PET IMAGING IN ALZHEIMER’S DISEASE

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**Purpose.** The purpose of this article is to explore the potential of positron emission tomography (PET) in early diagnosis of Alzheimer’s disease (AD), monitoring of disease progression and assessment of treatment effectiveness. And also, to become familiar with advantages and disadvantages of application of various radiopharmaceuticals.

**Materials and methods.** The material for the study was the scientific results of publications in professional scientific journals of the leading countries of the world of scientific and clinical activity over the past 10 years on the clinical significance of hybrid radiation imaging methods in the diagnosis and treatment of patients with AD. The study involved the use of PET radiation imaging methods in Alzheimer’s disease.

**Results.** The efficacy of PET at different stages of AD has been demonstrated. The advantages and disadvantages of using different PET techniques and different radiopharmaceuticals are discussed. PET, unlike other biomarkers, is able to assess the prevalence of lesions, evaluate progression and make a prediction of the further course of the disease.

**Conclusions.** Positron emission tomography in patients with AD is an effective diagnostic technique that can be used at different stages from the prodromal period in the form of mild cognitive impairment to assessing the progression or effectiveness of treatment in numerous clinical trials.

**Key words:** positron emission tomography, Alzheimer’s disease, mild cognitive impairment.

**Introduction.** Alzheimer’s disease (AD) is a neurodegenerative progressive disease. AD is the most common cause of dementia and is responsible for 60-80% of dementia cases [1]. At present, there are around 50 million AD patients worldwide and this number is projected to double every 5 years and will increase to reach 152 million by 2050 [2]. In Ukraine, according to the Institute of Gerontology, every tenth elderly person suffers from AD.

Age is the biggest risk factor for patients with AD and dementia. Most often, AD begins in people over 65, affecting about 1 in 14 people. For people over 80, this figure is already 1 in 6. However, we should not forget about the 10% of cases that affect people aged 30 to 60 [3]. Among the genetic risk factors are changes in apolipoprotein E (APOE), which plays an important role in the binding of lipids to proteins in lipoprotein particles. As well as mutations in one of the three genes that affect the production of beta amyloid: presenilin’s (PSEN): PSEN1, PSEN2 and amyloid-beta precursor protein (APP) [4]. Potentially modifiable factors include smoking, diabetes, vascular disease, hypertension, alcohol abuse, depression, obesity, social isolation, physical inactivity, and severe head or traumatic brain injury [4].

The initial symptoms of AD are often confused with age-related changes or stress. Symptoms include impaired short-term memory (people forgetting recent conversations or events) and minor problems with abstract thinking, planning or attention. Behavioral changes such as apathy or depression are also possible [5]. Together they form a disorder called mild cognitive impairment (MCI). MCI is usually a prodromal period of AD [6].

In the early stages of AD, the main symptoms worsen and may be accompanied by speech problems (including a reduced vocabulary and pauses in word selection) and motor impairments (apraxia, coordination problems). Despite these changes, people retain the ability to perform most tasks, but may need help with complex ones [7]. In the middle stages of the above symptoms, the symptoms increase. Patients’ reading and writing skills deteriorate, and problems with coordination can lead to falls. Also, there are problems with long-term memory (patients do not recognize close relatives), which was previously intact, and behavioral changes, including emotional lability, wandering, irritability and aggression. It becomes much more difficult to care for patients and there is a need for medical assistance [7]. In the later stages, speech is reduced to phrases or single words, and apathy and exhaustion are the leading manifestations of behavioral changes. The simplest skills are lost and the patient is mostly in bed [7].

Unfortunately, there is currently no cure for AD. However, there are medications that can slow down the development of symptoms and improve quality of life. There are also a large number of clinical trials to find a cure. Therefore, there is a need for early diagnosis of AD. There are various
tools for diagnosing the transition from MCI to AD. Among them, positron emission tomography (PET), unlike other imaging methods, is more sensitive and able to provide information at the stage of pathophysiological changes when there are no structural ones [8].

The purpose of this article is to explore the potential of PET in early diagnosis of AD, monitoring of disease progression and assessment of treatment effectiveness. And also, to become familiar with advantages and lacks of application of various radiopharmaceuticals.

Diagnostics. According to the National Institute on Aging and Alzheimer’s Association (NIA-AA) report, AD refers to a set of neuropathological changes and is therefore determined in vivo using biomarkers or postmortem studies, rather than by clinical manifestations [9]. The development of AD is characterized by β-amyloid (Aβ) – containing extracellular plaques and tau – containing intracellular neurofibrillary tangles (NFT). Aβ plaques are formed from the APP under the influence of β-secretase and γ-secretase. These enzymes cleave APP into several amino acid fragments, reaching the final forms Aβ40 (which is more often accumulated in leptomeningeal and cerebral cortical and cerebellar blood vessels) and Aβ42 (from which plaques are actually formed) [10]. The accumulation of denser plaques in the hippocampus, amygdala, and cerebral cortex can cause astrocyte and microglia stimulation, axonal and dendritic damage, and synapse loss, in addition to cognitive impairment [11].

