

## VIII. 2. Imaging Prion Amyloid Plaques Using [<sup>11</sup>C]BF-227

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### Introduction

Prion diseases are a group of fatal neurodegenerative disorders, including Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and kuru<sup>1</sup>. These diseases are characterized by progressive deposition of abnormal prion protein (PrP) in the brain. CJD is the most common type of human prion disease. GSS is a familial neurodegenerative disorder associated with mutations of the PrP gene. Abnormal PrP deposition in the brain is suggested to start before the occurrence of clinical symptoms. Thus, preclinical diagnosis and early disease-specific therapeutic interventions can be beneficial for people affected by prion diseases.

Several positron emission tomography (PET) imaging agents have been recently developed and used for in vivo detection of brain amyloid- $\beta$  (A $\beta$ ) plaques in patients with Alzheimer's disease (AD). Most of these PET agents show high binding affinity to PrP amyloid because PrP aggregates form  $\beta$ -pleated sheet structures and share a common secondary structure with A $\beta$  deposits in AD brain. Therefore, these agents would be useful for the in vivo detection of PrP amyloid in the brain. We have demonstrated in vitro and in vivo binding of benzoxazole derivatives to both A $\beta$  and PrP amyloids<sup>2,3</sup>. One of these derivatives, BF-227, was used for a clinical PET study where it successfully visualized amyloid deposits in the brain of AD patients in vivo. Therefore, [<sup>11</sup>C]BF-227 appears to be a promising candidate for PET imaging of PrP deposits. The purpose of this study was to

evaluate the clinical utility of [ $^{11}\text{C}$ ]BF-227 PET for the noninvasive detection of abnormal PrP deposits.

### **Subject and Methods**

Two sporadic CJD patients [63-year-old female (CJD1) and 58-year-old male (CJD2)] and 3 GSS patients [69-year-old female (GSS1), 61-year-old male (GSS2), and 30-year-old female (GSS3)] underwent PET scans with [ $^{11}\text{C}$ ]BF-227. For comparison, [ $^{11}\text{C}$ ]BF-227 PET studies were also performed in AD patients and aged normal controls. CJD1 health was unremarkable until the manifestation of depressive symptoms at the age of 62 years. The patient then developed subacutely progressive dementia, motor disturbances, and myoclonus. CJD2 showed subacutely progressive dementia and gait disturbance and then developed psychotic symptoms, dysarthria, and myoclonus. Both CJD patients had no mutations and showed methionine homozygosity at codon 129 of the PrP gene. PET studies in CJD1 and CJD2 were performed when they reached grade 4 of the modified Rankin scale at a 3- and 4-month after onset of symptoms, respectively. Both patients showed periodic synchronous discharges in electroencephalograms and hyperintensity in the caudate, putamen, and cerebral cortex on diffusion-weighted magnetic resonance (MR) images. Diagnosis of probable CJD was made according to the WHO criteria. Each GSS patient was from a different pedigree and had a family history of the same disease, carrying a proline-to-leucine mutation at codon 102 and methionine homozygosity at codon 129 of the PrP gene. GSS1 and GSS2, having a 9- and 20-month clinical duration from the onset, respectively, showed signs of moderate cerebellar ataxia, such as gait disturbance and slurred speech; however, they could walk unassisted and had slight or no cognitive impairment. GSS1 and GSS2 scored 22 and 26 points, respectively, on the Mini-Mental State Examination. GSS3, having a 27-month clinical duration, showed severe gait disturbance and slurred speech and was unable to walk unassisted; however, she had no cognitive impairment (30 points on the Mini-Mental State Examination) at the time of this study. This study was approved by the ethics committee on clinical investigations of Tohoku University School of Medicine and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained after complete description of the study to the patients and subjects.

PET scans were performed using a SET-2400W (Shimadzu Inc., Japan). After intravenous injection of 211–366 MBq of [ $^{11}\text{C}$ ]BF-227, dynamic PET images were obtained for 60 min with the subjects' eyes closed. Standardized uptake value (SUV)

images of [<sup>11</sup>C]BF-227 were obtained by normalizing tissue concentration by injected dose and body weight. Average summations of SUV images were created from late frames (40–60 min post injection) of dynamic PET images. Deposition of PrP plaques is reportedly frequent in the cerebellum but scarce in the pons of GSS brain. Furthermore, BF-227 retention in the pons does not differ between AD patients and normal controls. Therefore, we used the pons as a reference region and calculated the regional to pons SUV ratio (SUVRp) as an index of BF-227 retention.

