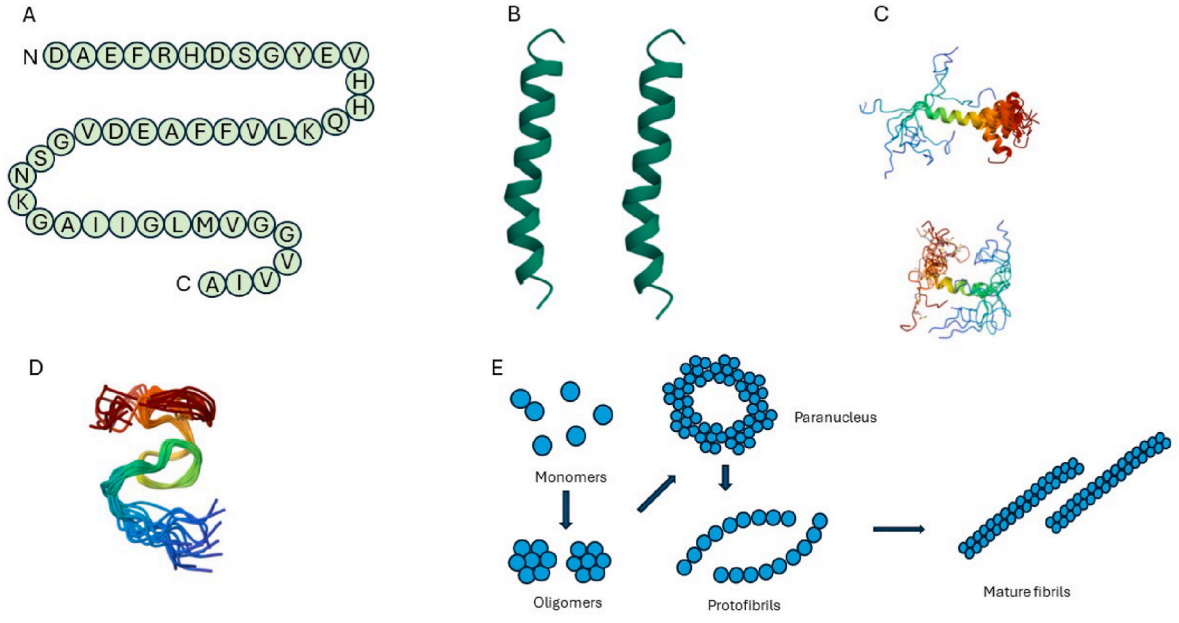

Fig. 1. Structures of Amyloid β (Aβ) peptide in different configurations. (A) Main Aβ isoform Aβ42. Aβ is characterised by groups of peptides of varying sizes, from 37 to 49 residues. (B) The structure of the beta-amyloid peptide (1–28) is characterised by an alpha-helical configuration but can be transformed into a beta-sheet in membrane-like media (PDB code: 1AMC, 1AMB). This structure is the main component of the amyloid plaques that characterize Alzheimer's disease. (C) Solution structure of amyloid beta peptide (1–40), characterised by an alpha-helical portion and an unstructured portion, which is probably solvated by water (PDB code: 1BA4, 1BA6). The van der Waals and electrostatic forces maintain its conformational stabilization. (D) Amyloid beta peptide (10–35) forms a collapsed coil structure (PDB code: 1HZ3). The van der Waals and electrostatic forces maintain its conformational stabilization. (E) Representation of the conversion of amyloid-beta monomers into oligomers, protofibrils and higher-order fibrils. They can be characterised by a different molecular weight.

18F-FDG is therefore a non-specific radiotracer, in fact used for various pathologies. Considering this, PET with the aforementioned radiopharmaceutical is used when the cause of dementia remains unclear [15].

To date, in addition to 18F-FDG, three amyloid-specific radiotracers are commercially available: 18F-Flobetapir, 18-F-Florbetaben, 18-F-Flutemetamol (Fig. 2), which are equivalent in clinical practice. Amyloid PET has a sensitivity and specificity of 93 % and 56 %, respectively [14].

On the other hands, a multi-target approach is currently under review for the treatment of AD aimed at preventing the modifiable risk-factors strictly associated with aging. Phytochemical compounds are of key importance as multi-target agent's co-adjuvant of the traditional pharmacological approach. Diverse plant-derived compounds have shown their ability to counteract processes such as the Aβ aggregation, neuroinflammation, oxidative stress and insulin resistance [16,17] due to their poor pharmacokinetic profiles, many strategies have been applied in the field of nanotechnology and synthetic chemistry. Polyphenols and monoterpenes are two major classes able to act in this sense [18].

