PET/MRI IN ALZHEIMER'S DISEASE: ADVANCES IN THE INTEGRATED PET/MRI SYSTEM

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ABSTRACT

Introduction: *Alzheimer's disease (AD) is the most common type of senile dementia in clinical practice, and the incidence has increased year by year, imposing significant economic burden on the society.*

Materials and methods: *With the gradual deepening of AD's study, the diagnosis of early AD patients by analyzing imaging features can achieve the purpose of early diagnosis and prompt treatment. Imaging methods include multimodality magnetic resonance imaging (MRI), such as structural magnetic resonance imaging, resting-state functional magnetic resonance imaging, and diffusion tensor imaging, as well as positron emission tomography (PET) imaging, especially specific tracer amyloid and tau imaging, which are of great value in early clinical diagnosis.*

Results: *At present, functional MRI and PET are the main imaging techniques for the diagnosis of AD. Recent studies have shown that integrated PET/MRI can provide morphological, functional, and molecular level imaging information simultaneously, offering a new value for the early diagnosis and differential diagnosis of AD patients.*

Conclusion: *The application of integrated PET/MRI, which can perform MRI and PET scans simultaneously, has unique advantages for pathogenesis and early AD diagnosis. This article reviews the current status and recent applications of PET/MRI in AD.*

Keywords: *Positron emission tomography, magnetic resonance imaging, PET/MRI, alzheimer's disease.*

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Introduction

Neurodegenerative diseases are chronic diseases with predominant onset in middle-aged and older people, mainly in the central or peripheral nervous system. Neurodegenerative diseases are characterized by a gradual loss of neuronal structure and function, ultimately leading to neuronal death[1]. The most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), with a rapid increase in incidence with age. By 2025, the number of AD patients worldwide is expected to reach three times higher than now, and the prevalence of dementia will double in Europe and triple worldwide[2]. AD is a neurodegenerative disease characterized by progressive cognitive dysfunction and behavioral impairment, which is the most common type of senile dementia. At present, the origin and pathogenesis of AD are still being explored, and it is divided into three stages[3]: preclinical AD, mild cognitive impairment (MCI), and AD. MCI patients have been classified into two forms based on severity: early MCI (EMCI) and late MCI (LMCI)[4]. Studies[5, 6] have shown that the prevalence of MCI reaches 10% -20% in the elderly over 65 years of age, and the annual

conversion rate from MCI to AD is approximately 10.2% to 33.6%. It has been shown that the risk of conversion of LMCI to AD is far higher than that of EMCI to AD(7). Early detection and treatment with rehabilitation training and medication can reduce the number of AD by one-third[8]. Imaging studies such as MRI, CT, magnetoencephalography, SPECT/CT, and PET/CT have been widely used to diagnose neurodegenerative diseases[9]. The imaging techniques for the diagnosis of AD are mainly functional MRI (fMRI) and positron emission tomography (PET)[10].

CT examination of AD patients may show brain atrophy, ventriculomegaly, deepening and widening of sulci, and atrophy of gyri. CT is difficult to accurately show the hippocampal formation, so it has low specificity for the diagnosis of AD and is clinically mainly used for the screening examination of suspected AD. Previous studies[11, 12] have demonstrated that the combination of PET and MRI predicts MCI to AD better than MRI or PET alone. However, in most clinical practice, MRI and PET studies are obtained at different times and locations in individual patients with MCI. The findings were interpreted by different radiologists and there was no opportunity to reach consensus. The integrated PET-MRI system is a recent technological innovation that allows simultaneous acquisition of PET and MRI images by a single radiologist and real-time evaluation of the images. Interpretation by a single reader and familiarity with the structural MRI and metabolic patterns of AD contribute to a more comprehensive and effective interpretation. The advent of the integrated PET/MRI system has made it possible for researchers to explore AD[13].

The following article mainly reviews the current status and recent applications of the PET/MRI in AD. We hope this review provokes readers to reconsider the role of the integrated PET/MRI in the workup of AD.

Materials and methods

Clinical symptoms and diagnosis of AD

Memory loss is the core and early most common AD symptom, including the progressive decline in episodic memory, rapid forgetting, and semantic language impairments[14].

