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THERAPIES

HEADING: Neuropsychopharmacology

Contributions of PET and MRI imaging in the evaluation of CNS drugs in human neurodegenerative diseases.

PET and MRI imaging in the evaluation of CNS drugs in human neurodegenerative diseases

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Abbreviations

¹¹C-PIBPET: [¹¹C] Pittsburg compound-B

A β : β amyloid

AADC: aromatic amino acid decarboxylase

AD: Alzheimer's disease

APP: amyloid precursor protein

BBB: blood brain barrier

CNS: central nervous system

DAT: dopamine transporter

LBD: Lewy body disease

MCI: mild cognitive impairment

MRI: magnetic resonance imaging

MSA: multiple system atrophy

NFTs: neurofibrillary tangles

PET: positron emission tomography

PHF: paired helicoid filaments

SERT: serotonin reuptake transporter

VMAT2: vesicular monoamine transporter

Summary

This manuscript reviews the contributions of the neuroimaging methods including PET, conventional and advanced MRI methods to monitor the effect of new disease modifying drugs in neurodegenerative diseases. It now seems obvious that in many pathologies these two techniques are more and more complementary

KEYWORDS

Neuroimaging, Neurodegenerative diseases, PET, MRI, clinical trials.

Introduction

In the past decades positron emission tomography (PET) and magnetic resonance imaging (MRI) neuroimaging has been widely used in neurosciences to validate and follow specific treatments in central nervous system (CNS) diseases.

Those approaches have been principally used in neurodegenerative disorders such as dementia or parkinsonism, in stroke and in neuroinflammatory disease (multiple sclerosis).

The specificity of PET radiopharmaceuticals is to allow the labelling of small molecules able to cross the blood brain barrier with respect of their biological properties. The short physical period of ^{11}C (20 minutes) limiting its use to specific centres so the tracers labelled with ^{18}F (110 minutes half-life time) has been widely developed. Molecular imaging with PET is one of the biomarkers indispensable for pharmacological research. Currently, in neurosciences field, the treatment options for several pathologies, especially neurodegenerative diseases, remain supportive and symptomatic. Therefore, treatments allowing to slow down or reverse disease progression are the subject of numerous studies in which molecular imaging is promising. If it is well known that radiopharmaceuticals could improve the diagnosis of many neurologic diseases it is also obvious that this neuroimaging approach could be used to screening patients eligibility for potential new treatment, or for treatment follow-up.

In the other hand, the specificity of MRI is to provide high contrast between different water-containing CNS tissues according to their relaxation times (T_1 , T_2). Thus, high resolution-high contrasted MR images give access, not only to the depiction and progression monitoring of macroscopic lesions, but also to the evaluation of global, regional and local CNS atrophy through image segmentation procedures. Conventional MRI allows also to probe the integrity of the blood brain barrier (BBB) using injection of Gadolinium contrast media on T_1 -weighted MRI. More quantitative MRI methods enable to probe CNS microstructure (diffusion and magnetization transfer MRI), CNS iron contains (T_2^* , susceptibility-weighted imaging, quantitative susceptibility mapping), metabolism (MR spectroscopic imaging), vascularization (MR angiography) and

hemodynamic (perfusion MRI). Finally, functional MRI allows to study brain activation and reorganization at rest and during specific task.

To date, a vast majority of clinical trials have used MR imaging endpoints based on conventional MRI (number and volume of lesions, presence and topography of Gd enhancement, global and regional volumetry of brain structures). More specific advanced MRI methods appear very promising to probe efficacy of new drugs but suffer for difficulties to standardize acquisitions across sites and manufacturers. Several international initiatives have been launched for two decades to provide standardized protocols, database and post-processing pipeline, and still ongoing works are running to reach this goal, integrating continuously the new advances in the MR field to provide robust and fast protocols compatible with large clinical trials.

The aim of this short review is to map out major innovative PET radiotracers used in neurodegenerative diseases, and to explain their part in clinical research and in parallel explain the adds-on of MRI in the monitoring of dementia and parkinsonism.

Neurodegenerative diseases

Dementia

PET imaging

Amyloid gras

β -amyloid (A β) plaques in the brain are one of specific histopathologic lesions of Alzheimer's disease (AD) [1]. Progress in the understanding of the physiopathology of AD suggest that progressive amyloid accumulation begins during the presymptomatic phase, followed by synaptic dysfunction, tau-mediated neuronal injury, a reduction in brain volume, and finally the emergence of cognitive symptoms, followed by a clinical syndrome of overt dementia. This suggest that A β imaging is a critical step for the early diagnosis of AD [2].

