Role of Positron Emission Tomography as a Biologic Marker in the Diagnosis of Primary Progressive Aphasia: Two Case Reports

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Abstract

Primary progressive aphasia (PPA) is a heterogeneous neurodegenerative disorder characterized by declining language and speech ability. Various underlying neuropathologies can induce PPA, and the disorder is divided into three subtypes—progressive non-fluent aphasia, semantic variant aphasia, and logopenic aphasia—according to clinical features. Accurate disease classification and prediction of underlying diseases are necessary for appropriate treatment, but proper use of imaging tests is important because clinical information alone often makes it difficult to make accurate decisions. Because there is a characteristic metabolic pattern according to the subtypes, F-18 fluorodeoxyglucose positron emission tomography (PET) can indicate subtype classification. In addition, PET studies for imaging amyloid or dopamine transporters play an important role in demonstrating underlying disease. The present case showed that PET imaging studies are useful in diagnosis and could be used as a biomarker in PPA.

Keywords Primary progressive aphasia · Positron emission tomography · Fluorodeoxyglucose · Amyloid · Dopamine transporter · Biomarker

Introduction

Primary progressive aphasia (PPA) is a clinical syndrome characterized by progressive deterioration, of the brain language network, predominantly in language function due to neurodegeneration, while other cognitive domains, such as episodic and topographic memory as well as constructional praxis, remain intact [1, 2]. PPA can be classified into three distinct subtypes based on language phenotypes: progressive non-fluent aphasia (PNFA), semantic variant aphasia (SVA),

and logopenic aphasia (LPA) [3]. These PPA subtypes are related to various underlying pathologies, including tau-positive and TAR DNA-binding protein-43-positive variants of frontotemporal lobar degeneration (FTLD), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and Alzheimer's disease (AD) [4–6].

Diagnosis and classification of PPA are mainly made clinically [2, 3]. Conventional imaging studies such as magnetic resonance imaging (MRI) or cerebral perfusion single-photon emission computed tomography (SPECT) supported clinical diagnosis [3]. Although the definitive diagnosis can be made based on the pathologic evaluation, its application is possible only in selective cases. Recently, positron emission tomography (PET) imaging studies using radiopharmaceuticals for glucose metabolism, amyloid, and dopamine transporter have been routinely applied for evaluation of neurodegenerative disease. Since these PET imaging studies can reveal molecular status in the brain, we thought that these imaging studies could help classify diseases by identifying the underlying pathology of PPA.

Herein, we reviewed the role of PET imaging in two cases for evaluating PPA.

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Case Reports

Case 1

A 59-year-old woman who had a history of progressively worsening language function over 3 years was referred to the department of neurology in our hospital. Neuropsychological examination revealed she had difficulty in naming objects and finding correct words; for instance, she said a monitor was a keyboard. She also sometimes failed to respond or hesitated during the confrontational naming test. Her motor and sensory function was intact. She had mild memory impairment with 0.5 clinical dementia rating (CDR) score. Laboratory and biochemistry investigations were normal. Clinically, she had been diagnosed with LPA, with AD or FTLT as the suspected underlying pathology.

On imaging tests, MRI showed a mild atrophic change in both hippocampal gyri (Fig. 1a). F-18 Fluorodeoxyglucose (F-18 FDG) PET with Biograph mCT flow scanner (Siemens Healthcare, Knoxville, TN, USA) demonstrated marked reduction of cerebral glucose metabolism in both

temporal and parietal lobes, as well as the left frontal lobe (Fig. 1b–d). This finding was much more pronounced in the left hemisphere. Next, amyloid PET with F-18 florbetaben (Piramal Imaging, Berlin, Germany) imaging was performed to evaluate underlying pathology, and high uptake of the radiotracer was seen throughout the brain (Fig. 1e). After considering the imaging findings, AD was thought to be an underlying pathology of LPA. The patient was treated for AD with donepezil and memantine for more than a year after diagnosis, but a reduction of language and cognitive function continued, and memory function gradually decreased. Follow-up neuropsychological test revealed that simple comprehension was still intact, but complex sentence comprehension got worse and phonemic paraphasia appeared. CDR score got worse to 1 from 0.5.

Case 2

A 58-year-old woman visited the department of neurology in our hospital due to progressive difficulty in speaking over a period of 2 years. Her family said that she understood what the

Fig. 1 Coronal T1-weighted brain MRI showed diffuse cortical atrophy in both parahippocampal gyri (yellow arrows, a). F-18 FDG PET showed asymmetric hypometabolism in both parietal and temporal lobes as well as the left frontal lobe (b–d). Decreased glucose metabolism was seen in

the left hemisphere compared with the right hemisphere. F-18 Florbetaben PET revealed diffusely increased uptake throughout the brain (e)

other person was saying, but sometimes she said something incomprehensible or used inappropriate words. In the neuropsychological examination, it was hard for her to say phrases over three syllables and she sometimes had an inaccurate pronunciation. Ideomotor apraxia and bradykinesia of the right arm was observed. Sensory function of the patient was intact, and laboratory and biochemical results were also normal. She complained about memory impairment with 0.5 in the CDR score. Clinically, she had been diagnosed with PNFA; underlying pathology was suspected to be either CBD or AD.

