Progressive Ataxia and Palatal Tremor Showing Characteristic Tau Depositions in [^{18}F]PM-PBB3 PET

Progressive ataxia and palatal tremor (PAPT) are slowly progressive neurodegenerative diseases characterized by progressive ataxia and palatal tremor, which has been described as a novel tauopathy based on neuropathological findings.[1,2] The novel tau positron emission tomography (PET) tracer [^{18}F]PM-PBB3 could detect 3- and 4-repeat tau deposits with high contrast in non-Alzheimer's disease tauopathies.[3,4] Here, we report the first case of PAPT in which ante-mortem evaluations of tau retention were made using [^{18}F]PM-PBB3.

A 65-year-old Japanese male became aware of gait disturbance and visited our hospital. Neurological examination showed mild dysarthria, 2- to 3-Hz palatal tremor, saccadic eye movements, mild upper limb ataxia, and mild ataxic gait, but no vertical gaze palsy or parkinsonism (Video S1).

Brain magnetic resonance imaging (MRI) demonstrated T2 hyperintensities in bilateral inferior olivary nuclei (IONs) and mild cerebellar atrophy (Fig. 1A,B). Dopamine transporter scintigraphy showed normal uptake in striatum. We performed [^{18}F]PM-PBB3 tau PET for evaluating tau deposits. Regional standardized uptake value ratios (SUVRs) were calculated using the occipital area as a reference because it is known to carry low tau burdens in PAPT.[1,2] Strong [^{18}F]PM-PBB3 retentions were observed in the pons and dentate nucleus (DN), and moderate retention in red nucleus (RN) and cerebellum, which are components of Guillain-Mollaret triangle (GMT). These

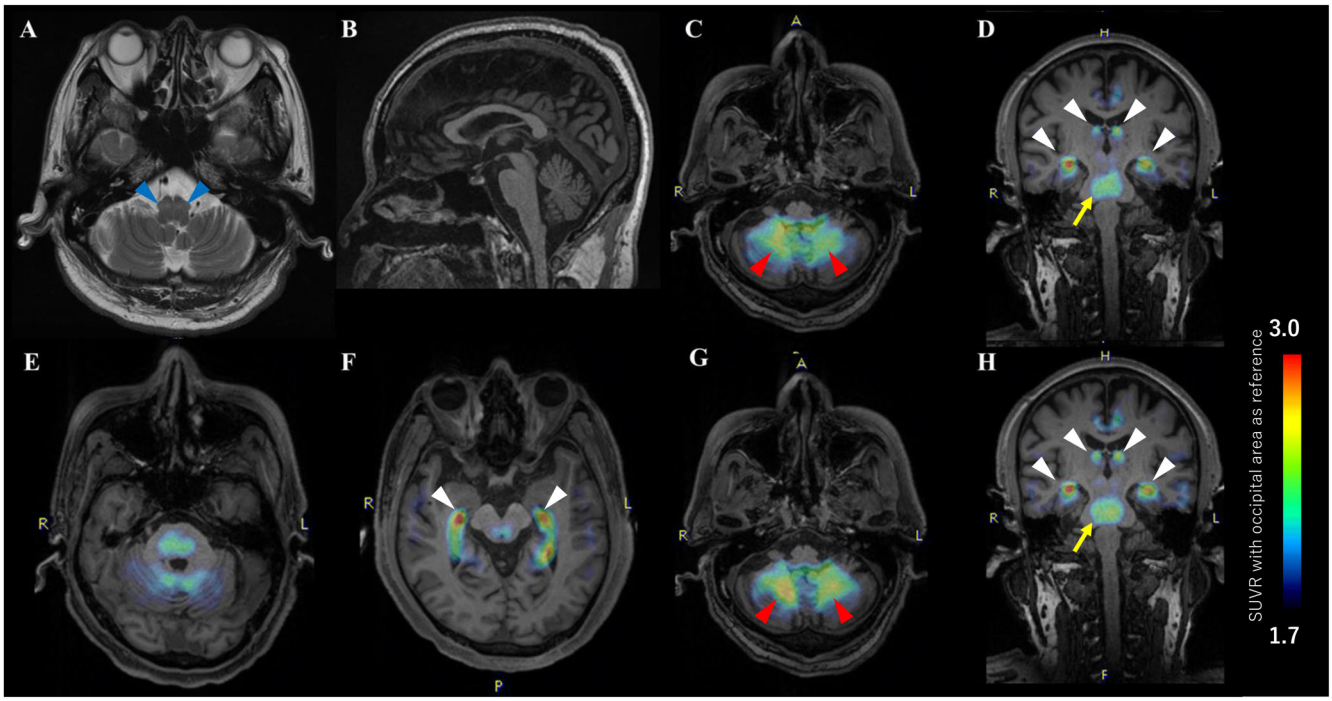

FIG. 1. The patient's brain MRI findings and [^{18}F]PM-PBB3 tau PET scan. Brain MRI showed increased signal intensity on T2-weighted sequences, hypertrophy of the bilateral IONs (blue arrowheads) (**A**), and mild cerebellar atrophy (**B**). Accumulation of [^{18}F]PM-PBB3 was detected in the dentate nucleus (**C**, red arrowheads), pontine central tegmentum tract (**D,E**, yellow arrow), red nucleus (**F**), and cerebellar cortex (**C,E**). A very low accumulation of [^{18}F]PM-PBB3 was detected in the thalamus, subthalamic nucleus, globus pallidus (**D**), and substantia nigra (**F**). Two years after the first [^{18}F]PM-PBB3 PET examination, the patient's follow-up tau PET showed slightly increased accumulation in the dentate nucleus (**G**, red arrow heads) and pontine central tegmentum tract (**H**, yellow arrow). White arrowheads point to the choroid plexus (non-specific binding) (**D,F,H**).