## Results

GSS patient showed obvious retention of [<sup>11</sup>C]BF-227 in the cerebellum, and lateral and medial temporal cortices. The three GSS patients showed significantly higher SUVRp in the lateral temporal cortex, thalamus, and cerebellum (Figure) when compared to aged normal controls. Furthermore, when compared to the AD group, the GSS group showed significant elevation of SUVRp in the medial temporal cortex, thalamus, and cerebellum. Although 2 GSS patients showed retention of BF-227 in most brain regions, the youngest GSS patient showed BF-227 retention only in the cerebellum, thalamus, and medial temporal cortex, but not in the neocortex. Furthermore, 2 sporadic CJD patients showed no obvious BF-227 retention in any of the brain regions examined<sup>4)</sup>.

## Discussion

GSS is a rare form of prion disease occurring in only about 3% of prion disease cases in Japan. However, GSS is probably one of the prion diseases most likely to benefit from early therapeutic interventions because the disease can be confirmed earlier using PrP gene analysis and progression occurs much slower than that in sporadic CJD, which comprises the majority of prion disease cases. Recently such compounds as pentosan polysulfate and doxycycline have been clinically used for experimental treatments for prion diseases to prevent deposition of abnormal PrP in the brain, because these compounds slowed the disease progression in animal disease models when administered in an earlier stage of the disease. Reliable surrogate markers are also required to evaluate the efficacy of these experimental interventions. [<sup>11</sup>C]BF-227 PET might be one of the best candidates to assess PrP amyloid deposition in GSS.

## References

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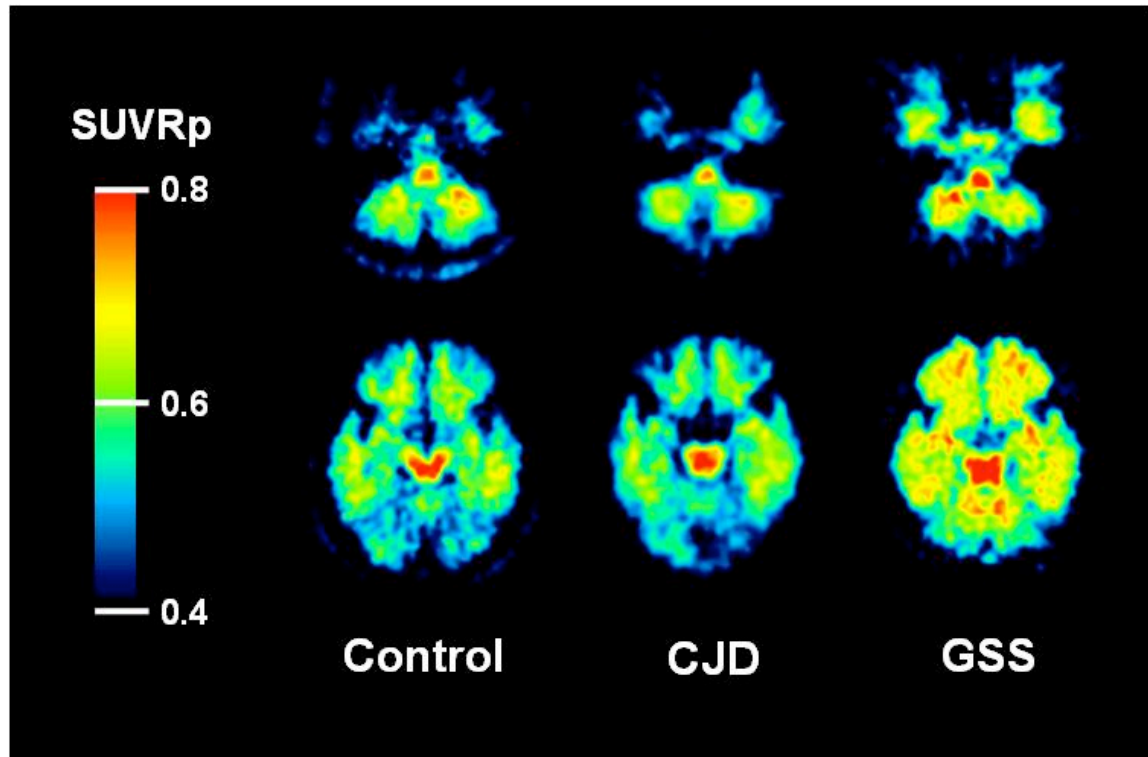


Figure 1. Regional to pons standardized uptake value ratio (SUVRp) images between 40 and 60 min post injection of [ $^{11}\text{C}$ ]BF-227 in an aged normal subject (64-year-old male), a sporadic CJD patient (63-year-old female), a GSS patient (61-year-old male).