OBSERVATION

Clinical and Pathologic Evidence of Corticobasal Degeneration and Progressive Supranuclear Palsy in Familial Tauopathy

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Background: Corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) are neurodegenerative tauopathies. Sporadic and familial cases of PSP and CBD have been noted, but both have not been reported in a single family.

Objective: To describe the clinical, oculomotor, balance, functional imaging, histopathologic, and genetic studies in a family with CBD and PSP.

Design: A report of the clinical and pathological features in a familial tauopathy.

Setting: University of Minnesota.

Patients: We evaluated 2 siblings and clinically assessed 20 additional family members.

Main Outcome Measures: Demonstration of salient features in deceased and living family members.

Results: Histopathologically confirmed CBD in one sibling and PSP in another deceased sibling were demonstrated; both had clinical features of corticobasal syndrome. In addition, 3 siblings had probable PSP by clinical criteria. Genetic studies of 4 affected family members demonstrated the H1/H1 haplotype but did not reveal pathogenic *tau* mutations. The family history revealed consanguinity.

Conclusions: This is the first report, to our knowledge, of CBD and PSP in 2 individuals in a single family who presented with corticobasal syndrome and had other affected siblings with clinical PSP. Despite clinical and pathologic heterogeneity, a unifying genetic etiology appears likely in this familial tauopathy.

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CORTICOBASAL DEGENERATION (CBD) and progressive supranuclear palsy (PSP) are considered separate diseases with distinct diagnostic criteria.[1] Previously, CBD and PSP have not been reported in the same family. Both conditions exhibit phenotypic variability, even in different members of the same family.[2-5] Although clinically CBD and PSP may overlap, histopathologic features usually allow for a separation of the conditions.[6,7]

Genetic studies have not resolved the issue of pathogenesis of these 2 tauopathies. Several pedigrees have reported autosomal dominant transmission in PSP along with reduced penetrance and variable expressivity.[5] Presumed autosomal recessive inheritance has also been reported in families with PSP.[8] Rarely, pathogenic *tau* mutations have been described in familial PSP pedigrees, whereas most do not have *tau* mutations.[8,9]

Conrad et al[10] provided the first evidence of an association between the *A0* allele of the *tau* gene and sporadic PSP. The *A0* allele was later shown to segregate with a tau haplotype, designated H1.[11] Case-control studies have demonstrated a significant association between the H1 haplotype and both PSP and CBD.[11,12] The exact mechanism by which the H1 haplotype confers an increased risk for these conditions is not known, and postmortem studies suggest that the tau protein appears to undergo distinct processing in each of these 2 conditions.[13] Therefore, additional genetic or environmental factors may interact to dictate the exact pathologic findings.

METHODS

We evaluated clinical features, laboratory findings, and *tau* pathologic features of 2 siblings (patients VI:1 and VI:4) and clinically assessed 20 additional family members. The study