Patients may experience disorientation, such as going out and getting lost or even being unable to distinguish day and night and decreased comprehension and judgment[15]. At a later stage, AD patients cannot even recognize themselves in the mirror or lose the ability to read, judge distance, and recognize color. The above changes in the patient's daily living activities are easily detected, and the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCa) tests can reflect the decline in the patient's activities of daily living[16]. The dementia symptoms may also occur due to vascular dementia, Lewy body dementia, frontotemporal dementia, Parkinson's disease, neurological tumors, severe depression, poisoning or metabolic abnormalities, hypothyroidism, and vitamin B12 deficiency in clinical practice[17-20].

As biological markers change, the diagnosis of AD is no longer limited to the dementia stage and can even be advanced to the preclinical stage. Cerebrospinal fluid (CSF) biomarkers of AD are mainly β-amyloid protein (Aβ) 42, Aβ 42:Aβ 40, total tau (T-tau) and phosphorylated tau (P-tau)[21]. Because cerebrospinal fluid P-tau is significantly higher in patients at the initial stage of MCI, P-tau can be used as an early marker of AD[22].

In the preclinical AD phase, patients have predominantly asymptomatic cerebral amyloidosis with no cognitive changes. At that stage, the level of Aβ is increased, and it can be already identified by PET analysis. In the MCI phase, patients have early neuronal degeneration with mild changes in cognitive function, following positive Aβ and Tau protein on PET scan or CSF examination[23].

Resting-state fMRI in AD

Studies[24, 25] have quantified gray matter by morphometric methods using structural MRI (sMRI) and showed atrophy of the hippocampus, entorhinal cortex, limbic system, and amygdala in AD patients. Resting-state fMRI is functional imaging of the brain, which can obtain functional information of the human brain and has been widely used in the study of AD and another disease.

Resting-state fMRI furtherly determined lots of brain networks in resting state, such as the default modal network (DMN), attentional network, salient network, visual network[26]. For AD patients, the DMN has currently received attention[27]. The DMN is similar to the predilection sites typical of AD pathology, mainly including the posterior cingulate gyrus, precuneus, medial temporal lobe, temporoparietal lobe, and medial prefrontal cortex[28]. Patients with AD have reduced functional connectivity within the DMN of the anterior wedge and posterior cingulate gyrus, and MCI patients have

functional connectivity values intermediate between normal subjects and AD patients. Posterior DMN connectivity decreases early in the disease, while anterior and ventral DMN connectivity is enhanced, with all network connectivity decreasing as the disease progresses[29]. A longitudinal study(30) has found that functional connectivity in hippocampal subregions helps differentiate MCI from AD patients with sensitivity in 83.3% and specificity in 83. 3%. In addition to the above studies focusing on the DMN region, most previous studies suggest that the cerebellum is not easily involved in AD patients.

However, Luo et al.[31] found that cerebellar functional connectivity changes may be related to amnestic MCI pathogenesis. Still, more studies are needed to confirm the role of the cerebellum in AD. Besides, Regional Homogeneity (ReHo) and Amplitude of Low-Frequency Fluctuations (ALFF) are commonly used in resting-state fMRI. ReHo can be used to detect regional activity correlations.

He et al.[32] found that the ReHo values of the posterior cingulate gyrus and anterior wedge were reduced in AD patients. The ReHo values of the left inferior parietal lobule were significantly increased in MCI patients, which may be a compensatory change. Moreover, calculating ReHo values distinguished AD patients from MCI and normal subjects with 85% accuracy. ALFF is a method to observe brain neurons' spontaneous activity through the changes in resting-state blood-oxygenation-level-dependent (BOLD) signal[33].

Compared with normal controls, AD patients had decreased ALFF values in the bilateral posterior cingulate cortex, anterior wedge lobe, inferior parietal lobule, and multiple temporal regions. Still, they had increased ALFF values in the cortex hippocampus, para-hippocampal gyrus, middle temporal gyrus, and inferior temporal gyrus[34]. The peaks of N-acetyl-L aspartic acid (NAA) and Cho were significantly decreased, and the level of inositol (MI) was increased in AD patients who received proton magnetic resonance spectroscopy (MRS) [35]. Chao et al.[36] suggested that hypoperfusion detected by arterial spin labeling (ASL) can predict subsequent clinical, functional, and cognitive decline for AD. The results showed that parietal, frontal, and posterior cingulate perfusion was reduced in AD patients.

