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Three sib-pairs of autopsy-confirmed progressive supranuclear palsy

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Abstract

Objective—To describe the clinical, pathological, and genetic features of three sib-pairs of pathologically-confirmed progressive supranuclear palsy (PSP).

Methods—We searched the Mayo Clinic neurodegenerative diseases brain bank for cases of PSP in which more than one family member had pathologically-confirmed PSP. Clinical and pathological data were reviewed and all individuals were screened for mutations in *MAPT*, by sequencing exons 1, 7, and 9 – 13.

Results—We identified three sib-pairs of pathologically-confirmed PSP. Sufficient information was available to suggest an autosomal dominant inheritance in two. The mean age at symptom onset was 41 years in one pair, and 76 in the other two. The young onset pair had a p.S285R mutation in *MAPT*, but no mutations were detected in the other two.

Conclusions—All sib-pairs had typical pathological features of PSP; however, the age at onset of the sib-pair with *MAPT* mutation was significantly younger than sporadic PSP. Future studies are warranted to identify a possible genetic basis for PSP associated with late onset and typical PSP pathology.

Keywords

progressive supranuclear palsy; MAPT; p.S285R; tau pathology

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INTRODUCTION

Progressive supranuclear palsy (PSP) is a relatively rare neurodegenerative disorder [1]. Patients with PSP typically present with an akinetic-rigid syndrome, supranuclear gaze palsy, cognitive impairment, and falling that is present at the onset of their illness [2]. Pathological hallmarks are neurofibrillary tangles, coiled bodies, tufted astrocytes, and neuropil threads immunoreactive for 4-repeat tau [3]. In some familial and sporadic cases of PSP, mutations in the tau gene (*MAPT*) have been reported [4–7] of which only three cases fulfilled the pathological criteria for PSP [7–9].

Here, we describe three sib-pairs with pathologically-confirmed PSP, including one pair with a tau p.S285R substitution, previously identified as a probable *de novo* mutation in a Japanese 46-year-old man with clinically probable PSP [6]. We describe the clinical and pathologic features of 3 sib-pairs of pathologically-confirmed PSP and review the literature on *MAPT* mutations presenting with a PSP clinical syndrome.

METHODS

Genealogical and clinical studies

We extracted clinical information, including cardinal clinical features of PSP, from the available medical records and constructed pedigrees.

Pathologic analysis

All cases had a standardized neuropathologic evaluation as part of the brain bank for neurodegenerative diseases at the Mayo Clinic Jacksonville. All cases had semiquantitative assessment of neuronal and glial tau pathology with immunohistochemistry for phospho-tau (CP-13; mouse IgG1, 1:1000), as well as screening for other pathologies with routine histologic methods, as well as thioflavin-S fluorescent microscopy and immunohistochemistry.

MAPT mutation screening

Genomic DNA was isolated from brain tissue using the Gentra Puregene kit (Qiagen, Venlo, Netherlands). Polymerase chain reactions (PCR) were performed by using primer sets designed to flank intronic sequences of exons 1, 7, and 9 through 13 and labeled with unique M13 sequences to facilitate sequencing. Purified PCR products for each exon were sequenced on both strands using M13 primers and Big Dye Cycle Sequencing chemistry (Life Technologies, Carlsbad, CA). Sequencing reactions were run on an ABI3730xl Genetic Analyzer and data were analyzed using Sequencher 4.5 software (Gene Codes, Ann Arbor, MI).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Mayo Clinic IRB Committee. Informed consent was obtained from living participants. Autopsies were performed after informed consent by the legal next-of-kin.

RESULTS

Clinical descriptions

We identified three sib-pairs with pathologically-confirmed PSP in independent families (Fig. 1A). In two families (Families A and C), autosomal dominant inheritance was possible. The mean age at symptomatic onset was about 64 years, but with a wide range from 40 to 79 years. The mean disease duration was approximately 5 years, with a range from 3 to 7 years. All cases were clinically diagnosed as PSP during the course of their illnesses. Detailed clinical findings of Cases 3, 4, 5, and 6 are available in the esupp Details of Clinical and Pathological Findings.