Abnormal hyperphosphorylated tau protein is the basis of NFT formation and its corresponding changes reflect different morphological stages of the process. At the first stage, they accumulate in the somatodendritic compartment. At the second stage, the filaments begin to twist to form a paired helical filament that accumulates in the cytoplasm of axons and dendrites, leading to the loss of cytoskeletal microtubules and tubulin-related proteins. The accumulation of a large amount of tau protein at the third stage results in neuronal death and the release of NFTs into the intracellular space. These partially resistant to proteolysis NFTs are called ghost NFTs [2].

Computed tomography and magnetic resonance imaging (MRI) have long been used to diagnose AD, but due to their lack of sensitivity and specificity, they have been difficult to integrate into a full-fledged AD diagnostic model. The first step was the emergence of Amyloid PET imaging in 2004, which substantiated the role of PET and MRI as methods for detecting neurodegeneration. MRI is most commonly used at the initial assessment stage to determine macroscopic brain atrophy (in the form of tissue loss) and to exclude other causes of cognitive impairment [12].

Amyloid PET. To determine Aβ, both its level in the cerebrospinal fluid and its distribution using PET can be used. The use of PET is more appropriate in long-term studies because it is more specific and eliminates the need for lumbar punctures, which are quite painful procedures.

Among the radiopharmaceuticals used for amyloid PET, 11C Pittsburgh compound-B (11C-PiB) has become the most commonly used. It was pioneered in 2004 and became the first tracer capable of quantifying brain Aβ in vivo. It is also capable of detecting Aβ deposits before the onset of clinical signs [13].

Quantitative measures such as the standardized uptake volume ratio (SUVR) and distribution volume ratio (DVR) have been used to effectively differentiate healthy individuals from those with AD. Studies have shown that in patients with MCI and AD, 11C-PiB binding in the cerebellum is negligible and that the cerebellum is the best choice as a comparison region for PET quantification. The SUVR of each brain region can be obtained by dividing the standardized 11C-PiB uptake values in each brain region by the cerebellar uptake value [14].

Although there is a strong inverse correlation between 11C-PiB accumulation and Aβ42 levels in the cerebrospinal fluid, the technique is more accurate than cerebrospinal fluid biomarkers [15]. In turn, autopsies have shown significant similarities between 11C-PiB distribution and Aβ distribution areas [16]. Aβ imaging allows us to study the relationship between amyloid deposition and brain structure in patients with AD. In addition, it also helps to understand the function of Aβ through normal aging and the changes that occur during progression to AD.

Most commonly, increased accumulation is noted in the frontal, parietal, precuneus, striatum, cingulate, and lateral temporal cortices. Because the distribution of amyloid differs in different dementias [17], spatial patterns of amyloid deposition measured with PET can help differentiate AD from other neurodegenerative diseases.

Among other advantages, it should be noted that 11C-PiB has great potential for assessing treatment response, providing information on the reduction of amyloid load and its impact on cognitive decline, and is a sensitive predictor of the transition from MCI to AD (Fig. 1) [18].
Studies have shown a linear relationship between increased amyloid deposition and memory dysfunction and suggested a threshold SUVR of 1.3 to identify MCI populations at risk of progression to AD [19].

The limitation in the use of 11C-PIB is its short half-life (20 minutes), which allows it to be used only in centers with available cyclotrons. To solve this problem, the second generation of fluorine-18-labeled amyloid PET indicators was created. These are 18F-florbetapir, 18F-flutemetamol, and 18F-florbetaben. Today, their use is approved by the US. Food and Drug Administration (FDA).

Recent studies have shown that the three 18F-labeled markers are also highly consistent in terms of diagnostic accuracy and have 89-97% sensitivity and 63-93% specificity in differentiating AD from MCI with similar results in visual and quantitative analysis [20]. Despite the different characteristics of white and gray matter retention, cortical retention for each F18 indicator was strongly correlated with 11C-PIB, which allowed for the conversion of thresholds into indicator measurement scales with a high level of internal consistency [20, 21] (Fig. 2). Standardization of these analysis methods and measurement scales may facilitate the comparison of amyloid PET data obtained with different indicators. In general, the study [22] confirms the basic hypothesis that these agents provide generally similar information.

However, studies with 18F-flutemetamol have shown its usefulness in patients with cognitive impairment of unclear etiology and as a molecular imaging method aimed at various aspects of multiple sclerosis (MS), including demyelination [23, 24].