2. Parkinson's disease: an overview

Parkinson's disease (PD) is one of the most common motor disorders and is the second most common neurodegenerative condition after Alzheimer [19]. According to statistical studies carried out by the Parkinson's Foundation, more than ten million people worldwide and nearly one million in the United States are affected by Parkinson's disease, by 2030, this number is expected to reach 1.2 million [20]. Lewy bodies rich in alpha-synuclein fibrils have been found in the neurons of patients with the disease, but for which the cause is unknown, but also in those affected by genetic forms. In particular those caused by mutations in the SNCA gene, which codes for alpha-synuclein. In particular, point mutations have been identified in its central region. These are variations induced by the substitution of a single amino acid in the protein that favour aggregation either directly or indirectly [21] (Fig. 3).

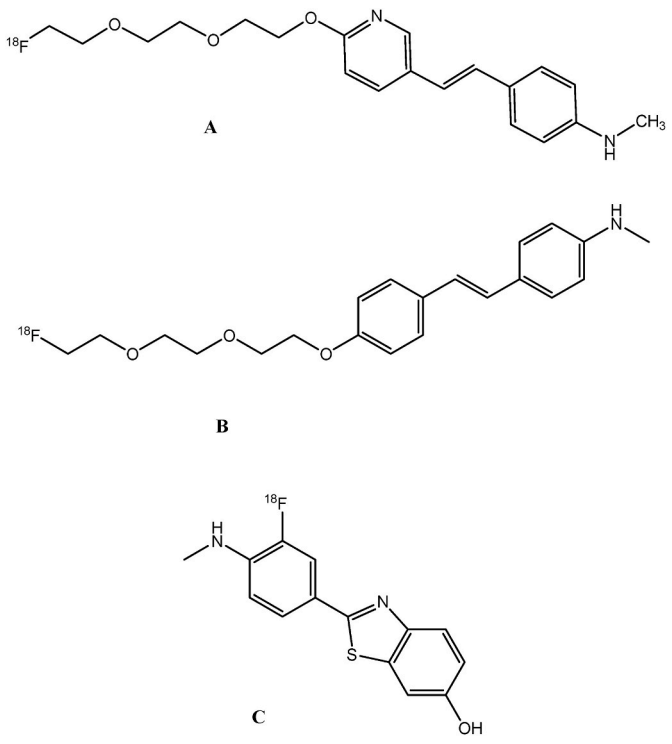

Fig. 2. Structures of radiopharmaceuticals used in Alzheimer's disease. A) Structure of 18F-Florbetapir. B) Structure18F-Florbetaben. C) Structure18F-Flutemetamol.

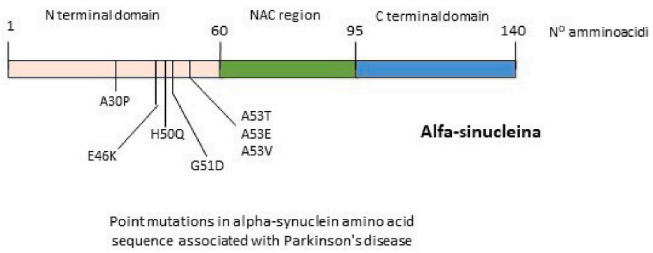

Fig. 3. Representation of the alfa-synuclein with its main domains and point mutations associated with Parkinson's disease. The N-terminal domain is mainly involved in the protein's interaction with cell membranes. The NAC (non-amyloid beta component) domain determines aggregation of the protein. The C-terminal domain is little involved.

The disease is mainly characterized by symptoms that together determine parkinsonian syndrome. The main ones are difficulty in movement and therefore bradykinesia, the tremor that occurs when the patient is at rest, rigidity and instability in posture. The motor symptoms typical of Parkinson's disease are the result of the death of nerve cells that synthesize and release dopamine, a neurotransmitter important for movement control and mood regulation.

The main pathophysiological feature of Parkinson's disease is the formation of misfolded enriched protein aggregates of ÿ-synuclein (ÿ-syn), called Lewy bodies (LBs), which accumulate significantly in dopaminergic (DA) neurons, the substantia nigra pars compacta (SNc) and other regions of the brain related to late symptoms, causing their decline. In fact, the development of Parkinson's disease is related to the misfolding and aggregation of ÿ-Synthesis monomers, causing the formation of pathological oligomers and fibrils within neurons. This, therefore, causes interference with the signal transduction pathways in the brain, generating the characteristic symptoms of the disease. The function of ÿ-Syn protein aggregates is not yet well understood, but it is involved in synaptic maintenance, including regulation of dopamine vesicle size, dopamine transporter (DAT) localization, and dopamine biosynthesis [19,22].

