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Letter to the Editor

Pallidonigroluysian atrophy associated with p.A152T variant in MAPT

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Progressive supranuclear palsy syndrome (PSPS) is one of the most common atypical parkinsonian syndromes. PSPS is characterized by postural instability leading to early falls, axial rigidity, and vertical supranuclear gaze palsy [1]. PSP, the most common pathological correlate of PSPS, is a 4-repeat tauopathy. Pallidonigroluysian atrophy (PNLA) is a pathological entity characterized by severe neuronal loss in the globus pallidus, substantia nigra and subthalamic nucleus. While PNLA has been characterized as a 4-repeat tauopathy, others have suggested absence of tau suggests PNLA [2,3]. PNLA is considered a variant of PSP due to significant clinicopathological overlap, although PNLA patients typically present at a younger age (57.1 versus 65.1 in PSP) with gait freezing, eyelid apraxia and hand writing abnormalities; falls, rigidity and dysphagia tend to occur later in PNLA than PSP [4]. Herein, we present a case with atypical PSPS features that was followed serially and discovered to harbor a microtubule-associated protein tau (MAPT) mutation in which PNLA was diagnosed at autopsy.

Report of a case

A 62-year-old right handed patient presented to Neurology with less than a 1-year history of gait freezing, speech difficulty, micrographia and severe photosensitivity. He also complained of reduced arm swing and stooped posture. While the patient had postural instability, there was a relative paucity of falls throughout his clinical course. An adequate trial of 1200 mg of levodopa did not improve his symptoms. His neurological examination was notable for apraxia of eyelid opening, bradykinesia, mild axial rigidity, and hypokinetic dysarthria. He had downgaze supranuclear gaze palsy with slowing of upgaze saccades. The patient was followed from less than one year after onset to 4 months before death. The total disease duration was 7 years. Towards the end of his disease he had severe eyelid apraxia, with persistent eye closure. Gait freezing worsened over time. Fig. 1A shows changes in bedside test scores over the disease course. There was little change in general cognitive function, executive function and behavior over time, all which remained relatively mild. On the contrary, there was a more noticeable worsening of motor function over time. His PSP rating scale showed greater progression in disease severity, almost doubling in score from year 1 to year 6 (26–50). His gait also progressively worsened over time, although he maintained ambulation without the use of any assistive device. The patient completed multiple volumetric head MRI scans which qualitatively showed subtle progressive midbrain atrophy (Fig. 1B). Quantitative midbrain area measurement using the Analyze Software (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) showed an initial loss of midbrain area of 16.3% over the first 4 years with an increased loss of 20.7% occurring over the last 2 years mirroring his decline in gait. The patient's mother was also evaluated by Neurology for similar symptoms at age 72. She had presented with gait freezing and rigidity. Her neurological examination was notable for downgaze palsy, axial rigidity, and a gait characterized by freezing. Due to his family history, the patient underwent genetic testing for a mutation in the *MAPT* gene. He was found to have a p.A152T substitution.

He died at age 68, approximately 7 years after onset from aspiration pneumonia. Gross pathological brain examination showed mild discoloration of the globus pallidus, severe atrophy of the subthalamic nucleus and severe depigmentation of the substantia nigra (Fig. 2). Detailed histological examination revealed the deposition of significant tau pathology in these same regions, with a relative paucity of tau pathology in neocortical areas (Fig. 2), consistent with a pathological diagnosis of PNLA [4].

The tau p.A152T variant, originally found in a patient with PSPS, increases the risk of frontotemporal dementias and Alzheimer's disease, including atypical neurodegenerative conditions with abnormal tau deposition [5,6]. Our case expands on these previous reports highlighting the clinical and pathological variability associated with the p.A152T mutation, as well as the clinical and imaging differences from typical PSPS. While our patient's clinical presentation of parkinsonism, postural instability, downgaze supranuclear palsy, and axial rigidity meets current criteria for probable PSP [1], the early and prominent eyelid apraxia, gait freezing and micrographia in our patient are features that distinguish PSP pathology from PNLA [4]. In fact, these clinical features were most consistent with a variant of PSP referred to as pure akinesia with gait freezing including early micrographia, speech difficulty and prominent gait freezing [2]. This variant of the PSPS has been associated with PNLA pathology [4]. Intriguingly, the patient's mother also had a similar phenotype with early gait freezing also suggesting a diagnosis of PNLA.

