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VIII. 3. *In vivo* Visualization of α-Synuclein Deposition by $[^{11}\text{C}]$BF-227 PET in Multiple System Atrophy

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To confirm *in vivo* visualization of α-synuclein deposition in glial cytoplasmic inclusion (GCI) in multiple system atrophy (MSA), we compared the carbon-11-labeled 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy) benzoxazole ($[^{11}\text{C}]$BF-227) PET findings of eight MSA cases to those of age-matched normal controls. The PET data demonstrated significantly high distribution volumes in the GCI-rich brain areas in the MSA. The $[^{11}\text{C}]$BF-227 PET is a promising surrogate marker for monitoring intracellular α-synuclein deposition in the living brains\(^1\).

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disease characterized by variable severity of parkinsonism, cerebellar ataxia, autonomic failure, and pyramidal signs. MSA is currently classified into a single disease, which consists of MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C)\(^2\). The histopathological hallmark of MSA is the appearance of intracellular inclusion bodies, named glial cytoplasmic inclusions (GCIs), which are mainly composed of α-synuclein fibrils\(^3\). Previous neuropathological studies indicated that the appearance of GCIs preceded the clinical onset of MSA\(^4\) and the amount of α-synuclein deposition correlated with the disease progression\(^5\). Therefore, it is plausible that the
formation of α-synuclein deposits plays a key role in the neurodegeneration and that compounds that inhibit this process may be therapeutically useful for MSA and other synucleinopathies such as Parkinson’s disease and dementia with Lewy bodies. In fact, some compounds including antioxidants and non-steroidal anti-inflammatory drugs were reported to have potent anti-fibrillogenic and fibril destabilizing effects on aggregated α-synucleins and received much attention as possible new therapeutic agents. Detection of α-synuclein deposition in vivo could theoretically allow early diagnosis even at the presymptomatic stage, as well as assess disease progression and possible therapeutic effects in the living brain of MSA patients.

Although the Pittsburgh Compound B and other compounds were reported to be useful in detecting senile plaques in vivo, there were no imaging probes currently available for in vivo detection of α-synuclein deposition. Recently, 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole (BF-227), known as a PET probe for in vivo detection of dense β-amyloid (Aβ) deposits in humans, was reported to bind with synthetic α-synuclein aggregates as well as Aβ fibrils in vitro.

To demonstrate that BF-227 could bind to α-synuclein-containing GCIs in postmortem tissues, we stained brain tissues taken from 3 autopsy cases with MSA, using BF-227 and anti-phosphorylated α-synuclein antibody. The above diagnosis was confirmed both clinically and histopathologically. Double-labeling experiments using BF-227 and anti-phosphorylated α-synuclein antibody demonstrated that BF-227 fluorescent signal in the most of GCIs in the pontine base (Fig. 1a, b). Not all GCIs stained by anti-phosphorylated α-synuclein antibody were always positive for BF staining (Fig. 1a, b). In the process of oligodendroglial pathology, it was believed that α-synuclein deposits as amorphous state and then forms fibrillar structures. In fact, part of GCIs were reported to be ubiquitin-negative and therefore, it seems reasonable that some of GCIs were not composed of β-sheet fibrils and were negative for BF-227 staining.

To confirm in vivo visualization of α-synuclein deposits by carbon-11-labeled BF-227 ([11C]BF-227) PET in the living brains of patients with MSA, we compared the distribution volume (DV) of [11C] BF-227 of eight MSA cases to those of age-matched controls. All probable MSA patients were diagnosed on the second consensus criteria for probable MSA. The clinical features of these patients are summarized (Table 1). There were no significant differences in age, disease duration, and unified MSA rating scale score between MSA-P and MSA-C subgroups. The normal control group comprised volunteers without impairment of cognitive and motor functions who had no cerebrovascular lesions
on magnetic resonance images. Tissue time activity curves of $[^{11}\text{C}]$BF-227 in the brain indicated more gradual clearance from the brain in MSA patients compared to normal subjects following initial rapid uptake of radioactivity. Relatively high concentrations of $[^{11}\text{C}]$BF-227 radioactivity were observed in the subcortical white matter and lenticular nucleus in MSA, in which relatively intense $\alpha$-synuclein deposits were found in the postmortem brain. $[^{11}\text{C}]$BF-227 exhibited linear regression curves on Logan plot analysis in all brain regions examined. Since the slopes of the regression lines represent the DV of the tracer, these findings indicated a higher DV of $[^{11}\text{C}]$BF-227 in MSA than in normal control (Fig. 2). The regional DV values were significantly high in the subcortical white matter (p<0.001), putamen and posterior cingulate cortex (p<0.005), globus pallidus, primary motor cortex and anterior cingulate cortex (p<0.01), and substantia nigra (p<0.05) in MSA patients compared to the normal controls. The regional DV of $[^{11}\text{C}]$BF-227 was increased in the subcortical white matter and lentiform nucleus, in which GCIs were densely distributed in the postmortem brains$^9$, suggesting specific binding of $[^{11}\text{C}]$BF-227 to the $\alpha$-synuclein deposits in vivo. On the other hand, regional DV in other brain regions, such as the cerebellum and pons, did not show significant increases relative to the normal control group. Due to the remarkable cerebellar and pontine atrophy, the DV in these regions might be underestimated. Correction for partial volume loss is therefore needed to improve the accuracy of quantification in the cerebellum and brainstem of MSA.

In conclusion, the BF-227 could bind to $\alpha$-synuclein-containing GCIs (Fig. 1a, b) in the postmortem brain, and the $[^{11}\text{C}]$BF-227 PET demonstrated significantly high signals in the GCI-rich brain regions including subcortical white matter, putamen, globus pallidus, primary motor cortex, and anterior and posterior cingulate cortex. These results suggest that $[^{11}\text{C}]$BF-227 PET is a suitable surrogate maker for monitoring $\alpha$-synuclein deposits in living brains with MSA and could be a potential tool to develop neuroprotective therapy for MSA. Further studies are warranted to verify whether Lewy bodies in other synucleinopathies as well as GCIs can be detected by $[^{11}\text{C}]$BF-227 PET.

References


Table 1. Subject profiles.

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<th>Normal control</th>
<th>MSA Total</th>
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<th>MSA-C</th>
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<td>Age (years)</td>
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<td>UMSARS score</td>
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<td>41.5±9.39</td>
<td>30.8±4.27</td>
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</tbody>
</table>

Data are mean ± SD.
MSA: multiple system atrophy, UMSARS: unified MSA rating scale
Figure 1. Neuropathological findings of BF-227 fluorostaining and anti-phosphorylated α-synuclein antibody immunostaining (a quotation from reference 1). BF-227 fluorostaining (a) and anti-phosphorylated α-synuclein antibody immunostaining (b) were codetected in GCIs in the pontine base of a patient with MSA. BF-227 histofluorescence was observed in the most of GCIs (arrows). Bars = 10 µm.

Figure 2. [11C]BF-227 PET findings in MSA (a quotation from reference 1). In a representative patient with MSA-C, the regional DVs were mapped to the subcortical white matter and lentiform nucleus compared to normal control.