Movement Disorders
CLINICAL PRACTICE

CASE REPORT

MAPT-Associated Familial Progressive Supranuclear Palsy with Typical Corticobasal Degeneration Neuropathology: A Clinicopathological Report

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Corticobasal degeneration (CBD) is a rare, 4-repeat (4R) tauopathy characterized by astrocytic plaque neuropathology. Although ~25% of sporadic CBD cases present with progressive supranuclear palsy-Richardson's syndrome (PSP-RS),[1] only one other case of microtubule-associated protein tau gene (*MAPT*)- related CBD with a PSP-like phenotype has been reported.[2] We aim to highlight important issues regarding the classification of *MAPT*-associated tauopathies and the implications for clinical research.

Case Report

This left-handed man presented age 42 with a 9 month history of difficulty focusing on near objects and unsteadiness causing one fall. He had been treated with sertraline for depression 6 months earlier. There was an autosomal dominant family history of young-onset PSP-RS with associated behavioral symptoms and a L284R *MAPT* mutation was identified in his mother (Fig. 1).[3] Limb rigidity was detected 1 year later and a DaTscan showed severe bilateral nigrostriatal dopaminergic deficiency. He did not benefit from ropinirole and within 2 years of onset, he was having recurrent falls, trouble with manual dexterity and behavioral change characterized by apathy, irritability, obsessive behavior and disinhibition manifesting as blunt jokes. He also developed difficulty with multitasking suggestive of executive dysfunction. On examination, there was frontalis overactivity, a supranuclear gaze palsy, mild dysarthria, symmetric upper limb hypokinesia and increased tone, and positive palmomental reflexes. There was no limb ataxia, dyspraxia or dystonia. His gait was slow and rigid (Video 1). There were executive function deficits on neuropsychometry (Table S1) with mainly midbrain and very mild frontal and parietal atrophy on neuroimaging (Fig. 1). The phenotype was consistent with the movement disorder society criteria for probable PSP-RS[4] and he was confirmed to have the same *MAPT* mutation as his mother. He participated in the PROgressive Supranuclear Palsy CorTicoBasal (PROSPECT) and GENetic Frontotemporal Dementia Initiative (GENFI) studies and completed 52 weeks of placebo on the Gosuranemab tau antibody trial (Biogen). Over the final year of his illness he developed severe dysarthria, dysphagia and neck rigidity that was unresponsive to levodopa. He died age 45 following a disease duration of 4 years.

A neuropathological examination was undertaken including an evaluation by a second neuropathologist blinded to the clinical history (TR). Macroscopic examination demonstrated marked atrophy of the subthalamic nucleus, pallor of the substantia nigra and locus coeruleus and reduction in size of the dentate nucleus (Fig. 2). Histological examination revealed neuronal and glial 4R tau pathology, with frequent astrocytic plaques typical of CBD (Fig. 2). CBD pathology was most prominent in the posterior frontal lobe, deep gray nuclei and tegmental regions of the brainstem. In addition, there were rare grain-like inclusions in the hippocampus, deep gray nuclei, and midbrain and pontine tegmentum. Notably, histological examination showed no evidence of tufted astrocytes—PSP hallmark pathology. Alzheimer's type neurofibrillary tangle tau pathology in the medial temporal

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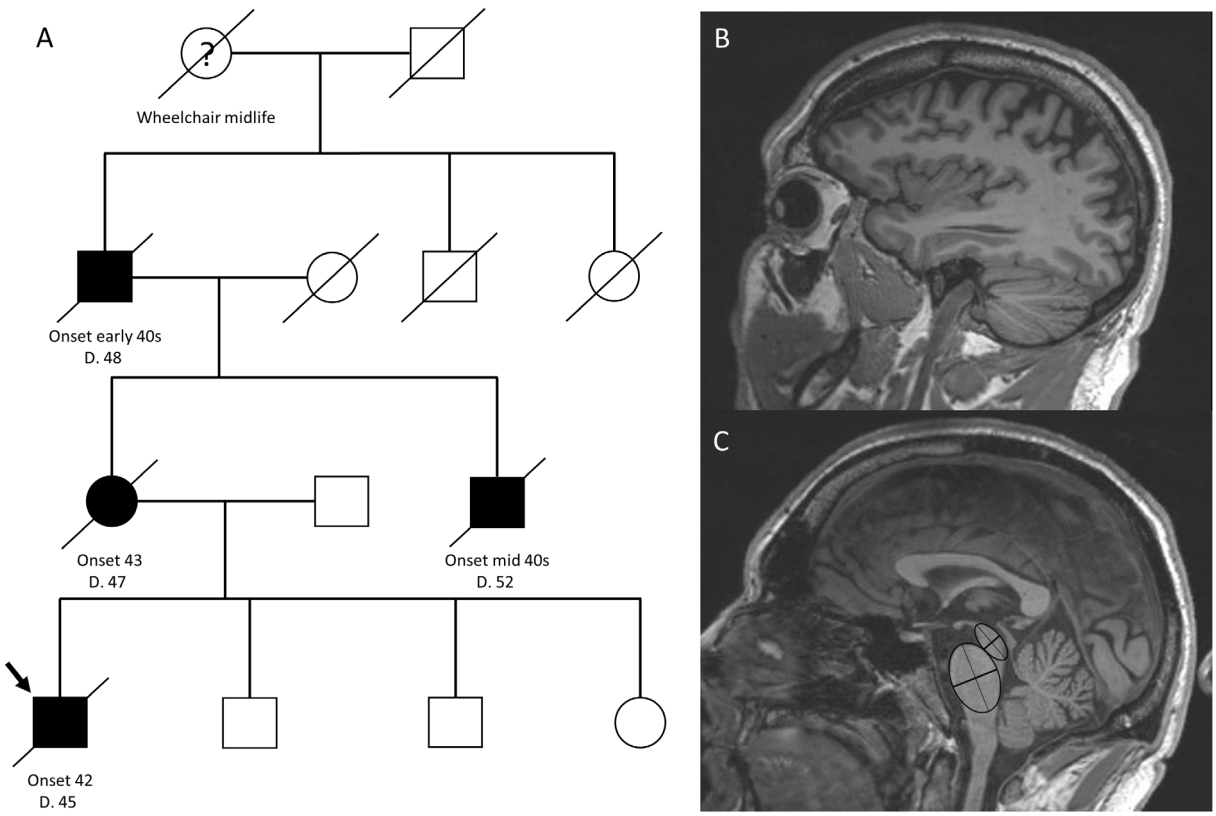