The degree of the inferior parietal lobule and posterior cingulate perfusion reduction was positively correlated with disease. The above techniques lay the foundation for integrated PET/MRI.

PET imaging in AD

PET is a molecular imaging technique using isotopic tracer-labeled radionuclides that enables the study of AD from 18F-fluorodeoxyglucose (18F-FDG) metabolic imaging(37), Aβ imaging[38], and tau imaging[39]. 18F-FDG-PET evaluates neuronal functional status by the metabolism of 18F-labeled FDG, which is the most commonly used PET tracer[40]. 18F-FDG-PET can show reduced uptake of 18F-FDG in the temporoparietal lobe, cingulate gyrus, and hippocampus in patients with early AD. Moreover, the reduction of glucose metabolism in the posterior cingulate gyrus was more pronounced than that in the temporal and frontal cortices[41]. MCI patients mainly showed hypometabolism in the posterior cingulate and hippocampus.

Frontotemporal dementia (FTD), a common form of early-onset dementia, is characterized by reduced metabolism in the frontotemporal cortex[42]. Typical FTD patients are easily differentiated from AD. Dementia with Lewy bodies (DLB) has decreased metabolism in the parietotemporal association, posterior cingulate, and occipital lobes. In particular, primary visual cortex metabolism is much decreased in patients with DLB than in those with AD[43, 44]. 18F-FDG-PET cannot only differentiate AD from other types of dementia but also predicts whether MCI patients convert to AD with high sensitivity and specificity, which is of importance for monitoring disease progression[45, 46].

AD's pathological basis is senile plaques formed by Aβ accumulation and neurofibrillary tangles (NFTs) composed of aggregated tau protein. In recent years, imaging techniques for AD-related proteins have been well-established, and the diagnostic accuracy for potential AD has been increasing. Studies[47-50] demonstrated that Aβ imaging agents (e.g., 11C-Pittsburgh compound-B (11C-PIB) and 18F-AV) and tau imaging agents (e.g., 18F-AV1451 and 18F-THK5351) had been gradually applied in clinical or scientific research. 11C-PIB is the most studied Aβ molecular probe and belongs to the thioflavin derivative class, which can specifically bind to Aβ[51]. A prospective cohort study[52] showed that Aβ accumulation was found 17 years before the onset of dementia symptoms in AD patients. Tau protein is a significant component of NFTs in AD[53]. Tau ligands are highly bound to neurofibrillary tangles in AD patients. Besides, tau-PET can show tau protein accumulation, which plays an essential role in revealing the mechanism of neurodegeneration and cognitive impairment in patients.[54]

Ossenkoppele et al.[55] found a neuroanatomical correspondence between the uptake of PET tracer 18F-AV1451 (tau) and clinical phenotype in patients with atypical AD, indicating that tau-PET can provide a valuable reference for the diagnosis of atypical AD. Aβ-PET and tau-PET can show the site and level of amyloid and tau protein accumulation, which minimize the pathological changes of cranial nerves. However, because tau protein is located within neural cells, the tracer's binding to tau protein requires crossing the blood-brain barrier and membrane. Besides, the expression level of tau protein in the brain parenchyma of AD patients is lower than that of Aβ, and there are multiple subtypes of tau protein. Hence, tracers for tau-PET are therefore still under development.

