Clinical/Scientific Notes

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SIMILARITIES BETWEEN FAMILIAL AND SPORADIC AUTOPSY-PROVEN PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is a relatively common neurodegenerative tauopathy clinically characterized by parkinsonism, axial rigidity, and supranuclear gaze palsy. Pathologic findings of PSP are neuronal loss, gliosis, and neurofibrillary tangles in basal ganglia, diencephalon, and brainstem; there is increasing recognition of clinicopathologic variants of PSP.[1]

PSP is usually a sporadic condition; however, there are reports of familial aggregation in PSP.[2] Recently, a genome-wide association study (GWAS) identified several genes associated with increased risk of PSP.[3] This report describes clinical, pathologic, and genetic differences in familial and sporadic autopsy-proven PSP.

Methods. We identified cases of autopsy-proven PSP with family history of neurodegenerative disease, including PSP, parkinsonism, or dementia from available medical records in the brain bank at Mayo Clinic in Jacksonville, FL. Cases considered to have a positive family history were those who had at least one first- or second-degree relative with parkinsonism or dementia. We excluded cases with pathogenic mutations in *MAPT*. All brains were acquired with appropriate ethical approval, and all autopsies were approved by legal next of kin. Available medical records were abstracted for clinical information in a consecutive series of cases from the period 1998 to 2008, including cardinal clinical features of PSP, such as parkinsonism and unexplained falls, as well as other notable neurologic findings. All cases had standardized neuropathologic evaluation as part of CurePSP brain bank, including assessment of neuronal and glial tau pathology with phospho-tau immunohistochemistry in 21 brain regions.[4] Atypical PSP included cases with extensive cortical involvement or paucity of tau pathology in cardinal regions.[1] For each case, DNA was extracted from frozen brain tissue and genotyped for *APOE* and *MAPT*. A subset of PSP cases (n = 375) was included in the CurePSP GWAS[3] (tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org). *MAPT* H1/H2 was determined from a single nucleotide polymorphism, rs8070723. For comparison, genotypes were available on healthy, living control subjects collected from neurologically normal family members or caregivers of patients with Parkinson disease followed at Mayo Clinic Florida.

Student t test was used to compare continuous variables. Fisher exact test or χ^2 test was used to compare group differences for categorical variables. Pathologic tau lesion scores were compared with the Mann-Whitney rank sum test. Statistical significance was considered for p values <0.05. Statistical analysis was performed with SigmaPlot version 11.0 (Systat Software Inc., San Jose, CA).

Results. Of the 375 PSP cases, 58 (15%) had a family member with clinical history of PSP, parkinsonism, or dementia. Eleven cases (3%) had a family member with clinical history of PSP. Table 1 summarizes select demographic, clinical, pathologic, and genetic features of familial and sporadic PSP. Pathologically, familial PSP had more frequent atypical pathology compared with sporadic PSP ($p = 0.004$). In most regions, the severity of tau lesion scores was lower in familial than sporadic PSP, although there were no significant differences after adjustments for multiple comparisons (tables e-1 and e-2). Table e-3 provides genotype and allele frequencies for familial and sporadic PSP for genome-wide significant single nucleotide polymorphisms from the CurePSP GWAS.

Discussion. We found very few differences in pathologic and genetic characteristics between familial and sporadic PSP. Moreover, on a range of clinical features (table 1), familial and sporadic PSP did not differ regardless of whether one used stringent or liberal criteria for defining familial PSP. We defined familial PSP when probands had either a first- or second-degree relative with either parkinsonism or dementia; however, we acknowledge the difficulty of defining familial PSP based solely on clinical criteria, given the increasing recognition of clinical heterogeneity of pathologically confirmed PSP.[1] In this study, we used different levels of stringency to overcome this weakness, by including dementia, parkinsonism, and the most stringent diagnosis, PSP, to define familial PSP.