Figure 1. Pedigree chart (**A**) Sagittal T1-weighted MRI of the brain showing very mild cortical atrophy (**B**) and midbrain atrophy as indicated by a pons to midbrain ratio of 0.45 (**C**).

VIDEO 1. Physical examination recorded approximately 2.5 years after the onset of symptoms. The patient has prominent frontalis overactivity and mild dysarthria. His range of vertical pursuit eye movements is mildly restricted, and he has marked difficulty generating vertical saccades when asked to quickly look from the horizontal plane to a target above (examiner's fist). He walks with slow, short strides and turns around "en bloc." His arms are held rigidly by his sides and do not swing while walking. There is no retropulsion on the pull test.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13706

lobe corresponded to Braak and Braak stage II at most. There was no amyloid-β pathology, indicating no evidence of Alzheimer's disease neuropathological change. There was no limbic TDP43 proteinopathy or α-synuclein pathology in the brainstem or limbic regions examined.

Discussion

This case highlights the controversial issue of whether the histological features of *MAPT*-associated familial tauopathies are the same, similar or distinct from their sporadic counterparts.[5–7] The glial and neuronal tau pathology seen in this case was indistinguishable from sporadic CBD, even though the clinical phenotype and pattern of regional brain atrophy were typical of PSP-RS. Although most *MAPT*-associated tauopathy cases can be shoehorned into a specific frontotemporal lobar degeneration-tau subtype, these cases often, albeit not always as reported here, have atypical histological characteristics in terms of the morphology or 3R/4R tau isoform composition of cellular inclusions.[8,9] Moreover, neuropathological findings can differ between and within families with the same mutation.[5] As previously suggested,[5,7] using the term frontotemporal dementia and

