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The role of Amyloid PET Scan in Alzheimer's Disease and Dementia

Amiloid PET Görüntüleme Yönteminin Alzheimer Hastalığı ve Demansta Yeri

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ÖZET

Alzheimer hastalığı ve demansın görülme sıklığının zamanla artmasıyla birlikte tanı konulamayan hasta sayısı da çoğalmaktadır. Bu hastaların tanısı şu anda temel olarak klinik incelemelerle konmakla birlikte, yardımcı tanı yöntemlerine duyulan ihtiyaç artmaktadır. Tıp alanındaki yenilikleri takiben bu hastalarda kesin tanıyı bu görüntüleme yöntemleri ile ulaşamasak bile, klinik olarak karşımıza çıkan bulguları destekleyerek ya da klinik açıdan tanısında zorlanılan hastaların tanısında yol gösterici olacak şekilde bu görüntüleme yöntemleri kullanılabilir. FDG PET ve MR görüntülemenin yetersiz kaldığı durumlarda seçili vakalarda Amiloid PET incelemeleri kullanılabilir. Kullanımda olan Amiloid PET ligandları arasında; *11C-Pittsburgh compound B, Florbetapir (18F), Florbetaben (18F)* ve *Flutemetamol (18F)*. sayılabilir. *11C-Pittsburgh compound B* aralarında en kısa yarılanma ömrüne sahip olan ligand olması nedeniyle, görüntülemenin yapılacağı merkezde halihazırda bulunması gerekmektedir. Diğer ligandların yarılanma ömrü *11C-Pittsburgh compound B*'ye kıyasla daha uzun olmakla birlikte yine de görüntülemeler belirli merkezlerde yapılabilmektedir. Bu ligandlar beyinde bulunan β-Amiloid plaklara yerleşerek bize görüntü sağlamaktadırlar. Tartışmalı olmakla birlikte bu incelemeler bize bazı klinik olarak bulgu vermeyen hastaların tanısının konulmasında yardımcı olarak kullanılabilir. İleriye yönelik bakıldığında hastalara spesifik tedaviler uygulamada ve bu tedavilere karşı cevabı takip etmede de yeri olduğu düşünülüyor.

Anahtar kelimeler: *Amiloid PET, Alzheimer Hastalığı, Demans, Nöroloji*

ABSTRACT

Following the increase in the number of patients with Alzheimer's disease and other types of dementia, the number of patients who are harder to diagnose is increasing as well. The diagnosis of Alzheimer's disease and other types of dementia relies on clinical presentation and various helpful diagnostic tools. In recent years, advances in molecular imaging have increased the sensitivity and specificity of the diagnosis of Alzheimer's Disease. Amyloid PET examinations increase diagnostic accuracy in cases where FDG PET and MRI scans are insufficient for diagnosis. Amy-

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loid PET ligands in use include; 11C-Pittsburgh compound B, Florbetapir (18F), Florbetaben (18F), and Flutemetamol (18F). 11C-Pittsburgh compound B has the shortest half-life amongst them, therefore it has to be produced in the facility where the imaging will be done. Although other ligands have a longer half-life, the imaging still can be done in a limited number of facilities. Although not recommended for routine clinical practice, these imaging modalities are also useful in identifying asymptomatic patients. In addition, amyloid imaging has also been used to monitor the treatment in some studies and continues to be used to this day.

Keywords: *Amyloid PET, Alzheimer's Disease, Dementia, Neurology*

INTRODUCTION

The number of people over the age of 65 has tripled in the last century considering Western societies in particular, and, looking forward, it will constitute 35% of the total population in about 50 years. Following this increase in the population over the age of 65, the number of people diagnosed with dementia will increase by 50% as we approach 2030. This will result in dementia becoming not just a disease but also a serious socio-economic problem (1).

CT, MRI, and FDG-PET have been used for many years in the diagnosis and differential diagnosis of Alzheimer's Disease and other dementias. While conventional imaging methods such as CT and MRI provide the physician with more structural information, molecular imaging methods such as FDG-PET provide more functional information. Another method used in diagnosing Alzheimer's Disease, both in research and in the clinical field is the Amyloid PET, which has become increasingly popular in recent years. The aim of this review, which was prepared by examining relevant data and articles about Amyloid PET, is to convey current developments, review general information, and guide physicians about the advantages of Amyloid PET by emphasizing the importance of dementia diagnosis and differential diagnosis of dementia-causing diseases.

ALZHEIMER'S DISEASE AND AMYLOID PET

Neurocognitive disorders include diseases such as Alzheimer's Disease (AD), Dementia with Lewy Bodies (DLB), Vascular Dementia (VaD), and Frontotemporal Dementia (FTD). AD is an irreversible and progressive neurocognitive disorder, first defined by Alois Alzheimer in 1906. Amyloid plaques and neurofibrillary tangles, which are now considered pathognomonic for AD, were described for the first time in the post-mortem examination of a patient with progressive cognitive decline, named Auguste D. (2).