2.1. Diagnosis and treatment of Parkinson's disease

Parkinson's disease is another neurodegenerative disease for which some drugs have been developed. This disease has a variable progression and for this reason the response to drugs is related to the speed at which the disease progresses. As a result, this is also determined for the progression of the patient's symptoms. The main drugs used are carbidopa-levodopa, monoamine oxidase-B inhibitors, and dopamine agonists. A study has shown that treatment with levodopa promotes mild mobility in the patient but still lasts for more than seven years. A downside is related to the increase in dyskinesia. On the other hand, as far as dopamine agonists are concerned, it has been found that patients who discontinue their treatment may be subject to impulse control disorders and withdrawal [23]. In order to improve the patient's life expectancy and use the right therapeutic approaches to better manage the subject, it is important to try to diagnose Parkinson's early. The only limitation is related to the fact that parkinsonism is an early sign that also characterizes other neurodegenerative disorders such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Differentiating these disorders in the early stages can be tricky [24]. Regardless of this, however, diagnosis remains a fundamental element for clinical research. PET imaging is the best method currently used, as it is characterized by high sensitivity and temporal resolution, a fast acquisition procedure, and better cost-effectiveness, compared to single photon emission computed tomography (SPECT) of the dopamine transporter. Currently, the approved radiopharmaceuticals are 18F-DOPA, 18F-FDG (Fig. 4) and

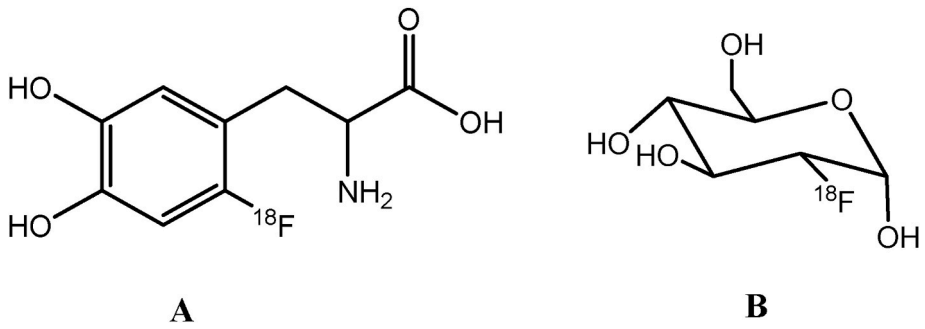

Fig. 4. Structures of radiopharmaceuticals used in Parkinson's disease by PET imaging. A) Structure of 18F-Dopa. B) 18F-Fluorodeoxyglucose (18F-FDG).

[123I]FP-Y-CIT. The latter, however, is used in the SPECT diagnostic technique [22].

Polyphenols such as flavonoids, phenolic acids, stilbenes, lignans, and terpenes are primarily described as phytochemicals with antiparkinsonian effects; alkaloids, cinnamates, carbohydrates, amino acids, and fatty acid amides, have been also reported as active against PD. Their antiparkinsonian effect includes mechanisms such as apoptosis suppression via reduction of Bax/Bcl-2, caspase-3, -8, and -9, and α-synuclein accumulation, decreasing dopaminergic neuronal loss and dopamine depletion, reducing the expression of proinflammatory cytokines and modulation of nuclear and cellular inflammatory signalling, elevation of neurotrophic factors, and improvement of antioxidant status. Plant-derived natural products are future pharmaceutical drugs or adjuvant treatment with conventional therapeutic approaches to improve their efficacy and alleviate their psychological adverse effects in the management of PD [25,26].

3. Discussion

Amyloid PET scan is a diagnostic test that allows the main neuropathological features of Alzheimer's to be directly identified. In particular, the accumulation of β-amyloid plaques, which are currently identifiable with commercially available radiopharmaceuticals, such as 18F-Flobetapir (Amyvid), 18-F-Florbetaben (Neuraceq), 18-F-Flutemetamol (Vizamyl) [14,27]. 18F-Florbetapir is characterized by a strong affinity and selective binding to amyloid plaques. After the injection of the radiotracer, absorption takes place in a short time, in fact the scanning time for the execution of the PET is 10.50 min. For 18F-Flutemetamol (Vizamyl), the PET scan provides a complete image after 20 min. In addition, sensitivity and specificity values of 93.1 % and 93.3 % respectively were obtained [12].

