Researchers visualize α-synuclein pathology in living patients with a neurodegenerative disorder

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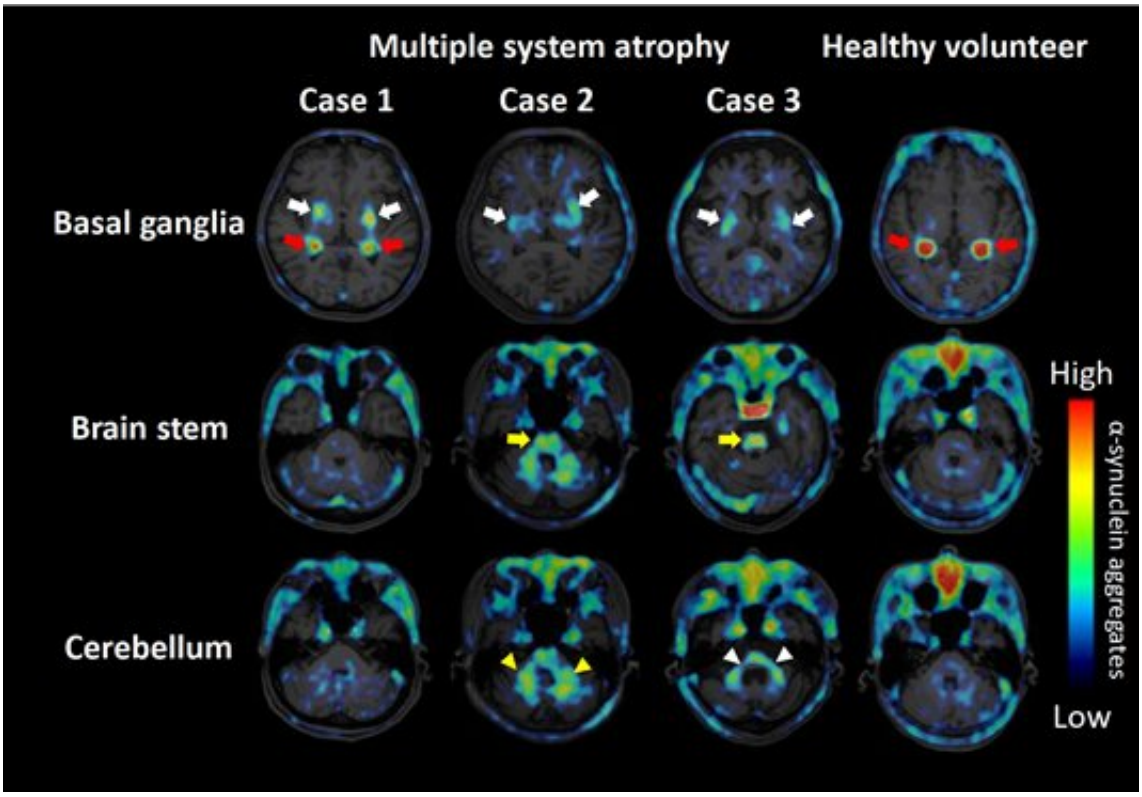

White arrows indicate accumulation of 18F-SPAL-T-06, suggesting α-synuclein aggregates in the putamen, yellow arrows in the pons, yellow triangle in the cerebellar white matter, and white triangle in the peduncles. On the other hand, red arrows indicate accumulation of 18F-SPAL-T-06 in the choroid plexus outside the brain tissues, which is considered independent of α-synuclein aggregates. MSA-P: multiple system atrophy with predominant parkinsonism; MSA-C: multiple system atrophy with predominant cerebellar ataxia. Credit: Makoto Higuchi, National Institutes for Quantum Science and Technology

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by the aggregation of α-synuclein in the brain. Now, scientists from Japan, in collaboration with three pharmaceutical companies, have developed a radioligand that facilitates the imaging of α-synuclein aggregates in patients with MSA. Their findings have the potential to completely change the scenario of diagnosing neurodegenerative diseases.

α-synuclein is a neuronal protein involved in functions like vesicle trafficking and neurotransmitter release. It is typically found in abundance in a healthy brain. However, the aggregation of α-synuclein has been closely linked to several neurodegenerative disorders, including Parkinson's disease, multiple system atrophy (or MSA), and Lewy body dementia.

MSA is a movement disorder that also affects the autonomic nervous system, which controls essential functions such as movement, breathing, and digestion. Thus, the imaging of α-synuclein aggregates in vivo (or directly in a living organism), could be a potential diagnostic confirmation of MSA. However, the road to the live imaging of α-synuclein has been marred by obstacles, including the lack of sensitive imaging agents.

Now, a collaborative effort by researchers from the National Institutes for Quantum Science and Technology, including Dr. Makoto Higuchi and Dr. Kiwamu Matsuoka from the Quantum Life and Medical Science Directorate, Institute for Quantum Medical Science has completely changed the scenario with three pharmaceutical companies—Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Company Limited. They have successfully visualized α-synuclein aggregates in the brains of patients.

To achieve this feat, the team developed a radioligand, ^{18}F-SPAL-T-06, to be used as a probe for positron emission tomography (PET). "The pre-competitive collaboration between a research institute and three pharmaceutical companies enabled us to develop the radioligand, ^{18}F-SPAL-T-06, for the in vivo imaging of α-synuclein aggregates," says Dr. Higuchi, crediting teamwork for their success. The team's findings have been published in the journal *Movement Disorders*.

Prior to the clinical assessments, in vitro studies on the binding properties of ^{18}F-SPAL-T-06 had been conducted on the postmortem brain tissue of patients with MSA and healthy individuals, showing promising results. For the first-in-human imaging studies, the researchers enrolled three patients who were clinically diagnosed with MSA and one 72-year-old healthy control (HC). Among the three patients with MSA, two were identified as having MSA with predominant Parkinsonism (MSA-P) and one with MSA with predominant cerebellar ataxia (MSA-C). PET scans with ^{18}F-SPAL-T-06 was performed on all the patients and specific binding was estimated by the radioligand retention in the tissue.

"Remarkably, we observed enhanced ^{18}F-SPAL-T-06 retention in the putamen, pons, and cerebellar white matter and peduncles of the patients with MSA-P and MSA-C, in sharp contrast to minimal radio signals in the corresponding areas in the brain of the HC," explains Dr. Higuchi.

The researchers also found that ^{18}F-SPAL-T-06 has a high affinity for MSA-type α-synuclein aggregates and that it does not cross-react with other off-target components, indicating its high specificity and consequent potential use as a probe for MSA diagnosis.

With respect to the long-term applications of their work, Dr. Higuchi and Dr. Matsuoka say, "We are encouraged by our findings, and investigations into the visualization of α-synuclein aggregates in other α-

synucleinopathies are currently underway."

More information: High-Contrast Imaging of α-Synuclein Pathologies in Living Patients with Multiple System Atrophy, *Movement Disorders* (2022). DOI: 10.1002/mds.29186

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