Dementia can be defined as an acquired impairment in a person's cognitive functions that interferes with their ability to perform daily tasks. Dementia is most often characterised by memory loss and the most important risk factor is the age which gets higher as the person gets older. Memory loss and dementia are usually progressive and irreversible. However, the pacing is highly variable and impossible to predict. AD is the most common neurocognitive disorder and it is seen in more than 50 million people worldwide (3-4).

To provide clinical diagnosis, a working group established by the Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association in 1984, determined the international criteria that have been used for more than 20 years and have undergone little modification over time (5-6). Although these clinical evaluations often bring us closer to the diagnosis, additional diagnostic methods are required in clinically unclear and complicated cases. These additional diagnostic methods include FDG PET, Amyloid PET, MR imaging, and examination of specific molecular biomarkers in the cerebrospinal fluid. Although cerebrospinal fluid examinations are a potential alternative, their use has been more limited due to the fact that it is a more invasive procedure and can be applied in only selected cases (7).

Our current knowledge of the pathogenesis of AD is based on the "Amyloid Cascade Hypothesis". The mechanism involved in the pathology here is thought to be overproduction and inadequate clearance of amyloid beta plaques in the brain (8). The amyloid hypothesis is still controversial and not generally accepted (9). For example, in a study by Rowe et al., high levels of amyloid deposits were observed in approximately 30% of healthy elderly individuals (10). In addition, as studies over time have shown, amyloid beta levels in the brain are an inadequate measure of clinical disease severity (11).

β-Amyloid plaques are not seen in frontotemporal dementia and pure vascular dementia (12). On the other hand, there are reports that it can also be seen in Lewy body dementia (DLB) and Parkinson›s disease dementia (PDD) (13-14). DLB patients had higher rates of amyloid compared to healthy individuals (15).

Although amyloid deposition rates were lower in PDD patients than in others, in selected cases the rates were the same as in people with AD (12). In studies of Parkinson's patients, high amyloid levels have been observed with an increase in cognitive impairment. In addition, a better response to cholinesterase inhibitors was observed in this patient group (16-17).

Positron emission tomography (PET) is a neurological imaging method used to demonstrate in vivo molecular ac-

tivity in the brain. PET ligands bind to specific targets such as receptors, transporters, or enzymes, making imaging possible. The ligand-binding rate and reuptake vary according to neuropathology (18). More than one ligand has been tested in order to visualize the amyloid deposits in the brain. The goals of amyloid PET examinations are to confirm the diagnosis in atypical cases, to make an early diagnosis of AD in patients with mild cognitive impairment even though it is still controversial, and to measure the efficacy of the anti-amyloid therapy (19).

Pittsburgh Compound-B, also known as 2-(4' [11C] methylaminophenyl)-6 hydroxybenzothiazole, is one of the amyloid-binding dye thioflavin-T derivatives and is the oldest and first FDA-approved ligand used for Amyloid PET research (20). The use of this ligand, which has a half-life of approximately 20 minutes, is limited to centers with a cyclotron device. In a study comparing healthy individuals and Alzheimer's patients, it was observed that [11C]PiB uptake was higher in areas with amyloid plaques in Alzheimer's patients. In the same study, a negative correlation was observed between amyloid plaque deposition measured by [11C]PiB activity and cerebral glucose metabolism measured by FDG-PET (21). The cerebellar gray matter is used as the reference point when interpreting PiB images. This is due to the typically low amount of amyloid plaque in this region compared to the cortex. In cases where the number of plaques seen in the cerebellum is high, the pons can be used as an alternative reference site. While interpreting these images, the DVR (Distribution volume ratio) method is used. In this method, the amount of ligand in specific ROIs (region of interest) is compared with the uptake in the cerebellum. Alternatively, the SUVR (Standardised uptake volume ratio) method can be used.

In this method, neocortical ROI activity and plaque density are measured by adjusting the values according to the weight, surface area, and ligand ratio given to the patient (22). Studies show that the rate of false positives increases with age. A false-positive rate of 12% was found in patients in their 60s, 30% in patients in their 70s, and more than 50% in patients in their 80s (23). The degree of cortical attachment of the amyloid agent in individuals with AD is highly variable and does not correlate with clinical measures of the severity of cognitive impairment (24). Amyloid-β (Aβ) deposition is a slow process and studies show that it remains stable in the preclinical and prodromal stages of the disease. However, although Aβ accumulation is a defining feature of AD, many elderly people without AD and patients with clinical syndromes other than AD dementia also have high levels of Aβ accumulations. Therefore, the potential clinical use of Amyloid PET requires careful consideration. As a matter of fact, approximately 20% of individuals who are considered cognitively normal or patients with dementia without AD are positive for amyloid on PET imaging, and its prevalence increases with advancing age. In addition, although the etiology of Aβ accumulation is not fully understood, the APO ϵ4 allele is also an important risk factor for the diagnosis of high amyloid deposits and AD. Considering the results of studies on the cognitive effects of amyloid deposits, most studies did not find a significant relationship between the presence of Aβ and episodic memory performance losses, but in some studies, a moderate correlation between Aβ and low memory scores were found (10,29-30). However, the available literature is limited to samples of a small group of adults aged 60 and over.