In addition, it has been shown that by PET with this radiotracer, it is possible to identify patients with early-onset dementia [28]. 18F-Florbetaben (Neuraceq) is characterized by a specific binding to amyloid beta plaques [29]. Considering what has been said, we can therefore say that the three radiopharmaceuticals do not show any difference in terms of accuracy in diagnosing the disease, in fact they all have a specific link for amyloid beta plaques [30]. As defined above, the timing of administration, and thus the pharmacokinetic properties, and affinity of 18F-Fluorbetaben are such that PET imaging is allowed at appropriate times [31].

To date, however, the FDA (Food and Drug Administration) has not authorized the use of 18F-Florbetapir to affirm the positive diagnosis of AD, but as a control. Specifically, a PET scan performed with 18F-Fluorbetapir that provides a negative scan, highlighting the absence of neuritic plaques, indicates that there is a reduction in the likelihood that a patient's cognitive impairment is related to Alzheimer's disease [32,33]. Clinical studies have been carried out to demonstrate the effective diagnostic efficacy of 18F-Florbetapir, demonstrating a connection between in vivo PET imaging and post-mortem histopathological quantification of amyloid in the brain. Specifically, studies have shown that in patients with a clinical picture in which the disease has been diagnosed, the radiotracer selectively accumulates in cortical areas, which should be the regions characterized by high amyloid depositions. On the other hand, subjects who represent a negative control show minimal cortical deposition of the radiotracer. In addition, higher SUVR values were found for subjects with AD, compared to healthy subjects (SUVR = 0.98 for healthy subjects - SUVR = 1.68 for subjects with the disease) [31].

Talking about 18F-Flutemetamol, several studies have shown that has the ability to detect amyloid plaques. A fundamental aspect when performing PET is to evaluate the visual interpretation, which is expected to be a subjective and therefore variable study, depending on the experience of the nuclear doctor who interprets the results. On the basis of these considerations, a study carried out in Japan has demonstrated the correlation between visual and therefore qualitative interpretation, with quantitative results by measuring the standardized absorption value (SUVR), which could vary according to the target and reference regions used, but also according to the radiotracer taken into consideration. First of all, the study showed that after a negative scan, radioactivity accumulates more in the white matter. Conversely, for AD-positive subjects, gray matter radioactivity in at least one of the five pivotal regions (the posterior cingulate gyrus and precuneus, frontal cortex, lateral temporal cortex, parietal cortex, and striatum) is intense. In addition, as a demonstration of what has been said above, on the correlation between visual interpretation and the quantitative evaluation for the identification of the radiotracer 18F-Flutemetamol, 95 % concordance values have been obtained for amyloid plaque positivity, favouring the reduction of the error in the interpretation of the results. SUVR values for subjects with a positive PET scan are greater than 1. For subjects with negative scanning, the values are 1 or lower. Visual interpretation is related to these values [34].

In addition, a further study performed in 2019 was considered to evaluate the effective diagnostic capacity of 18F-Flutemetamol in patients with uncertain outcomes. In particular, the object of the present study was 18F-Flutemetamol, specific for the identification of Alzheimer's disease, and 18F-FDG, a radiopharmaceutical commonly used in PET scans. With the results obtained, it was possible to see that the specific radiotracer for AD has had an important impact from a diagnostic, management and pharmacological treatment point of view for those patients with a diagnosis that is not perfectly certain, thanks to its selective and specific capabilities [27].

Affinity and selectivity for amyloid plaques have also been identified for 18F-Florbetaben (18F-FBB). It is a stilbene derivative of polyethylene glycol. As defined for 18F-Flutemetamol, also for the present radiotracer the correlation between visual interpretation and quantitative analysis has been evaluated through studies, demonstrating that the visual evaluation of the brain is effective, sensitive and specific and this is in line with what has been quantified [35].

In China, where there is the largest number of people affected by Alzheimer's, a study was performed comparing 18F-Florbetaben and 11C-PiB, and taking into account healthy subjects, subjects with brief cognitive impairment (MCI) and subjects with AD [36]. The radiotracer

11C-PiB is a molecule that binds to extracellular and intravascular amyloid deposits. Being labeled with 11C, the radiotracer has a half-life of 20 min and this makes it disadvantageous compared to radiotracers labeled with 18F [12]. From the present study it emerged that through 18F-FBB, it is possible to differentiate PET images, based on the type of patient examined. In fact, it is possible to distinguish between healthy patients and patients with AD, as the radiotracer in question is reliable in assessing amyloid deposition in vivo. By comparing it with 11C-PiB, it emerged that the images are similar and comparable. The only difference is that 18F-FBB has a higher non-specific binding to white matter.