Clinical vignettes of Cases 1 and 2

Family A—Case 1 was a male who developed symptoms at age 40. He presented with dystonia and supranuclear gaze palsy during the course of his illness. A brain MRI obtained most likely at the beginning of the course of his illness was normal. He was clinically diagnosed as having PSP. He died at age 44. After his death, his brother (Case 2) developed symptoms of the disease and brought a VHS video tape to his doctor that taken when Case 1 was in the final stage of his illness. In the video, Case 1 had an opisthotonic posturing of the neck, a fixed open posture of the mouth with deep breathing, and flexed, dystonic posturing of the limbs. His eyes were fixed in mid-position.

Case 2 was the younger brother of Case 1 and developed his symptoms at age 41. He initially presented with unsteadiness of gait; however, he did not complain of falling. He had a propensity to lean forward when attempting to walk or move about. Subsequently, he developed generalized slowness. He also reported difficulty moving his eyes. Eventually his speech became slower and softer, and he developed emotional lability. On neurological examination at age 42, his mental status was intact. He had a mixed spastic-hypokinetic dysarthria and a fixed, staring facial expression. Eye blink frequency was markedly reduced and very slow. Saccadic eye movements were essentially absent. He had limited upgaze and absent down gaze. He had difficulty reversing the laterality of his gaze. Oculocephalic reflexes were intact. He had a moderate degree of left-side predominant bradykinesia and marked generalized rigidity, most prominent in his neck. Alternating movements in all four limbs were rapid but of small amplitude. Tendon reflexes were exaggerated throughout; extensor plantar reflexes were absent. Posture was erect; gait was slow and slightly wide based, with normal arm swing. On the pull test, he required a few steps to recover. He was clinically diagnosed with PSP. Amantadine (200 mg/day), ropinirole (3 mg/day), pergolide (2 mg/day), and pramipexole (3 mg/day) provided no benefit. He died at age 44.

The maternal grandfather (I-1) of Cases 1 and 2 developed memory impairment at age 65 and died at age 68 with a diagnosis of Alzheimer's disease (AD). The mother (II-4) of Cases 1 and 2 developed symptoms at age 46. Her disease course was reported to be quite similar to that of Cases 1 and 2, and she was diagnosed with PSP one year before her death. She died aged approximately 50 years.

Neuropathology

The pathology of the six cases is consistent with that of PSP. Five of the cases had concomitant AD-type pathology. Of the reviewed cases, only Case 5 had Lewy body (LB) pathology, showing moderate AD pathology (Braak stage IV-V) and LB pathology relatively restricted to the amygdala. None of the cases showed TDP-43 pathology. Detailed pathological findings of Cases 3, 4, 5, and 6 are available in esupp Details of Clinical and Pathological Findings.

Pathological vignettes of Cases 1 and 2

Family A

Case 1: The brain weighed 1,230 grams. Macroscopic examination revealed severe atrophy and a gray gelatinous consistency of the subthalamic nucleus. There was atrophy of the midbrain and loss of pigment in the substantia nigra.

Histologic examination revealed neuronal loss and gliosis in the globus pallidus, subthalamic nucleus, and substantia nigra. In the substantia nigra, the neuronal loss was most markedly visible in the ventrolateral cell groups. Tau immunohistochemistry revealed prominent tau-positive pathology in the motor cortex, basal ganglia, amygdala, basal nucleus of Meynert, ventral thalamus, subthalamic nucleus, midbrain tectum, oculomotor complex, red nucleus, substantia nigra, pons, medulla, and cerebellar dentate nucleus. AD type pathology was not prominent; LB pathology and TDP-43 positive inclusions were not seen.

The pathologic diagnosis was PSP with minimal concomitant AD pathology, tangles only (Braak neurofibrillary tangle stage II).

Case 2: The fixed left hemibrain weighed 670 grams and the calculated whole brain weight was 1340 grams. Macroscopic examination revealed a normal configuration of the cerebral hemisphere (Fig. 1B). There was severe atrophy of the subthalamic nucleus and midbrain (Fig. 1C). A marked decrease in pigment was seen in all regions of the substantia nigra and locus ceruleus (Fig. 1D). The superior cerebellar peduncle was attenuated (Fig. 1E). The cerebellar sections showed atrophy of the dentate nucleus and mild attenuation of the dentate hilus.