These deposits were first imaged in PET in 2004, using a thioflavin-T derivative: 11C-Pittsburgh compound B ([11C]-PIB) [3]. So, this "historical" compound is the best known but its use is restricted to the few research centres, owing to the short half-life of 11C. Numerous studies

have showed that [11C]-PIB uptake is correlate with binds to A β plaques cortical regions in patients with AD [3–5].

[11C]-PIB binding is linked with a reduction in cerebrospinal fluid A β 42 [6], cerebral atrophy [7], and episodic memory impairment in apparently healthy elderly individuals and those with mild cognitive impairment (MCI) [8]. These first studies have been followed by the development of several A β plaque tracers labelled with fluorine. To date, three radiopharmaceuticals with equivalent diagnostic performances have been authorized for imaging: 18F-florbetapir (Amyvid[®]), 18F-florbetaben (Neuraceq[®]), and 18F-flutemetamol (Vizamyl[®]) [8].

In PET-to-autopsy studies performed with these tracers in end-of-life populations, PET scans performed during life had 88% to 98% sensitivity and 80% to 95% specificity for detecting moderate-frequent (according to the consortium to establish a registry for Alzheimer's disease scale) [9] neuritic amyloid plaques at autopsy. These results suggest that 18F-labeled tracers have better sensitivity and specificity than clinical diagnosis and other biomarkers commonly used in practice, and are comparable to 11C-PiB. However, the extent and distribution of A β plaques and amyloid PET tracer binding in patients are only moderately correlated with patterns of neurodegeneration and cognitive deficits. This suggests that A β deposition, which is a hallmark for diagnosing AD, is only a biomarker of a cascade of other physiopathological events, rather than the cause of neurodegeneration and clinical disease progression [10].

In this respect, these radiopharmaceuticals are used for their very good negative predictive value. A negative scan (i.e., amyloid uptake extremely low) is considered to be incompatible with a diagnosis of AD. Although a moderate-to-high amyloid plaque density may point to AD, a positive test is not sufficient prove this disorder. So the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association delineated "appropriate use criteria" in 2013, identifying three clinical circumstances in which amyloid PET imaging is recommended to precise the diagnosis: "Patients with persistent or progressive unexplained mild cognitive impairment", "Patients satisfying core clinical criteria for possible (and not probable) Alzheimer's disease (i.e., atypical clinical course or etiologically mixed presentation)", and "Patients with atypically young-onset dementia" [11].

In spite of those results, the use of amyloid PET imaging in clinical practice is still limited especially with the lack of reimbursement in many countries and, in France, the absence of inclusion on the list of pharmaceutical specialties approved for use by communities.

Since the development of those compounds, amyloid PET has been widely used in clinical trials. As it is well known the treatment options for AD are unfortunately limited to symptomatic drugs, with no influence of the ultimate prognosis [12]. Numerous studies have been conducted to

find new treatments, as well as to better understand the pathophysiology of AD. One of the research approaches to develop new treatments involves targeting the two pathological features of AD: senile plaques (A β) and neurofibrillary tangles (NFTs) e.g. aggregates of hyperphosphorylated tau protein in paired helical filaments (PHF). According to the amyloid cascade hypothesis, toxic plaques are supposed to be the earliest manifestation of the disease, as demonstrated by evidence of A β up to 20 years prior to the onset of symptoms [12]. The main classes of medication under development are monoclonal anti-amyloid antibodies, and inhibitors of pathogenic cleavage of the amyloid precursor protein (APP). PET amyloid tracers in clinical trials evaluating the therapeutic potential of these medications are now used for selecting and including patients with significant A β , or monitoring disease progression under treatment [13]. Furthermore, such neuroimaging PET studies is a good way to optimize the dose for treatment as it was demonstrated for example recently in an exploratory study with gantenerumab [14].

TAU imaging

One of important lack of A β imaging is the impossibility to follow the evolution of the disease and a low correlation with glucose hypometabolism, disease severity, progression, and clinical cognitive assessment. Clinical trials assessing monoclonal anti-amyloid antibodies have mostly failed to show a significant clinical benefit in AD. The other main histopathological figure of AD, abnormal tau protein aggregates, has therefore be considered with much interest. As so, consider PET radiopharmaceuticals targeting abnormal tau protein conformations as an alternative. Whereas, A β levels reach a steady state at prodromal clinical stage, the presence and extent of NFTs and neuronal injury levels are correlated with disease duration and severity of symptoms [15]. Moreover, tau has been found to be more closely related to clinical features [16]. Abnormal aggregation of tau protein has also been observed in the pathophysiology of other neurodegenerative diseases such as frontotemporal dementia, corticobasal syndrome, progressive supranuclear palsy and Lewy body disease (LBD); the abnormal conformation of tau in these diseases are distinct from that observed in AD. These tauopathies differ by the isomeric form and ultrastructural morphology of aggregated tau, affected brain regions, and spatial patterns of tau accumulation [17].

