

A Case of Dementia Parkinsonism Resembling Progressive Supranuclear Palsy Due to Mutation in the Tau Protein Gene

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Background: Few cases of frontotemporal dementia parkinsonism (FTDP-17) have been described in the literature. To our knowledge, this is the first Italian case.

Objective: To report a case of FTDP linked to chromosome 17, exhibiting progressive supranuclear palsy on initial examination.

Patient: A 50-year-old woman had a 4-year history of behavior changes associated with slowly progressive mental decay and parkinsonism, with poor balance, supranuclear vertical gaze palsy, and bradykinesia. The symptoms were not responsive to dopaminergic therapy. Her father had died at age 46 years after a 7-year history of parkinsonism, and her brother, diagnosed as having progressive supranuclear palsy, died at age 45 years.

Results: Magnetic resonance imaging showed mild midbrain atrophy, results of an electroencephalogram were normal, and cognitive evaluation showed moderate cognitive impairment, especially evident in the executive and attentional functions. Genetic testing revealed a tau gene mutation at codon 279 (AAT→AAG) of exon 10.

Conclusion: Exon 10 mutations (including the N279K mutation) that result in overproduction of the tau isoform with 4 microtubule binding motifs seem to be associated with a mainly parkinsonian phenotype at disease onset.

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PROGRESSIVE supranuclear palsy (PSP) is a sporadic neurodegenerative disease characterized by a tetrad of neurologic manifestations: supranuclear gaze palsy, pseudobulbar palsy, axial rigidity, and subcortical dementia.¹ Behavioral modifications and cognitive deficits are always present, especially in advanced disease.^{2,3} Pathologically, abundant neurofibrillary tangles, mostly of the globose type, consisting of abnormally hyperphosphorylated tau protein, are found in association with variable neuronal loss and gliosis. These alterations are typically present in the subthalamic nucleus, globus pallidus, striatum, thalamus, substantia nigra, superior colliculi, oculomotor nuclei, periaqueductal gray matter, locus ceruleus, pontine nuclei, and raphe nuclei.⁴ Neurofibrillary tangles may also be found in the prefrontal, premotor, and motor areas of the cortex.⁵ Tau-positive inclusions may also take the form of neuropil threads, tufted astrocytes, and coiled bodies.⁶

More recently, families with an apparently autosomal dominant form of PSP have been described.⁷ In addition, fami-

lies with frontotemporal dementia parkinsonism (FTDP-17) due to mutations in exons 9, 10, 12, or 13, or the intron following exon 10 of the tau protein gene on chromosome 17, have been reported.⁸ The N279K mutation in exon 10 has been identified in 4 families⁹⁻¹²; its phenotype is one of dementia and parkinsonism, which in some cases resembles PSP. To our knowledge, this is the first Italian patient with a family history of dementia and parkinsonism clinically resembling PSP and with the exon 10 N279K mutation.

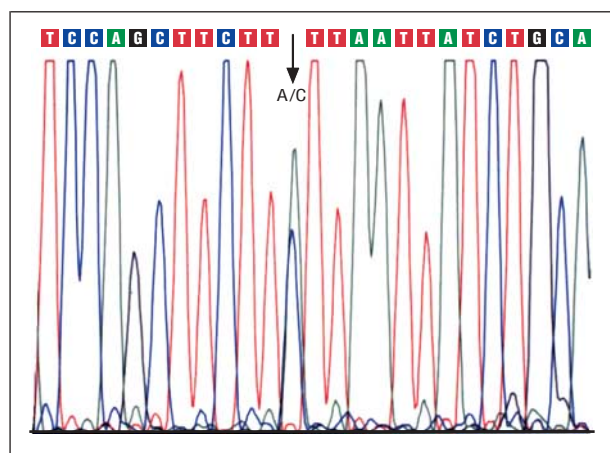
REPORT OF A CASE

A 50-year-old woman was admitted to our institute in December 2000 for behavioral changes, motor slowness, and disturbance of balance. Three years earlier, at the age of 47 years, subtle personality changes, including personal neglect and lack of initiative, became apparent and were unresponsive to antidepressants. Motor slowness, poor balance, and a tendency to fall appeared later. Disinhibition, hyperorality, and irritability, along with cognitive dysfunction manifesting as lack of attention, im-

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pairment of judgment, and cognitive flexibility, appeared 1 year before admission. At the time of admission, she also had dysphagia and urinary urgency and had been taking levodopa (600 mg daily) and ropinirole (0.75 mg daily) for 10 months, with no apparent benefit.

One of the patient's 2 brothers died at the age of 45 years in 1995. He had been admitted to another hospital in 1991 for symptoms that had manifested 3 years earlier, and was diagnosed as having clinically probable PSP. A review of his medical record showed global cognitive impairment with marked apathy and abulia, psychomotor slowness, axial rigidity, vertical oculomotor paresis, and a tendency to fall backwards. The patient's other brother was described as healthy and declined to be examined. The patient's father died at age 46 years after 7 years of a progressive illness diagnosed as parkinsonism. None of the father's brothers or sisters had any neurologic condition, and all died in old age.



A→C substitution on the antisense strand of exon 10, corresponding to T→G substitution of the coding strand, resulting in the N279K mutation.

Neurologic examination of our patient revealed unstable gait, stooped posture, poor balance with tendency toward en bloc backward falls, blank facial expression, supranuclear upward gaze palsy involving pursuit and saccades, dysphagia, dysarthria, moderately increased limb and neck muscle tone, bradykinesia, slight postural hand tremor, brisk tendon reflexes, and positive Babinski sign. On interviewing the patient, anosognosia, apathy, reduced spontaneous speech production, memory dysfunction, and palilalia became apparent.