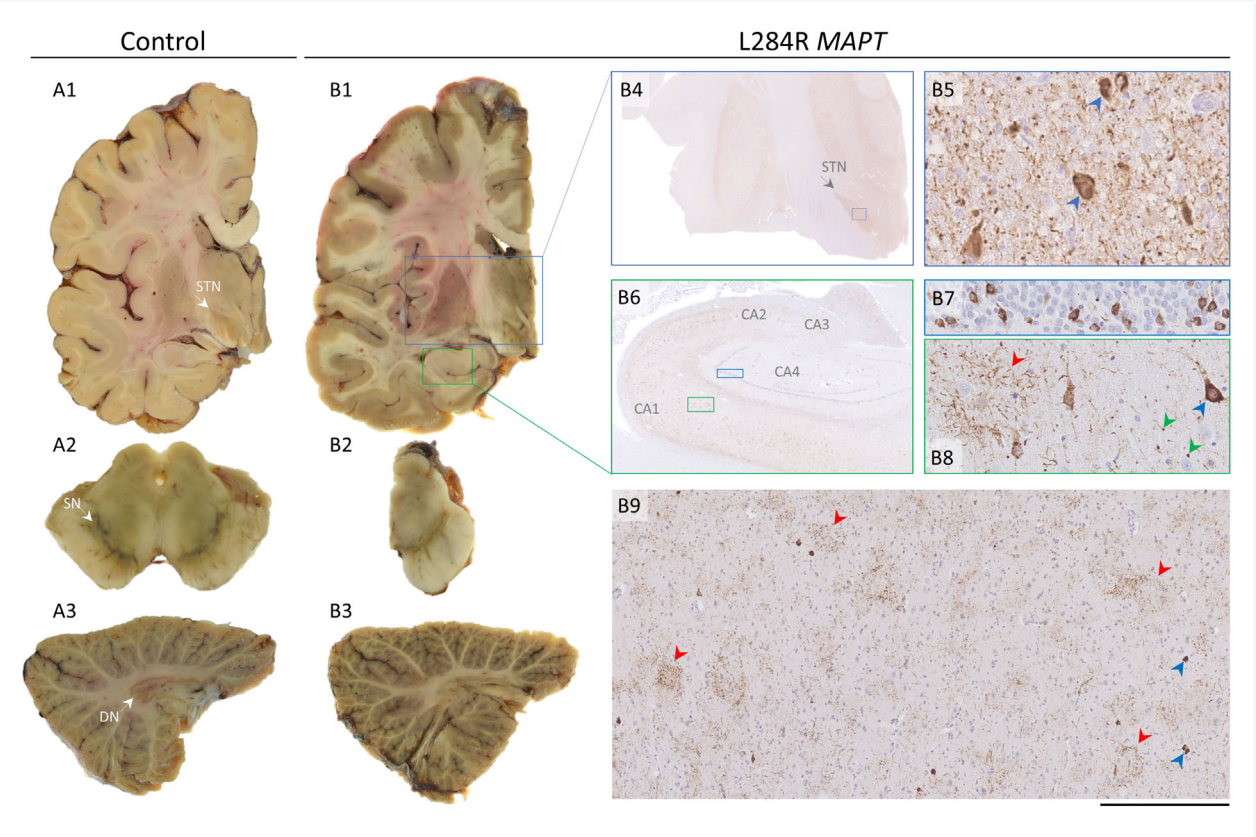

Figure 2. Macroscopic and microscopic pathology. Compared to the macroscopic appearances of a non-neurodegenerative control case (**A1–A3**), there is severe atrophy of the subthalamic nucleus (STN) (**B1**) and substantia nigra (SN) (**B2**) as well as mild atrophy of the dentate nucleus (DN) (**B3**). Immunostaining for phosphorylated tau (AT8, MN1020, 1:600; Invitrogen) shows dense glial and neuronal tau pathology across the putamen, globus pallidus, thalamus and STN (**B4**) including densely packed threads and globose tangle (blue arrowheads) pathology in the STN (**B5**). Abundant hyperphosphorylated tau pathology is also seen in the hippocampus (**B6**). In the dentate gyrus (blue rectangle in B6) this comprises frequent pre-tangles (**B7**), while in the CA1 region (green rectangle in B6), there are also occasional astrocytic plaques (red arrowhead) and occasional grain-like inclusions (green arrowheads) seen against a fine meshwork of threads, pre-tangles and tangles (**B8**). Frequent, pan-cortically distributed astrocytic plaques (red arrowheads) along with occasional pre-tangles, tangles and threads are seen in the frontal cortex (**B9**). Examination of the brain shows no α-synuclein, amyloid-β or TDP43 pathology (not shown). Scale bar: 15 mm in B4; 100 μm in B5; 4 mm in B6; 150 μm in B7 and B8; and 380 μm in B9.

parkinsonism linked to chromosome 17 (FTDP-17) to describe *MAPT*-associated tauopathies should be avoided because the progranulin gene, which is associated with TDP43 proteinopathy, is also located on chromosome 17. However, categorizing *MAPT* cases based on the sporadic tau inclusion morphology they resemble may also fail to highlight atypical histological features in some cases. In terms of structure-based classification, the tau filament structures identified from one intron 10 + 16 and two intron 10 + 3 *MAPT* cases were all identical to that of sporadic argyrophilic grain disease, consistent with the presence of argyrophilic grains in the +3 cases but not the astrocytic plaque-like pathology in the +16 case.[10] Whilst phenotypic variability is determined by regional involvement of neuropathology, the molecular basis for cellular tau inclusion heterogeneity is unclear. It may, amongst other reasons, be influenced by the variable involvement of tau produced by the non-mutant allele in the misfolding process and as yet unidentified or poorly characterized genetic and epigenetic factors.[8] These issues underline several challenges to the field including the use of transgenic animal models for studying sporadic tauopathies and identifying homogeneous patient cohorts for clinical trials as exemplified here.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,

C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

P.W.C.: 1A, 1C, 3A.
R.F.: 1C, 3B.
M.T.J.: 1C, 3B.
E.J.: 1C, 3B.
T.T.W.: 1A, 3B.
T.R.: 1C, 3B.
H.R.M.: 1A, 3B.
J.D.M.: 1A, 3B.
Z.J.: 1A, 1C, 3B.

Disclosures

Ethical Compliance Statement: Queen Square Brain Bank protocols have been approved by the NHS Health Research Authority, Ethics Committee London-Central (REC reference 18/LO/0721) and informed consent was obtained for publication. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Neuropsychometric testing.