Integrated PET/MRI in AD

There are currently three combined modalities for PET and MRI[56]:

• PET or PET/CT scanner and MRI scanner are located in two examination rooms to transport and support the system connection for image fusion by software;

• PET scanner and MRI scanner were placed on both sides in a coaxial manner, and a scanner table was set in the middle for image fusion after scanning, respectively. Due to postural changes and time-consuming, the above two techniques cannot achieve synchronous acquisition, making it difficult to align images with different modalities accurately;

• Integrated PET/MRI is a new imaging device that integrates PET detectors with MRI body coils to fuse PET and MRI technology and is currently the most advanced imaging system. The PET detector based on time-of-flight (ToF) technology is integrated into the MRI scanning system after static magnetic field shielding, radio frequency (RF) shielding, and r-ray shielding[57]. Integrated PET/MRI system can genuinely realize the accurate registration and fusion of anatomical structure, function, and molecular biochemical metabolism in time and space in one scan under the same respiratory, ECG, and pulse gating signals[58].

Results

Cerebral blood flow and cerebral blood volume information can be obtained by PET scanning 2 min after PET tracer injection. However, other quantifications such as metabolic, molecular, or functional tests require PET scanning 35 to 50 min after PET tracer injection. Generally, the shortest acquisition time of 18F-fluorodeoxyglucose (18F-FDG) PET brain scans is 10 to 15 min, while the shortest acquisition time of 18F-fluoroethyl-L-tyrosine (18F-FET) PET brain scans is 20 min. Therefore, the integrated PET/MRI system can simultaneously complete the scanning of multiple MRI sequences during PET data acquisition[59, 60]. The integrated PET/MRI system can accurately combine the picomolar level information quantified by PET function with the anatomy of MRI and obtain the dynamic enhancement and MRS imaging of MRI[61]. This simultaneous multiple examinations can reduce the number of examinations and shorten the examination time.

High-resolution MRI images provide reliable anatomical information and accurately registered fusion images for PET imaging. The integrated PET/MRI system reduces the interference of partial volume effect on the region of interest (ROI) delineation, which accurately corrects motion deformation artifacts, particularly for quantitative monitoring of metabolic changes, transmitter concentration changes, and enzyme expression changes in the ROI[62]. Integrated PET/MRI systems contribute to a better understanding of the interplay of functional (level-dependent-functional MRI), hemodynamic (arterial spin labeling), and metabolic (different radiotracers) effects on brain activation and various neurological diseases[63].

18F-FDG-PET and MRI are sensitive to brain function changes in AD patients. However, the significance of 18F-FDG-PET and MRI for the diagnosis of AD remains controversial. A study[64] based on the ADNI database suggested that the hippocampal volume measured by MRI can better reflect the memory impairment in MCI patients than 18F-FDG-PET. Although 18F-FDG-PET combined with MRI can improve the differential diagnosis between AD patients and normal controls, as a non-invasive and inexpensive biomarker, quantitative measurement of hippocampal volume by MRI is more suitable for early clinical diagnosis of AD than 18F-FDG-PET. However, another study[65] based on the ADNI database proposed that 18F-FDG-PET and MRI have the same value in reflecting memory function in AD patients. The results demonstrated that the 18F-FDG-PET metabolism, along with the MRI measurement of hippocampal volume and hippocampal neuronal activity, had a high diagnostic value in the diagnosis of AD classification. The results

also suggested that the decreased brain activity at resting-state in patients with mild AD was consistent with the reduced brain glucose metabolism. Shaffer et al.[12] evaluated the application of PET combined with MRI in predicting conversion of MCI to AD. The results showed that MRI had the lowest predictive value (area under the ROC curve of 0. 741), followed by 18F-FDG-PET (area under the ROC curve of 0. 871), 18F-FDG-PET combined with MRI was able to improve the sensitivity and specificity for predicting conversion to AD in MCI patients (area under the ROC curve of 0. 902). Therefore, PET combined with MRI improves the correct diagnosis rate of AD patients, which is more accurate than any imaging method alone in predicting the conversion from MCI to AD[66]. However, PET combined with MRI is not acquired simultaneously. The patients' disease status and brain activity are different between the two examinations, and the resting-state fMRI signal is changed at any time. Hence, the advantages of the integrated PET/MRI system can compensate for the shortcomings. The results of an integrated PET/MRI study[67] suggested that the correlation between glucose brain metabolism and resting-state fMRI was spatially heterogeneous in anatomical regions and functional networks, suggesting that the marginal network had the lowest correlation and the DMN had the strongest correlation.