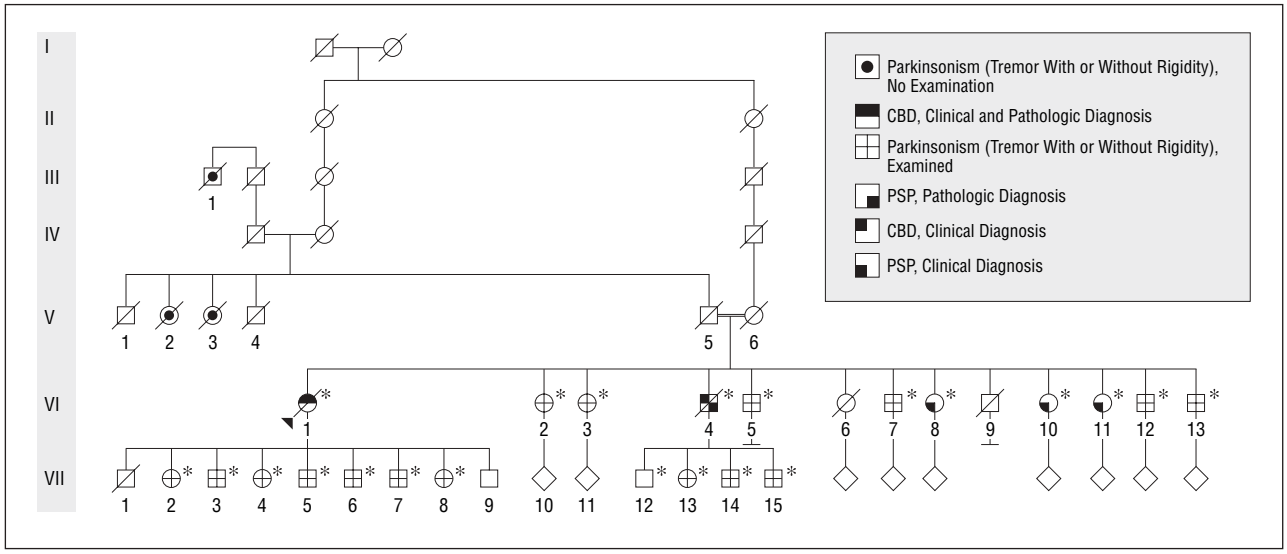

Figure 1. Family pedigree. CBD indicates corticobasal degeneration; PSP, progressive supranuclear palsy. Asterisk indicates patient was examined.

Table 1. Clinical Histories of 2 Sibling Probands With Tauopathy[18]

Finding	Patient 1 (VI:1)	Patient 2 (VI:4)
Clinical diagnosis	Corticobasal syndrome	Corticobasal syndrome
Sex	Female	Male
Age at symptom onset, y	57	63
Duration of illness, y	8	4
Initial symptom	Right leg clumsiness	Left hand clumsiness
Asymmetry	Yes	Yes
Rigidity or bradykinesia*	Yes	Yes
Dystonia*	Yes, right arm	Yes, left arm
Action tremor*	Yes	Yes
Myoclonus*	Yes	Possibly
Alien limb*	Yes	Possibly
Ideomotor apraxia*	Yes	Yes
Aphasia	Possibly	Possibly
Blepharospasm	Yes	Yes
Ophthalmoparesis	Yes	Yes
Apraxia of eyelids	Yes	Yes
Dysarthria	Yes	Yes
Pseudobulbar	Yes	No
Grasp reflexes	Yes	Unknown
UMN signs	Yes	Possibly
Quadriparesis	Yes	Yes
Response to dopamine	None	None
MRI white matter changes	Yes	Yes

Abbreviations: MRI, magnetic resonance imaging; UMN, upper motor neuron signs.
*Major diagnostic features of corticobasal syndrome.

was approved by the institutional review board at the University of Minnesota.

Two living siblings (patients VI:8 and VI:10, **Figure 1**) underwent brain magnetic resonance imaging (MRI) studies, genetic evaluations, and balance testing. Postural stability was evaluated using the Equitest protocol.[14] Patient VI:8 also underwent ocular motor testing and fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning.[15] Horizontal and vertical components of eye movements were recorded using the magnetic search coil technique.[16] A third sibling has recently presented with similar clinical findings (VI:11).

Genetic testing for *tau* mutations was conducted on paraffin-embedded brain tissue samples from the deceased patients (VI:1 and VI:4) and genomic DNA from patients VI:8 and VI:10 using polymerase chain reaction methods.[17]Exons 9, 10, 11, 12, and 13 of the *tau* gene were amplified using primers complementary to intronic sequences and sequenced using internal primers. The dinucleotide repeat in the intron downstream of *tau* exon 9 was also analyzed, as described elsewhere.[10]

PATIENTS

Relevant family history is illustrated in Figure 1. Patient VI:1 developed symptoms at 58 years of age, with right arm dystonic posturing. Ideomotor apraxia, generalized rigidity, supranuclear ophthalmoparesis, and blepharospasm were noted in subsequent examinations, and ultimately the patient became quadriparetic. After 8 years of symptoms, the patient died.

Patient VI:4 presented at 63 years of age with dystonia of his left arm. Blepharospasm with apraxia of eyelid opening was noted, as were generalized rigidity, ideomotor apraxia, and vertical ophthalmoparesis. The patient died less than 4 years after the onset of symptoms.