Over the past few years, several tau imaging agents have been developed: [11C]-PBB3, [18F]-AV-1451 (or flortaucipir), [18F]-T808, and the THK family [18F]-THK523, [18F]-THK5105, and [18F]-THK5351. The well-known of the first radiotracers developed for tau imaging was [18F]-FDDNP. In a recent study, an anti-tau drug exhibited a good safety profile and even

stimulated a positive immune response in human patients [18]. Several other early-phase trials of drugs that target tau protein are currently underway, although the results are yet to be published [19].

In this context, like amyloid tracers, tau radioligands have an important role to play in clinical studies assessing new treatments and measuring disease progression [20].

MRI imaging

For Alzheimer disease, patterns of cortical atrophy have been shown to accurately track disease progression [21]. Thus, MRI criteria in clinical trials are those related to the quantification of global and regional brain atrophy. The most common primary outcomes are the annualized percent change of total brain volume, annualized percent change of hippocampal volume, and annualized percent change of ventricular volume [22]. These parameters, first derived from manual segmentation are now obtained using semi-automatic [23] or automatic segmentation [24, 25] of high resolution (typically 1mm³ voxel size) volumic T1-weighted acquisitions, relatively easily standardized across sites.

Regional and voxel based atrophy maps were shown to be sensitive and specific enough to observe the progression of disease even in prodromal AD [26], and to distinguish between AD subtypes [27].

More precise automatic delineation of specific regions of interest such as the hippocampal or amygdalar subfields should contribute to improve monitoring of disease progression [28]. Concurrently, the development of ultra-high field MR scanner (7T and more) brings new perspectives to improve spatial resolution and signal to noise ratio of MRI, leading to the depiction of laminar abnormalities in hippocampal subfields, and improved sensitivity to magnetic susceptibility of b-amyloid aggregates [29] and iron accumulation reflecting neurodegeneration [30]. Standardization of protocols are ongoing in the UHF community to provide tools to construct large common database on neurodegenerative diseases [31].

But to date, no real efficacy of treatments in AD have been really observed [22]. One of the potential reasons, letting apart low effects of drugs on neurodegeneration, could be the difficulty to stratify groups of AD patients for inclusion in clinical trials. In this field, MRI could also help in the definition of more homogenous groups of patients through assessment of comorbid vascular pathologies using quantification of T₂ white matter hyperintensities [32].

In addition, combination of multimodal biomarkers derived from EEG, conventional MRI and resting state fMRI appear promising to track more sensitively subtle longitudinal changes related to disease progression even in the prodromal stage of AD [33, 34].

Parkinsonism

Today, the dopaminergic pathways is widely explored [22] by PET or SPECT radiopharmaceuticals and contribute to the diagnosis of Parkinson's disease (PD), other Parkinsonian syndromes, and LBD [35].

Historically The first radiotracer to be introduced for the non-invasive assessment of nigrostriatal terminals was [18F]-DOPA in 1983 [23]. This radiotracer reflects the enzymatic activity of aromatic amino acid decarboxylase (AADC), and conversion of L-DOPA to dopamine, through its subsequent accumulation in the dopamine neurons. Striatal F-DOPA uptake has been found to be closely related to the nigral cell count, except at the beginning of the disease as a consequence of functional compensation (F-DOPA uptake is preserved while motor symptoms can be already presents) [36]. This molecule has a history of more than 30 years in clinical research and for the diagnosis of PD. However, in the past decade, the clinical practice led to prefer structural targets such as membrane dopamine transporter (DAT). Those compounds have an high sensitivity for detecting presynaptic dopaminergic degeneration at early-stage of PD. F-DOPA has recently regained interest in the context of regenerative therapy for PD such as the implantation of dopaminergic cells or the infusion of drugs with regenerating effects for striatal cells [37]. The purpose of this therapy is to regenerate the dopaminergic presynaptic function by converting L-DOPA to dopamine. In that cases, DAT tracers are considered to be less relevant for measuring therapeutic response than F-DOPA.