The third generation of tracers includes 18F-flutafuranol, also known as 18F-AZD4694 (18F-NAV4694), a benzofuran derivative.
developed by AstraZeneca researchers in Sweden [25]. Its creation was driven by the information that 18F-flutemetamol and 18F-florbetaben have a high level of nonspecific white matter retention, which in turn may limit their use in cases of displaying Aβ plaque load in low-density areas and in the prodromal phases of AD.

Due to its rapid binding kinetics, it may perform better than other Aβ indicators such as 11C-PIB, which demonstrate, based on time-activity curves, slower kinetics with a blunt peak of specific binding followed by a slower decline [26]. On April 13, 2023, 18F-flutafuranol was licensed by Meilleur worldwide. However, more data are still needed to compare its effectiveness with other therapeutics.

Among the interesting drugs under development is 18F-FIBT, which has been described as the first high-contrast Aβ-imaging agent along with 18F-florbetaben. It has demonstrated remarkable pharmacokinetics, selectivity and high affinity for binding to Aβ fibrils in vitro and in vivo, comparable to the gold standard 11C-PIB [27]. However, human studies are still to come.

Among the potential options for the development of amyloid PET, attention should also be paid to prefibrillar Aβ imaging, the main task of which is a tracer capable of binding to soluble Aβ aggregates, which, according to recent data, are a neurotoxic form of Aβ and cause nervous dysfunction [28].

**Tau imaging.** Aβ is an excellent marker of the preclinical phase of AD, but the correlation between Aβ burden and clinical stage of the disease decreases over time. From the onset of AD to the onset of cognitive decline is usually a long way. Therefore, there is a need to create another biomarker to monitor the progression of the disease and assess the corresponding changes. This marker can be the accumulation of the protein tau.

Tau in the cerebrospinal fluid, total tau (t-tau), and phosphorylated tau (p-tau) are widely used. Studies have shown that the level of p-tau in the cerebrospinal fluid is a reliable indicator of the intensity of neuronal degeneration.

Tau is also a biomarker for other neurodegenerative diseases such as Pick's disease, frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy. Given this, it was proposed to study the visualization of tau load and its spatial distribution. It was found that it differs in different dementias [29]. A scheme of its stereotypical distribution in AD was also proposed. According to this scheme, tau accumulation first occurs in the transtentorial region, followed by spreading to the limbic lobes and finally to the neocortical areas [30].

Given all of the above, there is a need to develop tau-binding PET compounds. To date, the only FDA-approved PET indicator is 18F-flortaucipir (also known as 18F-AV-1451 or 18F-T807), which demonstrates high specificity and sensitivity for AD-related NFTs [31]. Uptake of 18F-flortaucipir strongly correlates with the level of p-tau in the cerebrospinal fluid and is able to distinguish between predementia AD and AD-related dementia [31]. It can also be used as a sign of future cognitive decline and the transition of MCI to AD [33].

Studies have shown that the accumulation of 18F-flortaucipir corresponds to the stereotypical accumulation of NFTs and their sequential distribution [34, 35] (Fig. 3). Due to this, it is possible to determine the stage of the disease and track the progression in vivo. This, in turn, leads to the increasing use of such a criteria as 18F-flortaucipir tau PET-positive status in clinical trials.

**Figure 3.** Representative PET images with 18F-fluoacicpyr of a healthy elderly person and a patient with Alzheimer's disease [35]
Another tracer from this group was 18F-T808 (also known as 18F-AV-680), but its testing was abandoned due to defluorination.

Quinoline derivatives or THK series. This is a group of tau-selective ligands that were developed and studied by a group of scientists from Tohoku University [36].

The first among them was 18F-THK-523. Despite rather optimistic initial studies that demonstrated binding to NFTs in brain sections and higher affinity for tau fibrils. Subsequently, they found significant retention in white matter and an inability to bind tau aggregates in tauopathies, which severely limited its diagnostic potential [37].

Later, they discovered 2 more - 18F-THK-5105 and 18F-THK-5117. The corresponding tracers have much higher selectivity for tau in the brain than 18F-THK-523, as well as faster clearance. In general, studies have shown a good correlation between drug accumulation in the cerebral cortex and changes in cognitive abilities [38]. 18F-THK-5117 performed well in studies comparing it with 11C-PIB and 18F-fluorodeoxyglucose (18F-FDG) in patients with MCI and AD.

The next in line was 18F-THK-5351 (Fig. 4) [39], which, compared to 18F-THK-5117, demonstrated a shorter delay in the white matter and brainstem [40].

Unfortunately, the data collected to date is insufficient and further studies are needed to demonstrate whether it is possible to introduce this group of drugs into routine practice.