Results of routine blood tests, electrocardiogram, chest x-ray, and electroencephalogram were normal. Cerebral magnetic resonance imaging with a 0.5-Tesla machine showed slight mesencephalic atrophy, moderately increased third ventricle size, and slight signal hyperintensity in the periaqueductal region. Positron emission tomography with 18 fluorodeoxyglucose showed hypometabolism in the mesial and dorsolateral frontal cortex bilaterally. A perineal electromyogram revealed chronic denervation of the external anal sphincter.

Genetic analysis was performed on the proband's DNA, extracted from peripheral lymphocytes. Exon 10 of the tau gene was amplified by polymerase chain reaction with flanking primers 5'-CGAGCAAGCAGC-GGGTCC-3' and 5'-GTACGACTCACACCACTTCC-3', using the following conditions: 95°C for 5 minutes; 95°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute, for 35 cycles. The polymerase chain reaction product was excised from 2.5% agarose gel after electrophoresis, purified with a silica matrix and sequenced in both directions by the dideoxy chain terminator method using an automated sequencer.

The sequence revealed a T to G substitution that resulted in the N279K mutation, giving rise to the substitution of lysine for asparagine (**Figure**). Analysis of exons 9, 12, and 13 showed normal sequences.

Results of Neuropsychologic Evaluation

Score	December 2000			June 2001		
	Crude	Adjusted	ES*	Crude	Adjusted	PE
MMSE	22	22.74	Deficit	15	15.74	Deficit
Digit span	4	4.25	2	4	4.25	2
Short tale	4	5.5	0	3	2.5	0
Word association learning	4.5	6	0		Not assessable	
Corsi span	2	1.75	0	2	1.75	0
Corsi supra span		Not assessable			Not assessable	
Phonemic fluency	4	10	0	3	10	0
Semantic fluency	11	15	0	9	15	0
Benton test		Not assessable			Not assessable	
Visual search test	23/60	22	0	20/60	19	0
Raven test		Test interrupted			Not assessable	
Nelson test (categories)	1	...	...	...	...	...
Nelson (perseverations)	11/11	100%	Perseveration		Not assessable	
Token test	20	19.75	0	15.5	15.25	0
Ideomotor apraxia	R 61/72	L 58/72	L probable deficit	R 62/72	L 53/72	R probable deficit
Constructive apraxia	8/14	7.75	0	3/14	2.75	0
Bucco-facial apraxia	20/20	...	4	19/20	18.75	2

Abbreviations: ES, equalizing test score; MMSE, Mini-Mental State Examination; ellipses, not applicable.

*Range, 0-4: 0 corresponds to a performance inferior to that of 5% of the population and 4 to a performance superior to that of 50% of the population; scores of 1, 2, and 3 refer to performances in between and are of equal population percentiles.

For neuropsychologic evaluation we used a battery of tests to assess global cognitive functioning (Mini-Mental State Examination and Raven test), verbal and spatial memory (short tale test, word association test, Corsi span, and supra-span), executive functions (semantic and phonemic fluency tests and the Nelson test for categorization and shifting ability), visuospatial abilities (Benton test), attention (visual search test), language comprehension (Token test), and apraxia (ideomotor, buccofacial, and constructive). The patient performed poorly on all tests.

A second examination 6 months later revealed urinary incontinence and worsened bradykinesia. There was also a marked deterioration in cognition, as revealed particularly by the appearance of spatiotemporal disorientation and a 7-point decrease in Mini-Mental State Examination score. Because of this deterioration, it was not possible to readminister many of the neuropsychologic tests (**Table**).

COMMENT

The characteristics of this patient are consistent with the diagnosis of probable PSP according to the clinical criteria of Litvan et al.¹ The alterations revealed by magnetic resonance imaging (mesencephalic atrophy) and positron emission tomography (frontal hypometabolism) also support the diagnosis of PSP.^{13,14} However, the early onset and rapid mental decay are uncommon in PSP, as are the upward rather than downward gaze palsy and the stooped posture rather than trunk hyperextension.

Four families with N279K mutations in exon 10 of the tau protein gene have been described so far, and in some cases, clinical phenotype and pathologic alterations were similar to those found in PSP, although the disease onset was early (around the fifth decade).⁹⁻¹² Another case that was clinically and pathologically consistent with PSP and had a silent mutation (S305S) in exon 10 has been described.¹⁵ This mutation did not result in amino acid substitution in the tau protein, but rather, resulted in increased production of the 4 repeat isoform of the tau protein. In all of these families, age and clinical presentation varied; in some patients, the onset was marked by frontal dementia; others had mainly parkinsonism and subsequent cognitive decay.

In view of the heterogeneity of clinical signs, particularly at the onset, it appears inappropriate to classify these cases as familial PSP; we prefer the term FTDP-17, suggested by Wszolek et al.¹⁶ A hyperphosphorylated tau protein was found in neuronal and glial cytoplasmic inclusions in all cases from the above families, studied at autopsy. This alteration is also a hallmark of sporadic PSP, corticobasal degeneration, Pick disease, and some other parkinsonism-plus diseases. Exon 10 mutations (including the N279K mutation)^{17,18} resulting in 4 repeat tau overproduction seem to be associated with a mainly parkinsonian phenotype at disease onset, as in our family. However, more cases need to be described before generalizing, since FTDP-17 is clinically heterogeneous. Why this characteristic form of degeneration affects differing neuronal populations even in family members with the same gene mutation is unclear. Presumably, other ge-

netic or environmental factors are involved the pathogenetic process.

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