DAT ligands target dopamine transporters located on dopaminergic nerve cell terminals. In contrast to the AADC, the DAT are only localized on dopamine neurons. However, the ligands used for its imaging may also bind to other transporters, such as the serotonin reuptake transporter (SERT) or the norepinephrine reuptake transporter [10]. Today in clinical routine, most of DAT tracers are developed for SPECT imaging. Due to the higher spatial resolution and better sensitivity of PET, some new radiopharmaceuticals labelled with fluorine has been developed recently.

Thus, based on the properties of PE2I a new DAT tracer LBT-999, exploited by Zionexa has been developed, which could be used in future PET explorations using fluorine-18 [38]. Because of its higher resolution, PET imaging is more useful than SPECT for accurate in vivo quantification of DAT density. LBT-999 is a phenyltropane derivative that has demonstrated its suitability for in vivo quantification of DAT in non-human primates [29]. An in vivo kinetic study in baboons confirmed that LBT-999 brain uptake is fast, high, and mainly located in the putamen and caudate, with peak uptake in these regions at 30 min postinjection instead of 3 to 4 hours for PET ligands. A third way of investigating the function of dopamine terminals is to measure the density of vesicular monoamine transporter (VMAT2), which is responsible for taking up neurotransmitters into presynaptic secretory vesicles. Although a majority of VMAT2 are expressed in dopaminergic terminals, this transporter is also located in various monoaminergic neurons, and is involved in the vesicular trapping of a wide variety of neurotransmitters including dopamine, serotonin, norepinephrine, and epinephrine. This target can be investigated with [11C]-DTBZ, or more recently with fluorinated analog [18F]-AV-133, by PET [30]. This presynaptic marker follows very typical patterns in several neurodegenerative diseases affecting dopaminergic function, such as PD, LBD, multiple system atrophy (MSA), PSP, and CBS. Their uptake/binding are altered in several brain areas, depending on the disease and its stage [31]. In contrast to AADC activity or DAT binding, it has been suggested that VMAT2 activity is less inclined to changes induced by medication or compensatory mechanisms. However, VMAT2 activity can be impacted by the density of vesicular dopamine, competing at the recognition site. Hence, the level of VMAT2 binding may decrease with levodopa administration [32]. These tracers have a future in early detection/screening, diagnosis, and neuroprotective treatment follow-up of these neurodegenerative diseases, as well as in the monitoring of neural grafted cells after transplantation [8].

In the other hand, dopaminergic neurotransmission can also be focused on postsynaptic D2 receptors with [11C]-raclopride and [18F]-fallypride [8, 31]. The concomitant study of DAT and D2 receptors may improve the diagnostic value of molecular imaging in differentiating between PD and other parkinsonian syndromes [33, 34]. In PD, at the beginning of the disease the lesions are only presents on the pre synaptic size to the difference of PSP or MAS. Molecular imaging of dopamine D2 receptors has also been used to study dopamine's role in drug abuse and addiction [36], and to evaluate several neuropsychiatric disorders [37].

MRI

Concurrently to nuclear medicine imaging which provides the extent of cellular, metabolic and synaptic dysfunction, MRI is used in Parkinson related disease for differential diagnosis [39], with development of automatic machine learning approaches [40].

The brain imaging working group of the JPNP has proposed a frameworks of neuroimaging biomarkers for clinical trials in atypical parkinsonian disorders [41]. In combination with Tau PET, probing dysregulation of cellular processes, FDG PET, probing metabolism abnormalities, and DAT SPECT probing synaptic dysfunction, volumetric MRI should contribute to characterize the extent of structural disintegration of specific regions or networks [42], resting state fMRI can probe functional network dysfunction [43] while task-related fMRI helps to evaluate the extent of brain reorganization and even the functional effect of exercise on cognitive systems (EXPAND trial) [44].

Neuronal loss within the dopaminergic system can also be estimated by MRI contrasts sensitive to the paramagnetic properties of neuromelanine. Promising advances using ultra high field MR scanners with high resolution T1-w MRI or susceptibility weighted MRI (T2*, SWI or QSM) aim at characterizing the neuronal loss in crucial – but small- structures such as the locus coeruleus, early involved in most of neurodegenerative diseases [45]. QSM and SWI are also useful to evaluate brain iron deposition that appear linked with cognitive impairment in Parkinson patients [46].

Multimodal and multiparametric imaging and functional index are developed and improved to provide prognostic factor of disease progression in PD and PSP [42,47,48].

Conclusion

There is a need for biomarkers to help with the early detection of neurodegenerative processes, the early differentiation of the underlying pathology, and the objective assessment of disease progression. In that way, PET and MRI appears to be complementary tools and can be obtained in a single scan with hybrid PET-MRI scanners.

Disclosure of interest

Authors have no competing interest to declare

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