Histologic examination revealed neuronal loss and gliosis in the globus pallidus, subthalamic nucleus (Fig. 1F), and substantia nigra (Fig. 1G). In the substantia nigra, the neuronal loss was most visible in the ventrolateral cell groups. Tau immunohistochemistry revealed prominent tau-positive pathology in the motor cortex (Fig. 1H), basal ganglia (Fig. 1I), basal nucleus of Meynert, ventral thalamus, subthalamic nucleus (Fig. 1J), midbrain tectum, oculomotor complex, red nucleus, substantia nigra (Fig. 1K), pons, medulla, and cerebellar dentate nucleus. Alzheimer type pathology was not prominent; LB pathology and TDP-43 positive inclusions were not seen. The pathologic diagnosis was pure PSP.

Genetics

Genetic sequencing of *MAPT* revealed a tau p.S285R substitution in two siblings, Cases 1 and 2, from Family A. Mutations in *MAPT* were absent in the other two families.

The demographics and clinical and genetic findings of the six cases are summarized in esupp Table 1 and the characteristics of tau pathology are summarized in esupp Table 2. Details of neuronal loss, AD pathology, TDP-43 pathology, and other pathology were summarized in esupp Table 3.

DISCUSSION

The affected subjects from all three families displayed both clinical and pathological features of PSP. According to the research clinical criteria for PSP[2], only Case 6 met stringent criteria for probable PSP. Cases 2, 3, and 5 met criteria for possible PSP due to the absence of falls within the first year; however, Cases 2 and 5 did have gait impairment within the first year of symptomatic disease onset. Clinical details were sparse for Cases 1 and 4, but both had several features indicative of PSP during the course of their illness. Pathologically, all cases fulfilled the criteria for PSP.[10]

To date, 37 familial or sporadic PSP cases have been reported with *MAPT* mutations (Table 1) [4–7, 9, 11] [esupp e-reference]. Among these cases, 14 had confirmed pathology, and three cases [7, 9] fulfilled the NINDS pathological criteria for PSP [10]. It is noteworthy that most of the cases would be classified as having clinically possible PSP using research criteria, due to absence of early falls. Morris et al. [4] suggested that the absence of early falls might indicate the possibility of *MAPT* mutations in clinically diagnosed PSP. That concept fits with most of the reported PSP cases with *MAPT* mutations; however, a subset meets the more stringent criteria. Interestingly, more than half of the patients carrying the tau p.G303V substitution had falls within one year of symptomatic onset [11]. For patients with the tau p.R5L, p.S285R, and p.G303S substitutions, early falls also were a common feature [6, 7, 9]. In our cases with *MAPT* mutation, both affected siblings had a young age of onset. Additionally, the mean age at symptom onset of PSP syndrome patients carrying *MAPT* mutations is much earlier than that of sporadic PSP, which is generally between 60 and 70 years old. Given that PSP is a relatively rare disorder, familial PSP, which is estimated to be 15% of PSP cases [12], is rare in clinical practice. However, *MAPT* mutations could be considered in patients who present with an early-onset (less than age 50) PSP syndrome, regardless of the existence of early falls or a family history of a similar syndrome.

Ogaki et al. previously reported the tau p.S285R substitution [6] in a patient with clinically probable PSP and no family history of neurologic disease, which presumably represented a *de novo* mutation. The mutation was absent in 182 normal Japanese controls, and the site of the mutation was highly conserved. An exon-trapping analysis revealed that the tau p.S285R substitution produced a marked increase in the splicing of exon 10, which leads to overproduction of the 4-repeat tau isoform, which is a characteristic feature of PSP. Unfortunately, no autopsy was obtained for this patient.

Here we report the clinical, pathological, and genetic features of three sib-pairs of definite PSP in which one sib-pair carried the tau p. S285R substitution. This is the first study to describe siblings who had a *MAPT* mutation and were diagnosed with PSP. For the remaining two families (Families B and C) in which two sib-pairs had definite PSP, genetic testing excluded a *MAPT* mutation. Further research is needed to determine whether the PSP in Families B and C has a genetic etiology. This investigation should include screening for mutations in other genes associated with tauopathies and next generation genetic methods to discover novel genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

We report the clinical, pathological, and genetic features of PSP in three sib-pairs.

One sib-pair carried the tau p. S285R substitution.

Our data suggests autosomal dominant inheritance.

PSP onset in the sib-pair with *MAPT* mutation occurred at a significantly younger age.

We are the first to present siblings who had a *MAPT* mutation diagnosed with PSP.