Another family of tau-selective ligands is phenyl/pyridyl-butadiene-benzothiazoles/benzo-thiazolines (PBBs), which bind strongly to NFTs in AD brains. Among them, 11C-PBB3 has the greatest potential. Its advantages include a 40-50 times higher affinity for NFTs than for senile plaques and the ability to accumulate in tauopathies not related to AD, which was found in comparison with 11C-PIB [41]. Among the disadvantages are the vulnerability of its structure to light, which complicates its synthesis and clinical use, as well as a short half-life [42].

18F-FDG PET. Although amyloid PET and tau imaging are rapidly evolving, we should not forget about 18F-FDG, which also plays an important role in the diagnosis of AD and MCI. 18F-FDG uptake in the brain reflects overall neuronal activity. Energy consumption by neurons occurs for various signal transduction processes and neurotransmitters, with synaptic currents and action potentials seemingly accounting for the majority of consumption [43]. Most of the energy is consumed by excitatory synapses, in particular glutamatergic synapses, which predominate among cortical synapses.

Uptake of 18F-FDG not only reflects local neuronal/synaptic activity, but can also demonstrate remote effects due to deactivation of projection neurons without local neuronal damage. An example of this phenomenon is cerebellar crossing diaschisis (CCD). Decreased 18F-FDG perfusion in the contralateral cerebellar hemisphere is caused by deactivated ponto-cerebellar neurons due to primary damage to cortico-bridge neurons from supratentorial lesions [44]. Such processes
occur during neurodegeneration, for example, in AD or frontotemporal dementia. Therefore, 18F-FDG PET is considered by the NIA-AA as one of the options for assessing the N-neurodegeneration criterion.

The absence of changes on 18F-FDG PET according to studies suggests clinical stability over several years of follow-up [45], and abnormal 18F-FDG PET is a factor of increased risk of progressive cognitive deterioration [46, 47] (Fig 5).

In addition to its differential role between healthy subjects and AD patients, 18F-FDG is able to predict the transition of MCI to AD by assessing changes in the middle and inferior temporal regions [48]. Subsequent studies have shown a similar degree of decline in the medial temporal lobe of AD patients [49]. Another study found that the combination of 18F-FDG, MRI, and cerebrospinal fluid parameters was the best method for assessing the conversion of MCI to AD [50]. In another study, hippocampal volume hypometabolism based on nuclear magnetic resonance flattening was used to assess conversion to AD, and had a specificity of 96% and sensitivity of 94% [51]. The use of 18F-FDG PET in recent years has significantly improved the treatment of AD and other dementias, but there are still some limitations. In particular, the significant variability of the images requires more research to build more automated approaches to assessment and improve the interpretation of the results.

Conclusions

1. Positron emission tomography is a valuable diagnostic method for the initial diagnosis of MCI and AD and can be an effective method for assessing progression in clinical trials.

2. The ability of radiopharmaceuticals to show the spatial distribution of tau protein or β-amyloid is useful both for understanding the course of the disease in general and can be used as a clear criterion for differential diagnosis with other neurodegenerative diseases.

3. The variability of techniques and radiopharmaceuticals allows to obtain the maximum amount of information that is indispensable in the search for treatment.

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ознайомитися з перевагами та недоліками зastosування різних радіофармпрепаратів

ПЕТ-ВІЗУАЛІЗАЦІЯ ПРИ ХВОРОБІ АЛЬЦГЕЙМЕРА

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Мета. Дослідити можливості позитронно-емісійної томографії (ПЕТ) у ранній діагностиці хвороби Альцгеймера, моніторингу перебігу захворювання та оцінки ефективності лікування. А також ознайомитися з перевагами та недоліками застосування різних радіофармпрепаратів.
Матеріали та методи. Матеріалом для дослідження стали наукові результати публікацій у фахових наукових журналах провідних країн світу, а також клінічна діяльність за останні 10 років щодо клінічного значення гібридних методів променевої візуалізації в діагностиці і лікуванні хворих з хворобою Альцгеймера. Дослідження включало використання ПЕТ методів променевої візуалізації при хворобі Альцгеймера.

Результати. Продемонстровано ефективність ПЕТ на різних етапах хвороби Альцгеймера. У роботі розглянуто переваги та недоліки застосування різних методик ПЕТ та різних радиофармпрепаратів. ПЕТ, на відміну від інших біомаркерів, здатна оцінити розповсюдженість ураження, оцінити прогресування та зробити прогноз подальшого перебігу захворювання.

Висновки. ПЕТ у пацієнтів з хворобою Альцгеймера є ефективною діагностичною методикою, яка може бути застосована на різних етапах від пронормального періоду у вигляді легких когнітивних порушень до оцінки прогресування чи ефективності лікування в численних клінічних випробуваннях.

Ключові слова: позитронно-емісійна томографія, хвороба Альцгеймера, легкі когнітивні порушення.

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