Recent studies show a 15 to 20-year delay between amyloid-β PET positivity and the onset of cognitive symptoms (31,32). In another meta-analysis, the prevalence of positive scans was 88% in patients with AD, 51% in patients with dementia with Lewy bodies (DLB), 30% in patients with cerebrovascular disease (CVD), and 38% in patients with frontotemporal lobar degeneration (FTLD) and corticobasal degeneration (CBD). It was found to be 24% in healthy elderly individuals who were in the control group (24).

In addition, BiP binds to cerebrovascular amyloids seen in cerebral amyloid angiopathy, especially in the posterior parietal and occipital cortex. Based on this information, BiP can be defined as a specific ligand of brain amyloidosis in general rather than being specific to AD amyloidosis (1).

Due to the half-life of the carbon-based PiB ligand, a new generation of fluorine-based amyloid ligands has been developed. One of them is [18F] Florbetapir. It has a high affinity for amyloid beta found in the structure of plaques (33). Its advantage over PiB is its longer half-life. It has a half-life of 110 minutes, which also allows the ligand to be transported from the centers where it is prepared to the center where PET examination will be performed (19). The ligand, which has excellent specificity in detecting amyloid beta, is also rapidly excreted from the bloodstream. Its biological distribution is stable up to 60 minutes after intravenous injection to the patient. This time provides a long interval to reach the recommended imaging protocol of 10 minutes. Considering the dosimeter measurements, the organs exposed to the highest rate are; the liver, gallbladder, bladder, and intestines (34).

[18F]Florbetaben and [18F]Flutematol are other ligands used. [18F] Flutematol reaches equilibrium in about 90 minutes, [18F] Florbetaben in about 130 minutes (35). Image acquisition time is usually 10 minutes. Ligands leave the systemic circulation rapidly and only 10% remain in the systemic compartment after 20 minutes. In individuals with aggregated amyloid beta [18F], maximum reuptake of florbetapir

occurs within approximately 30 minutes and then remains unchanged for 60 minutes (19).

In quantitative imaging analysis, the sensitivity and specificity of Amyloid PET examinations in differentiating Alzheimer's patients from healthy individuals were 92.3% and 90.5% (36).

One of the disadvantages of amyloid PET examinations is that it can rarely result in positive results in cases such as dementia with Lewy bodies, where amyloid deposition can be seen other than in AD. Another point where amyloid PET examinations are insufficient is that the incidence of false-positive results increases with age. Apart from these, the short half-life of ligands allows this process to be performed only in certain centers.

For the indications for amyloid PET use, Minoshima et al.'s study was determined by the joint task force of SNMMI and Alzheimer's Association;

1) Patients with persistent or progressive, unexplained mild cognitive impairment
2) Having the basic clinical features for AD, but; patients with atypical or etiologically mixed presentation
3) Patients with progressive dementia
4) Patients with an atypically early age of onset (usually defined as <65) can be listed. Again in the same study, as the cases outside the indications for Amyloid PET use;
1) Individuals with essential clinical features for a diagnosis of probable AD
2) Individuals in the typical age range for AD
3) Situations where disease severity does not need to be measured
4) Patients who are asymptomatic and have a family history of AD or are carriers of the ε4 allele in apolipoprotein E.
5) Patients with clinically unproven, cognitive complaints
6) Alternative for genotyping in individuals who are suspected carriers of an autosomal dominant mutation
7) Asymptomatic patients
8) The use of imaging in non-medical situations (eg legal, insurance coverage, employment screening) can be listed (37).

In the study by Jack et al., 218 MCI patients were examined. After a two-year follow-up of these patients, patients with an "Amyloid-positive" PET examination were more likely to progress to AD than others (38).

Although preclinical diagnosis and staging methods are still controversial, research on these issues continues.

CONCLUSION

The incidence of AD is increasing with the increase in the population over 60 years of age, and it is important not only in terms of the disease but also in terms of the socio-economic problems it creates when looking forward.

The amyloid cascade hypothesis, which is one of the theories involved in the pathogenesis of AD, is taken as the method of obtaining amyloid PET images. Specific radioligands that bind to amyloid plaques in the brain are preferred. These are 1C-Pittsburgh compound B, Florbetapir (18F), Florbetaben (18F), and Flutemetamol (18F). Although half-lives and image acquisition times vary among themselves, many of these radioligands are actively used in certain centers.

Although the use of amyloid PET has been going on for years, it is important to use it in the right indications in terms of the benefit it provides to individuals. Here, the responsibility of the physician is to interpret this information correctly and to use it in the most beneficial way for the patient. Interpretations of the severity, course of the disease, and the effectiveness of the treatment in the selected patient group make it possible to do so. Studies have drawn attention to the importance of Amyloid PET imaging in detecting the presence of the disease and in the differential diagnosis of diseases that cause dementia; however, it indicates that Amyloid PET examination is also effective in the early diagnosis of the disease.

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