On imaging tests, MRI showed diffuse and mild atrophic change in the cortex of the left hemisphere (Fig. 2a). F-18 FDG PET showed markedly asymmetric decreased cerebral glucose metabolism in the frontal, temporal, and parietal lobes (Fig. 2b–d). The hypometabolic areas were predominant in the left hemisphere and especially the left frontal lobe. Asymmetric decreased metabolism was also revealed in the left striatum (Fig. 2c). Amyloid PET with F-18 florbetaben revealed no significant amyloid accumulation in the brain (Fig. 3a). Due to her parkinsonian features and the clinical

suspicion of CBD, F-18 fluorinated-*N*-3-fluoropropyl-2-b-carboxymethoxy-3-b-(4-iodophenyl)nortropine (FP-CIT) PET was performed. F-18 FP-CIT PET showed asymmetrical and diffusely decreased uptake in the left caudate nucleus and putamen; however, the right striatum was normal (Fig. 3b, c). After considering the results from PET imaging, CBD was thought to be an underlying pathology of PNFA. The patient was treated for CBD with memantine, rivastigmine, and antidepressant, and more than 1 year had passed since her initial diagnosis. On follow-up evaluation, the patient was able to understand the words of others, but fluency became worse and showed little. Apraxia of the right arm was progressed further. CDR score got worse to 3 from 0.5.

Discussion

The classification of PPA into three subtypes is mainly based on clinical information, such as linguistic impairment and specific cognitive features [2]. In PPAs, motor

Fig. 2 Coronal T1-weighted brain MRI showed mild and diffuse cortical atrophy in the left hemisphere of the brain (a). F-18 FDG PET showed markedly asymmetric hypometabolism in frontal, temporal, and parietal lobes as well as the left striatum (b, c transaxial images, d coronal image). Prominent reduction of glucose metabolism was seen in the left hemisphere

Fig. 3 F-18 Florbetaben PET revealed that there was no evidence of amyloid deposition in the brain (a). F-18 FP-CIT PET showed diffusely decreased uptake in the left striatum, including the putamen and caudate nucleus (b transaxial image, c maximum intensity projection image)

speech deficit or agrammatism, comprehension impairment, and phonological short-term memory deficit are observed in PNFA, SVA, and LPA, respectively [3]. Accurate differentiation among PPA subtypes has importance for the prediction of underlying pathology. However, although PPA phenotypes have different neuropathologic causes (including FTLT or AD), different underlying pathologies can induce identical PPA phenotypes [7]. Due to this complexity of the disease, confusion may arise when the diagnostic criteria are not fulfilled.

Conventional imaging studies, such as MRI, cerebral perfusion SPECT, or F-18 FDG PET, have an additive role to support clinical diagnosis and classification [3]. These imaging modalities show cortical atrophy, decreased cerebral perfusion, or reduced glucose metabolism in the affected parts of the brain. F-18 FDG PET can demonstrate characteristic patterns of glucose metabolism: hypometabolism in the left fronto-insular area with the premotor area in PNFA, in the left anterior temporal lobe in SVA, and in the left temporoparietal lobe in LPA [8, 9]. It is well known that left dominant atrophy or hypometabolism is present in all PPA variants, explained by the fact that the language network, including Wernicke's and Broca's areas, is located on the left hemisphere of the brain [10, 11]. Similar results were observed in our cases: the patient in case 1 with LPA showed parietotemporal hypometabolism and the patient in case 2 with PNFA showed frontotemporoparietal hypometabolism. Left predominant hypometabolism was observed in the two patients, although they had hypometabolic lesions in both hemispheres of the brain. Considerable variability can be seen according to the localization and extent of the lesion in aphasic patients. In our cases, the imaging and clinical diagnosis were consistent with PPA classification, and the imaging studies were helpful in confirming the clinical diagnosis.

Since treatment of PPA can differ according to the underlying pathology, determining the underlying cause is important. As mentioned earlier, it is well known that each variant of PPA has a predominant pathology, but we cannot be sure at the individual level. In LPA, it is reported that more than half of the patients have AD pathology and the remainder have FTLT. Note that PNFA is mainly associated with FTLT tauopathy (70%), including PSP or CBD, but most other cases have AD pathology [4, 12]. In the first case, the metabolic pattern of F-18 FDG PET suggested AD as an underlying disease. Subsequently, amyloid PET scanning revealed diffuse amyloid accumulation in the brain; therefore, underlying pathology was thought to be AD in this patient. In the second case, a marked metabolic reduction was not only in the left cerebral cortex but also in the left striatum. These findings suggested CBD was the most likely diagnosis, although AD could not be excluded since both parietotemporal areas were also involved. Subsequently, amyloid PET and F-18 FP-CIT PET were performed to differentiate between the possible underlying pathologies. There was no amyloid accumulation in the amyloid PET, and uptake of the left striatum was diffusely, asymmetrically decreased in F-18 FP-CIT PET. In CBD, it is well known that dopamine transporter imaging including F-18 FP-CIT PET shows a characteristic imaging feature of asymmetric decrease uptake in the caudate and the putamen contralateral to the most affected side [13]. Based on these results, the underlying pathology of the patient was thought to be CBD. Although pathologic evaluation was not performed in cases, the diagnosis was unchanged at more than 1-year follow-up.

The previous study reported that the extent and severity of language dysfunction had a significant correlation with cerebral metabolic status [14]. Therefore, in the process of PPA diagnosis, F-18 FDG PET could be important diagnostic clues

for the subtype classification and predict the severity of the disease. Amyloid PET and F-18 FP-CIT PET could reveal the underlying pathology in the brain. PET cannot be used in all cases, but it can be used as a major diagnostic tool in certain cases of PPA, rather than simply aiding clinical diagnosis.

In this case, we observed the clinical usefulness of PET examination in PPA. We suggest that PET imaging studies with various radiotracers can be used as a biomarker to classify variants and to predict underlying pathology in PPA.

Compliance with Ethical Standards

Conflict of Interest Young Jin Jeong, Kyung Won Park, and Do-Young Kang declare that they have no conflict of interest.

Ethical Approval This article is a case report for which approval by an institutional review board is waived.

Informed Consent Informed consent was obtained from all subjects of this case report.

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