The progression of clinical and imaging features over the first four years of the disease course was slower than what has been typically observed in PSPS. The increased rate of midbrain atrophy in the last 2 years prior to death also mirrored the observed increased rate of gait/midline changes observed during this same time period. Patients with PNLA typically progress slowly and

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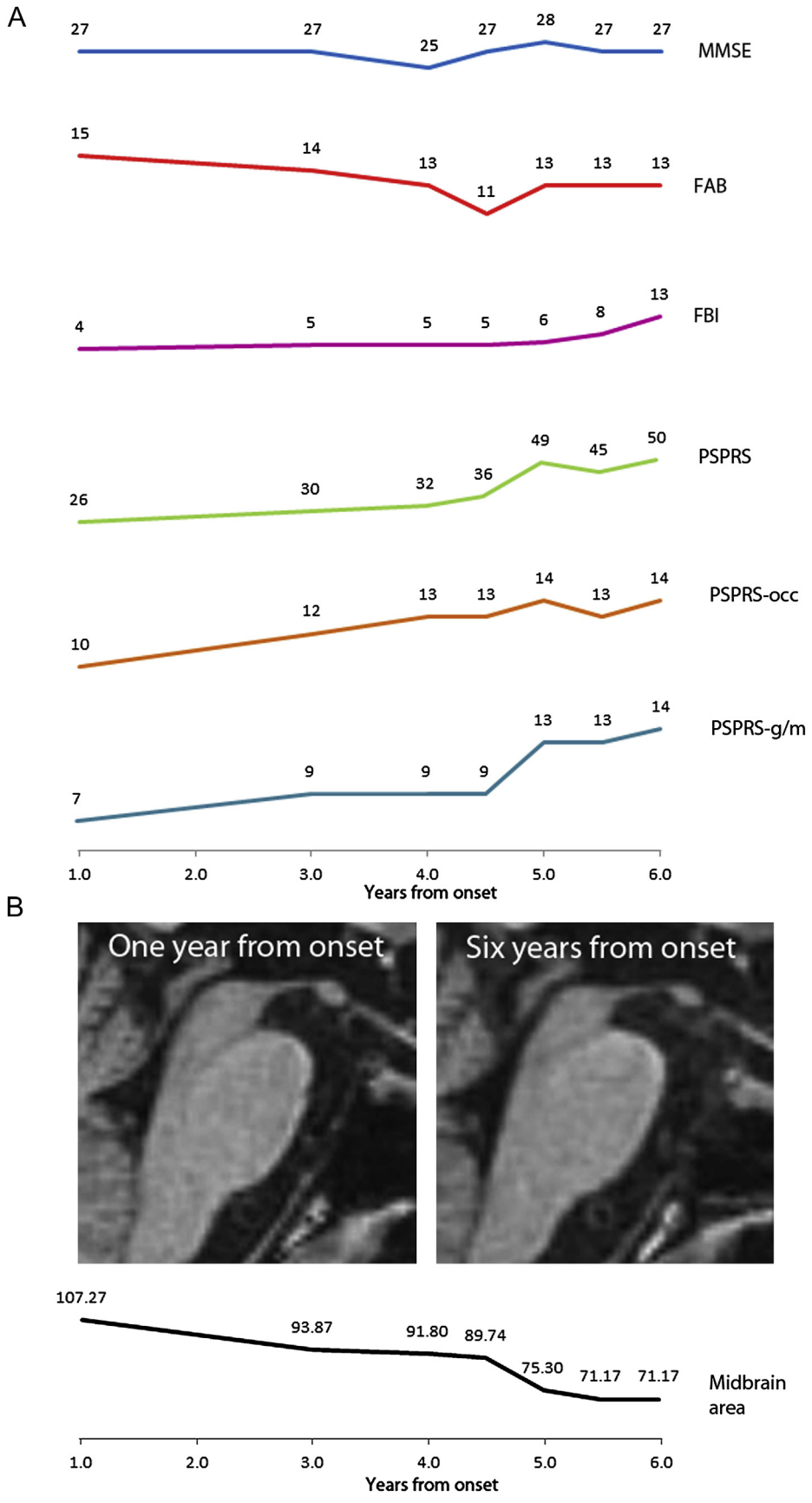

Fig. 1. A. Demonstrating changes in bedside test scores from initial presentation ~1-year after onset to ~1-year prior to death (total time of 5 years). Tests include: the Mini-Mental State Examination (MMSE) a measure of global cognitive function; the Frontal Assessment Battery (FAB) a measure of executive function; the Frontal Behavioral Inventory (FBI) a measure of behavioral dyscontrol; the Progressive Supranuclear Palsy Rating Scale (PSPRS) a test of global disease severity, the Ocular Motor sub-scale of the PSPRS (PSPRS-occ.) a measure of ocular motor function and the gait/midlines subscale of the PSPRS (PSPRS-g/m) a measure of gait and posture impairment. B) Demonstrating atrophy of the midbrain with quantitative midbrain area measurement using the Analyze Software, showing a loss of 33.7% of midbrain area from initial presentation 1-year after onset to 1-year before death.