Key Words: tau positron emission tomography, [^{18}F]PM-PBB3, progressive ataxia and palatal tremor, tauopathy, Guillain-Mollaret triangle

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Relevant conflicts of interest/financial disclosures:

Funding agency: This research was supported by Japan Society for the Promotion of Science KAKENHI grant number 16H06277.

Received: 14 December 2021; **Revised:** 16 February 2022; **Accepted:** 17 February 2022

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28983

TABLE 1 *We compared [^{18}F]PM-PBB3 SUVRs of this PAPT case with those of age-matched healthy controls (N = 6) in the brain regions composing Guillain-Mollaret triangle (pons, superior cerebellar peduncle, dentate nucleus, and red nucleus)*

			SUVR			
Case	Sex	Age, y	Pons	Superior cerebellar peduncle	Dentate nucleus	Red nucleus
PAPT (present case)	M	68	1.66	1.37	1.97	1.65
HC1	F	60	1.19	0.92	1.20	1.20
HC2	M	63	1.10	0.87	1.32	1.25
HC3	F	68	1.15	1.04	1.25	1.34
HC4	M	68	1.26	1.18	1.31	1.39
HC5	M	72	1.11	1.02	1.20	1.04
HC6	F	77	1.06	0.84	1.12	0.98
HC (average)	M:F = 3:3	68 ± 6.1	1.14 ± 0.07	0.98 ± 0.13	1.24 ± 0.08	1.20 ± 0.16

Regional standardized uptake value ratios were calculated using the occipital area as a reference.

findings were consistent with the previously reported pathology in autopsy cases of PAPT (Fig. 1C–F).[1,2] Compared with healthy controls (HCs), SUVRs of this PAPT case were higher in each brain region composing GMT (Table 1).

There was, however, very low [^{18}F]PM-PBB3 retention in substantia nigra, thalamus, subthalamic nucleus, and globus pallidus, which is a distinct pattern from that of our previously reported patient with progressive supranuclear palsy (PSP) with predominant cerebellar ataxia (Fig. 1F).[5] Over the subsequent 2 years, his ataxic gait slowly progressed, but he still had no vertical gaze palsy or parkinsonism. We followed [^{18}F]PM-PBB3 PET, which showed gradual increases in the retention of pons, DN, and cerebellum (Fig. 1G,H). Based on the combination and course of his symptoms and imaging findings, we made the diagnosis of PAPT.

To our knowledge, this is the first report of PAPT in which ante-mortem evaluations of tau deposits were performed using tau PET. There have been three autopsy reports of PAPT describing mixed 3- and 4-repeat tau-positive inclusions in IONs and in central tegmental tracts consisting of GMT.[1,2] Consistent with these neuropathological findings, our case showed increased tau retention in DN, pons, RN, and cerebellum. Whereas, IONs demonstrated no obvious accumulation of [^{18}F]PM-PBB3, unlike the neuropathological findings.

It should be noted that pathological findings of PAPT have been reported in autopsy cases with a long disease duration, whereas we evaluated the early-stage PAPT. Although it is possible that pathological changes other than tau deposition may be present in IONs, the findings of tau PET suggest that T2 hyperintensities in IONs may be secondary to degeneration of structures involved in the GMT rather than degeneration of IONs themselves.

In summary, we performed the first ante-mortem evaluation of tau pathology of PAPT using [^{18}F]PM-PBB3 PET, which may be a useful tool for early diagnoses and longitudinal follow-up in PAPT.

Acknowledgments: We are grateful to APRINOIA Therapeutics (Suzhou, China) for providing the tosylate precursor used for [^{18}F]PM-PBB3 radiosynthesis. We thank the patient and his family members who were involved in this research. None of the study participants received financial incentives. This research was supported by Japan Agency for Medical Research and Development (JP17pc0101006).

Ethics Approval

This study was approved by the Ethics Committee for Human Research of National Institutes for Quantum and Radiological Science and Technology (17–034). This study design and protocol were also approved by the Ethics Committee for Human Research of the Keio University School of Medicine, and informed consent (N20170237) was provided by all participants.

Data Availability Statement

The data that support the findings of this study are openly available in [repository name e.g "figshare"] at [doi], reference number [reference number].

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Imaging Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

T.T.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B
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M.H.: 1A, 1B, 1C, 2C, 3B
M.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

Financial Disclosures

M.H. received research funding partly from AMED (JP18dm0207018, JP19dm0207072, JP18dk0207026, and JP19dk0207049), MEXT KAKENHI (JP16H05324), and JST CREST (JPMJCR1652). M.H. holds patents on compounds related to the present report (JP 5422782/EP 12884742.3/CA2894994/HK1208672). All other authors report no financial relationships and no conflicts of interest with commercial interests.