Figure 1. Pedigrees of three sib-pairs of progressive supranuclear palsy (A), and pathological features of Case 2 (B–K)

Standard pedigree symbols were used. Round symbols indicate females; squares indicate males; and diagonal lines indicate that the individual is deceased. Diamonds were used to disguise gender. +/- indicates heterozygous S285R mutation genotype. Numbers within the diamonds indicate the number of siblings. The solid arrowhead indicates the proband. * indicates autopsy patients. Macroscopic features of the left hemibrain (B), severe atrophy of subthalamic nucleus (arrow) (C), midbrain atrophy and substantia nigra pigment loss (arrow) (D), and superior cerebellar peduncle atrophy (arrow) (E). H&E staining shows

severe neuronal loss and gliosis in the subthalamic nucleus (F) and substantia nigra (G). Tau immunohistochemistry reveal typical tau pathology in the motor cortex (H), striatum (I), subthalamic nucleus (J), and substantia nigra (K).

Table 1

Summary of characteristics of PSP cases with *MAPT* mutations clinically presenting with PSP phenotype

MAPT mutation	Genetic position	Mode of inheritance	AAO (years)	DD (years)	Early falls	NINDS-SPSP Clinical Criteria	Neuropath. Criteria	References ^d
N279K	R5L	Sporadic	62	5	+	Possible	+	Pookaj, et al.
	AD	41	5	–	Possible	–	Wszolek, et al. ^{e1} Reed, et al. ^{e2} Tsuboi, et al. ^{e3} Ferman, et al. ^{e4} Slowinski, et al. ^{e5}	
		41	NA	–	Possible	NA		
		41	8	–	Possible	–		
		46	NA	–	Possible	NA		
		57	NA	+	Probable	NA		
		44	8	NA	Possible	–		
		42	8	NA	Possible	–		
		46	13	–	Possible	–		
	AD	40	7	–	Possible	–	Delisle, et al. ^{e6}	
NA		NA	–	Possible ^{**}	NA			
L284R	AD	47	Alive	–	Possible	NA	Soliveri, et al. ^{e7}	
		42	12	–	Possible	–	Ogaki, et al. ^{e8} Shimura, e al. ^{e9}	
		44	12	–	Possible	NA		
		46	Alive	_#	Possible	NA		
	Sporadic	41	10	_#	Possible	NA	Ogaki, et al. ^{e8}	
	42	12	_#	Possible	NA			
	43	8	_#	Possible	NA			
	AD	43	4	+	Probable	NA	Rohrer, et al. ^{e10}	
	Sporadic	46	3	+	Probable	NA	Ogaki, et al. ⁶	
	AD	40	4	NA	NA	+	Our cases	
41		3	_#	Possible	+			
delN296	Undetermined	38	Alive	–	Possible	NA	Pastor, et al. ⁵	
	AD	39	3	–	Possible	NA		
	NA	39	9	+	Probable	NA	Rossi, et al. ^{e11}	

MAPT mutation	Genetic position	Mode of inheritance	AAO (years)	DD (years)	Early falls	NINDS-SPSP Clinical Criteria	Neuropath. Criteria	References ^a
N296N		AD	44	Alive	+	Probable	NA	Syioya, et al. ^{e12} & Ogaki, et al. ⁶
P301L		AD	NA	NA	NA	NA	NA	Donker Kaat, et al. ^{e13}
G303S		AD	37	8	+	Probable	+	Ros, et al. ⁹
G303V		AD	37	2.5	+	Probable*	NA	Choumert, et al. ¹⁰
			51	6.5	NA	Possible	NA	
			39	5	+	Probable*	NA	
			42	3	-	Possible	NA	
			32	3.5	-	Probable*	-	
N305S		AD AD	55	7	-	-	NA	Stanford, et al. ^{e14} Halliday, et al. ^{e15}
			48	4	-	Possible	-	
			49	7	-	Possible	NA	
+3	Intron 10	AD	47	8	NA	Probable	-	Spina, et al. ⁸
+16			52	6	NA	NA	+	
		Sporadic	40	5	-	Probable	-	Morris, et al. ⁴

AAO=age at onset; AD=autosomal dominant; DD=disease duration; NA=not available; PSP=progressive supranuclear palsy;

* =the patient could be diagnosed as probable PSP according to the clinical criteria for PSP except for early symptomatic disease onset;

** = the patient could be diagnosed as possible PSP according to the clinical criteria for PSP except for early symptomatic disease onset;

[‡] =the patient presented with balance problem as an initial symptom; however, he had not had any falls during the first year after his symptomatic disease onset;

=unpublished data.

^aFor additional references please see esupp e-references.