Discussion

There is a disconnection phenomenon in the central nodes of the brain network in AD patients, and Integrated PET/MRI provides a new method for AD pathogenesis research. Studies[68, 69] on the potential mechanisms of injury in different subregions of the hippocampus have found that the functional connectivity of the three hippocampal subregions(cornu ammonis (CA) 1, CA 2/3/ dentate gyrus (DG), and subiculum), 18F-FDG standardized uptake value rate (18F-FDG SUVR), and gray matter volume were reduced in AD and MCI patients (AD < MCI < normal subjects). In AD patients, the functional connection of the left CA 2/3/DG medial superior frontal gyrus is significantly negatively correlated with the hypometabolism and gray matter volume of the left CA 2/3/DG, and the gray matter volume is positively correlated with 18F-FDG SUVR, suggesting that the main subregion of hippocampal disconnection is the left CA 2/3/DG. Tahmasian et al.[70] performed PET/ fMRI in 40 AD patients, 21 MCI patients, and 26 healthy volunteers. The results showed that the local connectivity of the hippocampus global was increased in AD patients. Still, the connectivity with the anterior wedge was significantly reduced, suggesting that the hippocampus's metabolism was increased, while the metabolism of the anterior wedge was decreased. Morphology is not consistent with metabolic changes, which demonstrates the hippocampal disconnection hypothesis of AD.

Metabolic and perfusion changes in early neurodegenerative diseases can be assessed by integrated PET/MRI. Goubran et al.[71] performed 18F-FDG-PET/ASL MRI in three MCI patients, three AD patients, and four healthy volunteers. The results showed that AD and MCI patients had significantly reduced metabolism in the hippocampus and significantly decreased cerebral blood flow (CBF) in the subiculum compared with healthy volunteers. A study[72] that included 45 AD patients, 20 MCI patients, and 11 healthy volunteers with 18F-FDG-PET/ASL MRI showed that the hypoperfusion and hypometabolism of the temporoparietal cortex, anterior wedge, and posterior cingulate regions were highly consistent in the AD group. In contrast, only hypometabolism rather than hypoperfusion was observed in the MCI group. Garibotto et al.[73] first performed brain imaging in 4 patients with neurodegenerative diseases using 18F-FDG-PET/ MRI and found that the temporoparietal vasculopathy matched hypometabolism in AD patients.

An integrated PET/MRI study[13] showed that amyloid was negative in behavioral-variant frontotemporal dementia, with significant frontal atrophy and increased glucose metabolism. In contrast, amyloid was positive in logopenic aphasia but demonstrated left hemispherical or bilateral temporoparietal glucose metabolism decreased. Moreover, cerebral amyloid angiopathy was positive for amyloid without significant brain atrophy but showed microhemorrhages in susceptibility-weighted imaging (SWI). Henriksen et al.[74] reported that integrated PET/MRI combined with statistical image tools and hippocampal volume measurement tools have obvious advantages for diagnosing various types of dementia. Vercher Conejero et al.[75] performed integrated PET/MRI examination in two patients with dementia. One was found to have extensive Aβ accumulation in the gray matter of the brain on 18F-florbetapir PET/ MRI examination and was finally diagnosed with VaD. In the other patient, the clinical manifestations were similar to MCI. 18F-FDG-PET/MRI showed

mildly reduced metabolism in the anterior superior frontal gyrus and middle temporal gyrus bilaterally, and 18F-florbetapir PET/MRI scan results showed that no significant Aβ uptake was observed, and the final diagnosis was frontotemporal dementia. These results suggested that the integrated PET/MRI system is of great value in the differential diagnosis of AD. In this short review, we briefly comment on the biomarkers, resting-state fMRI, PET and integrated PET/MRI system for AD patients. The integrated PET/MRI system can provide functional and anatomical information at the same time. Featuring the high sensitivity and specificity of PET images, combined with the high resolution and multi-parameter image information of MRI, the advantages can be complementary.

Conclusion

In conclusion, the various advantages of integrated PET/MRI are of great value and significance for accurate diagnosis of AD in clinical practice as well as elucidating pathophysiological mechanisms.

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