Table 1 and **Table 2** summarize the clinical and pathologic findings of these patients. Clinically, both patients had features of CBD and symptoms that precluded a diagnosis of PSP by traditional criteria. Neuropathologically, patient VI:1, who had a longer course of illness, had features more consistent with CBD[19] (**Figure 2**A and B). The neuropathologic findings in patient VI:4 were more consistent with the changes seen in PSP[20] (Figure 2C and D). For both patients, the *A0/A0* genotype at the intragenic microsatellite marker of the *tau* gene was observed, but no pathogenic mutations were found in the sequenced regions of the *tau* gene.

OTHER FAMILY MEMBERS

As shown in Figure 1, 20 family members were examined in 1999 after the death of the second sibling. Of the 20 evaluated, 19 had subtle tremor with or without rigidity. In 2001 and 2002, patients VI:8 and VI:10 presented, and in 2004, patients VI:2 and VI:11 were again evaluated.

AFFECTED SIBLINGS

Case 1 (Patient VI:8)

Patient VI:8 was a 64-year-old right-handed woman with a 2-year history of bradykinesia, 2 unexplained falls when going up or down stairs, micrographia, neck stiffness, and depression. Her symptoms were "mild" and did not affect activities of daily living.

Her Mini-Mental State Examination (MMSE) score was 28 of 30. A cranial nerve examination showed slowed saccades, more marked vertically than horizontally, hypomimia, and hypophonia. A motor examination revealed mild rigidity in her neck and all extremities and a mild bilateral postural tremor of the upper extremities. Reflexes were hyperreflexic but symmetric in the upper extremities with unsustained ankle clonus. Extensor toe signs were absent. Postural stability was normal, and there was reduced right arm swing on ambulation.

An MRI study demonstrated periventricular white matter and basal ganglia T2-weighted signal changes consistent with small-vessel ischemic disease. An FDG PET scan demonstrated decreased glucose metabolism in the posterior frontal and parietal regions bilaterally, extending to the frontal operculum inferiorly.

Oculomotor testing showed hypometric saccades followed by a "staircase pattern" as the eye moved toward the target and an abnormal frequency of horizontal micro–square wave jerks, consistent with PSP. Quantitative posturography results were normal. Genetic testing revealed no pathogenic *tau* mutations and an *AO/AO* genotype at the intragenic microsatellite marker. Three years after presentation, she has increasing postural instability and saccadic impairment (more marked vertically) but no evidence of apraxia, an alien limb, or marked asymmetric parkinsonian signs.

Case 2 (Patient VI:10)

Patient VI:10 was a 59-year-old right-handed woman who presented for an evaluation because of concern about developing the familial tauopathy. She reported a 2-year history of slight difficulty walking and denied other characteristic symptoms. She had subtle cognitive and motor difficulties after a myocardial infarction and cardiac arrest (in 1986), which were stable until her recent symptoms developed.

Her MMSE score was 29 of 30. A cranial nerve examination demonstrated hypomimia and saccadic pursuit. A motor examination showed rigidity in the neck, arms, and legs and bilateral slowness of fine finger movements and foot tapping. An upper extremity postural tremor was noted bilaterally and was more prominent on the left side. She had normal postural stability and gait. A brain MRI study showed mild white matter hyperintensities and mild generalized cerebral atrophy, possibly greater in the frontal lobes. The results of the genetic testing were identical to those of patient 1. One year after presentation, she was noted to have increasing gait instability and impaired vertical saccades without profound asymmetric parkinsonism, alien limb, or apraxia.

Case 3 (Patient VI:11)

Patient VI:11 was a 61-year-old right-handed woman who requested an evaluation in 2004 because of concerns about the familial condition. Two years before consultation she had developed unsteadiness of gait, experienced several unexplained falls, developed slowness on the right more than the left side of her body, and noted softening of her voice.

When evaluated in 1999, she had a head tilt, mild rigidity of her limbs, and reduced arm swing. At her 2004 examination, her MMSE score was 27 of 30. She had saccadic pursuit movements with slowing of vertical saccades. Neck and appendicular rigidity was noted, with slightly greater rigidity and bradykinesia of her right than left arm. She had a subtle postural tremor and impaired postural reflexes. Imaging studies have not been performed.