The SUVR was higher in AD patients in cortical areas and in the global cortex, while there was a substantial difference between the SUVR of MCI patients and healthy subjects. This confirms the correlation between visual interpretation and quantitative study [36].

The radiopharmaceuticals just described have demonstrated reliability in detecting Alzheimer's pathology. Over time, however, the tau protein is becoming an increasingly important target. This protein, however, which gives rise to neurofibrillary tangles, is also characteristic of other dementias. For this reason, being able to identify amyloid plaques and tau protein would be a selective way to define the pathology. Clinical investigations for tau PET and selective results are already underway at the moment [37].

The PET scan is also used to diagnose the neurodegenerative disease called Parkinson's. The radiopharmaceutical used in this diagnostic method is 18F-Dopa, which allows the distinction between Parkinson's disease and the essential tremor of parkinsonian syndromes. The present radiotracer, 18F-di-hydroxy-phenyl-alanine, is a molecule with a structure very similar to the amino acid L-Dopa synthesized by our body, to which an atom of radioactive fluorine is added. As a result, it enters the process of dopamine synthesis, proceeding with decarboxylation and o-methylation. This last reaction is much slower than that undergone by Levodopa present in our body and consequently accumulates in dopaminergic neurons.

In addition, another radiotracer is [123I]FP-ÿ-CIT (DaTSCAN),® used in SPECT imaging, in order to identify the DAT transporter, a fundamental element involved in the reuptake of dopamine from the synaptic cleft and in the regulation of dopamine accumulation in synaptic vesicles. To date, several targets involved in Parkinson's are being studied, taking into account different radiotracers.

Compared to the SPECT imaging technique, PET has achieved numerous positive results for the diagnosis of Parkinson's. For this reason, the focus is on the radiopharmaceuticals used in this investigation. In particular, 18F-Dopa is a radiopharmaceutical used to evaluate brain dopaminergic activity and in a more specific way the presynaptic dysfunction of nigrostry neurons, the loss of which is characteristic of Parkinson's disease or other types of neurodegenerative diseases [20,22,38,39].

In addition, a study evaluated the possibility of association between 18F-Dopa uptake and characteristic symptoms (tremor, hypokinesia and rigidity). The group of patients examined showed that radiotracer uptake is reduced as symptoms of hypokinesia-rigidity increase. For tremor, on the other hand, no correlation was found [39].

In the diagnosis phase of Parkinson's disease, it is essential that the characteristics of atypical parkinsonian syndromes (APS), which are mistakenly diagnosed as Parkinson's, are able to be assessed. For this reason, PET with 18F-FDG has now been defined as useful, thanks to the fact that it allows the differentiation between PD and APS [40].

Therefore, PET studies with 18F-FDG are important for the diagnosis of Parkinson's. The radiotracer is a glucose analogue, radiolabeled with a radioactive fluorine atom. Its uptake increases as neuronal integrity increases [24]. For the diagnosis of Parkinson's it has a sensitivity of 91 % and a specificity of 89 %. Therefore, favourable values are fundamental to obtain excellent results [41].

4. Conclusions

Overall, this review, highlights the importance of the diagnosis of neurodegenerative diseases, particularly Alzheimer's and Parkinson's, in order to improve patients' living conditions [42,43]. Despite their complexity, there is experimental evidence demonstrating the ability of radiopharmaceuticals to diagnose these diseases. For Alzheimer's three radiopharmaceuticals, *e.g.* 18F-Flobetapir (Amyvid), 18-F-Florbetaben (Neuraceq), 18-F-Flutemetamol (Vizamyl) have been approved, which accumulate in the areas where amyloid plaques are present and have been found to be more specific than 18F-FDG. The ability to identify amyloid and tau protein could lead to great specificity in dementia diagnosis. Research on tau PET has produced several tau tracers that have already entered clinical investigations. For Parkinson's disease, however, the radiotracers 18-F-DOPA and 18F-FDG are essential for diagnosis, in particular 18-F-FDG was also found to be important in identifying Parkinson's disease from other atypical forms.

CRediT authorship contribution statement

Anna Tempesta: Resources, Methodology, Investigation, Formal analysis, Data curation. **Anna Tolomeo:** Supervision, Methodology, Conceptualization. **Azzurra Stefanucci:** Writing – review & editing, Formal analysis. **Lorenza Marinaccio:** Writing – review & editing. **Adriano Mollica:** Writing – review & editing, Formal analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data are not available.

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