Pathologically, we found that familial PSP tended to have less tau pathology compared with sporadic PSP. These results are contrary to those found in other familial neurodegenerative disorders, such as

Supplemental data at www.neurology.org

Table 1 Clinical, pathologic, and genetic information for familial and sporadic PSP

	Healthy controls	Sporadic PSP	Familial PSP (PSP, P, or D)[a]	Familial PSP (PSP or P)[a]	Familial PSP (PSP)[a]
Demographics					
Sex, male/total (%)		150/317 (47)	28/58 (48)	28/56 (50)	5/11 (45)
Age at onset of PSP, y (mean ± SD)		67 ± 8	68 ± 9	68 ± 9	67 ± 14
Disease duration, y (mean ± SD)		7.4 ± 3.4	7.4 ± 3.8	7.4 ± 3.9	7.2 ± 3.9
Age at onset of P, y (mean ± SD)		67 ± 8	68 ± 10	68 ± 10	67 ± 14
Neuropathology					
Braak stage, median (interquartile range)		2 (1–3)	1.5 (2–3)	2.5 (2–3)	2.5 (2–4)
Brain weight, g (mean ± SD)		1,166 ± 156	1,136 ± 152	1,145 ± 155	1,098 ± 182
Atypical PSP, n/total (%)		22/317 (7)	8/58 (14)	8/56 (14)	4/11 (36)[b]
Clinical signs and symptoms, n/total (%)					
Clinical diagnosis of PSP		281/314 (89)	50/58 (88)	49/56 (89)	11/11 (100)
Dementia		174/196 (89)	25/29 (86)	24/28 (86)	6/7 (86)
Frontal dysfunction		64/68 (94)	12/14 (86)	10/12 (83)	4/4 (100)
Personality change		150/173 (87)	22/26 (85)	21/25 (84)	4/5 (80)
Aphasia		55/83 (66)	12/18 (67)	10/16 (63)	3/4 (75)
Pyramidal sign		107/125 (86)	18/21 (86)	17/20 (85)	3/3 (100)
Genetics					
APOE, n	719	317	57	55	11
2 ε4:1 ε4:0 ε4, %	2:26:72	2:18:80[c]	0:23:77	0:20:80	0:19:81
ε4 (+):ε4 (−), %	15:85	11:89[c]	11:89	10:90	9:91
MAPT, n	714	190	50	48	6
H1H1:H1H2:H2H2, %	56:38:6	86:12:2[c]	98:2:0[c]	98:2:0[c]	100:0:0
H1:H2, %	75:25	92:8[c]	99:1[b,c]	99:1[b,c]	100:0

Abbreviations: D = dementia; *MAPT* = microtubule-associated protein tau; P = parkinsonism; PSP = progressive supranuclear palsy.
[a] Familial PSP (PSP, P, or D) = PSP with family history of PSP, parkinsonism, or dementia; familial PSP (PSP or P) = PSP with family history of PSP or parkinsonism; familial PSP (PSP) = PSP with family history of PSP.
[b] Significant difference ($p < 0.05$) is observed between familial and sporadic PSP.
[c] Significant difference ($p < 0.05$) is observed between healthy controls and PSP.

Alzheimer disease (AD); familial AD often has more severe pathology than sporadic AD.[5] Moreover, familial tauopathies due to mutations in *MAPT* invariably have severe tau pathology.[6] This unexpected finding may indicate that genetic factors other than *MAPT* may have an important role in familial PSP.

APOE ε4 allele frequency was significantly lower in PSP compared with controls, a finding that was noted in the CurePSP GWAS.[3] In previous studies, presence of the ε4 allele has been associated with increased AD pathology in PSP.[7] Familial PSP had a stronger association with the *MAPT* H1 haplotype than both controls and sporadic PSP. This finding suggests that *MAPT* H1 affects risk of familial PSP, but not necessarily the severity of tau pathology.

Although this report is based on a large series of autopsy-confirmed PSP, it is still underpowered to find small differences between familial and sporadic PSP, especially for genetic factors with small effect sizes, such as non-*MAPT* genes implicated in the CurePSP GWAS.[3]

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