Table 2. Neuropathologic Findings in 2 Probands With Tauopathy

Finding	Patient 1 (VI:1)	Patient 2 (VI:4)
Pathologic diagnosis	Corticobasal degeneration	Progressive supranuclear palsy
Neuronal loss and gliosis		
Frontal lobe	Moderate	Focally mild
Parietal lobe	Focally moderate	No
Putamen	Moderate	Mild
Globus pallidus	Moderate	Mild to moderate
Subthalamic nucleus	Mild	Mild
Substantia nigra	Severe	Severe
Cerebral white matter rarefaction	Yes	No
Cytologic pathologic findings		
Tufted astrocytes	No	Yes
Coiled bodies	Yes	Yes
Astrocytic plaques	Yes	No
Ballooned neurons*	Yes	No
Neuronal neurofibrillary tangles (corticobasal bodies)	SN	SN, GP, LC, RN, PAG, ION, STN, OMN

Abbreviations: GP, globus pallidus; ION, inferior olivary nucleus; LC, locus coeruleus; OMN, oculomotor nucleus; PAG, periaqueductal gray matter; RN, red nucleus; SN, substantia nigra; STN, subthalamic nucleus.
*Ballooned neurons were immunohistochemically positive for phosphorylated neurofilaments.

ADDITIONAL SIBLINGS AND FAMILY HISTORY

After the death of patient VI:4, in 1999, all surviving members of this sibship were examined, and DNA samples were collected. All 6 siblings had subtle parkinsonian features. Subsequently, 1 has been diagnosed elsewhere as having parkinsonism (VI:5), 1 continues to have mild parkinsonian findings (VI:2), and 2 have reportedly developed parkinsonism but have not yet been evaluated (VI:3 and VI:13).

Two family members in generation V (V:2 and V:3) were reported to have parkinsonism with similar features to patients VI:1 and VI:4, but no formal clinical or pathologic data were collected. An additional family member (III:1) was also reported to have parkinsonism. A review of marriage and birth records confirmed that patients V:5 and V:6 were consanguineous (third cousins). Evidence for additional loops of consanguinity in this family may exist, but these relationships have not been confirmed.

COMMENT

This family presents an opportunity to characterize factors that underlie PSP and CBD. The possibility of an environmental etiology seems unlikely in light of the preponderance of parkinsonian features in multiple

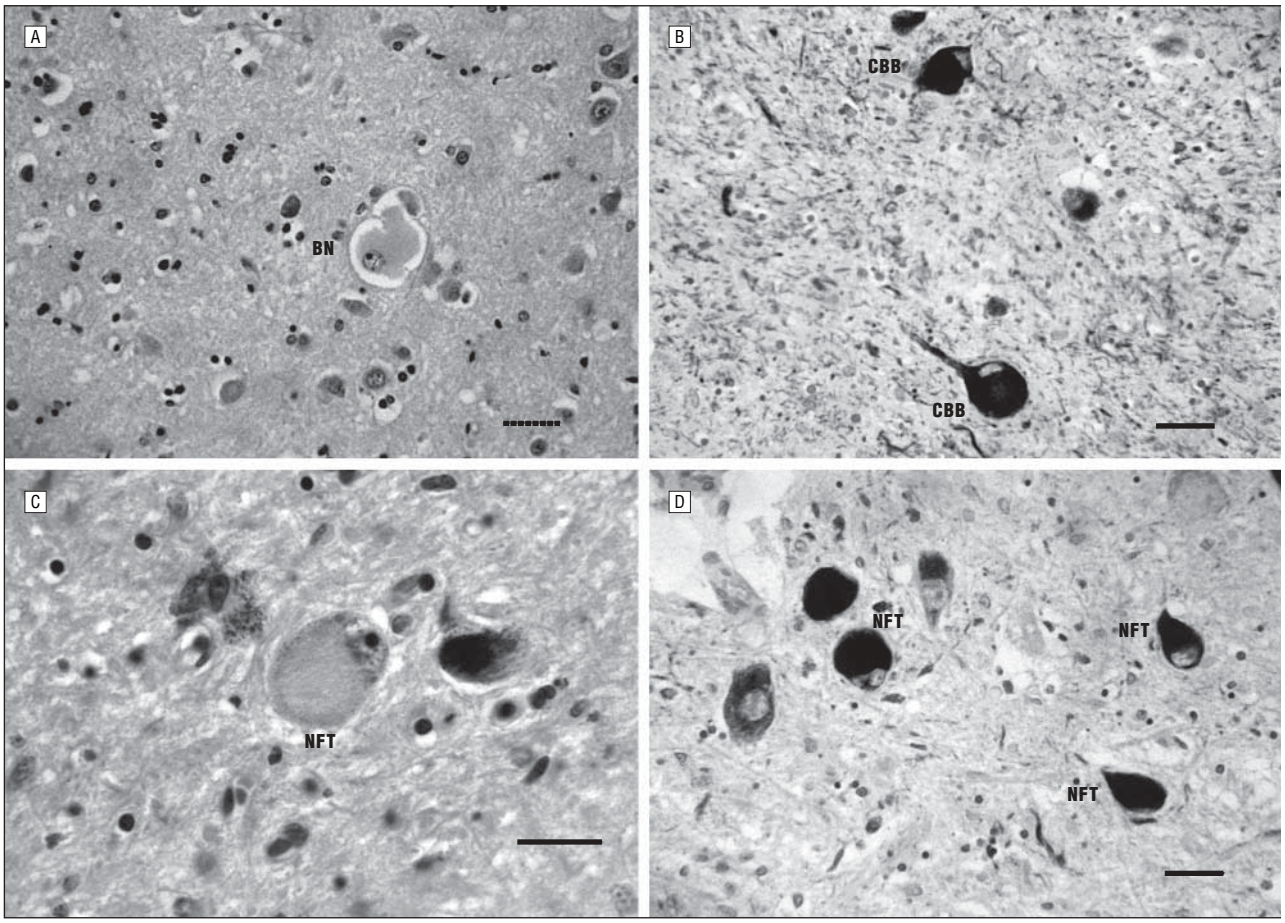

Figure 2. Histopathologic changes in patients with corticobasal degeneration (CBD) (VI:1) and progressive supranuclear palsy (PSP) (VI:4). A, Ballooned neuron (BN) in frontal cortex (hematoxylin-eosin, original magnification ×200). B, Glial plaque in cerebral cortex (*tau* immunohistochemistry with hematoxylin, original magnification ×200). C, Neurofibrillary tangle (NFT) in globus pallidus (*tau* immunohistochemistry with hematoxylin, original magnification ×300). D, Tufted astrocyte in striatum (*tau* immunohistochemistry with hematoxylin, original magnification ×200). CBB indicates corticobasal body. Scale bars=50 µm.

generations. Meanwhile, several factors complicate the search for a genetic basis. First, the segregation of the disease phenotype does not fit with classic inheritance patterns; this family may not have a single mendelian explanation. A somewhat analogous story relates to the parkin gene associated with familial parkinsonism, which has a clear manner of transmission.[21] Determining the mode of inheritance is further complicated by the uncertainty of clinical status for those with mild parkinsonism. Although some individuals have developed PSP, 1 individual has not experienced disease progression. It is also possible that this is not a single pathologic process; there may be 2 separate but related processes in this family. Nonetheless, despite differing clinical (corticobasal syndrome and PSP) and pathologic (CBD and PSP) features, a primary genetic basis remains the focus of research. To address this, the ongoing work is evaluating the *tau* locus, sequencing genes associated with familial parkinsonism, ascertaining a dosage effect of *tau*, and performing additional pathologic studies. Further characterization of this family may provide insights into the pathogeneses of sporadic CBD and PSP. Even if genetic markers remain out of reach, it is hoped that additional longitudinal studies with neuropsychological measures, brain MRI morphometry, and fluorodeoxyglucose positron emission tomography may prove useful as a means to predict risk of disease and allow for monitoring of disease progression.

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