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Clinical genetics of familial progressive supranuclear palsy

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Summary

Recent studies have shown that progressive supranuclear palsy (PSP) could be inherited, but the pattern of inheritance and the spectrum of the clinical findings in relatives are unknown. We here report 12 pedigrees, confirmed by pathology in four probands, with familial PSP. Pathological diagnosis was confirmed according to recently reported internationally agreed criteria. The spectrum of the clinical phenotypes in these families was variable including 34 typical cases of PSP (12 probands plus 22 secondary cases), three patients with postural tremor, three with dementia, one with parkinsonism, two with tremor, dystonia, gaze palsy and tics, and one with gait disturbance. The presence of affected members in at least two generations in eight of the families and the absence of consanguinity suggests autosomal dominant transmission with incomplete penetrance. We conclude that hereditary PSP is more frequent than previously thought and that the scarcity of familial cases may be related to a lack of recognition of the variable phenotypic expression of the disease.

Keywords: progressive supranuclear palsy; Steele–Richardson–Olzsewski syndrome; genetics; akinetic rigid syndrome; dementia

Abbreviation: PSP = progressive supranuclear palsy

Introduction

Progressive supranuclear palsy (PSP) is a neurodegenerative disease clinically characterized by a variable combination of akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and frontolimbic dementia. Pathological abnormalities include neuronal loss, gliosis and the presence of neurofibrillary tangles and neuropil threads, mainly in basal ganglia, diencephalon, brainstem and frontal and temporal lobes (Steele *et al*., 1964). Atypical cases with characteristic pathological findings but an incomplete clinical syndrome have been previously described (Hauw *et al*., 1994; Collins *et al*., 1995; Daniel *et al*., 1995; Litvan *et al*., 1996*a*; Verny *et al*., 1996).

The cause is unknown but toxic and infectious aetiologies have been considered, based upon the pathological similarities with post-encephalitic parkinsonism, metal poisoning and with the Parkinson–dementia complex of Guam (Jellinger, 1971; Steele, 1972, 1975; Jankovic, 1984; Kristensen, 1985; Jendroska *et al*., 1994; Lilienfeld *et al*.,1994). Because of the coexistence of cerebrovascular disease in some cases a vascular mechanism has also been postulated (Dubinsky and Jancovic, 1987; Winikates and Jankovic, 1994). PSP is still considered a sporadic disorder, despite a small number of recent reports suggesting familial clustering (David *et al*., 1968; Mata *et al*., 1983; Ohara *et al*., 1992; Brown *et al*.,

1993; Gazely and Maguire, 1994; Tetrud *et al*., 1994; de Yébenes *et al*., 1995; Golbe *et al*., 1995; Lanotte *et al*.,1996; Tetrud *et al*., 1996). In view of the few families reported it is not possible to decide whether familial and sporadic PSP are the same disease.

In this study we investigated our cases of PSP in order to describe familial aggregation, clinical phenotypes and pattern of inheritance.

Methods

A retrospective study of all patients with familial PSP seen by or referred to one of us (J.G.Y.) during the period 1991–97 was carried out. The index cases were seen at the Movement Disorders Clinic, Department of Neurology, Fundación Jiménez Díaz (five cases), the Institute of Neurology, Queen Square, London (two cases), Hospital General de Segovia (one case), Hôpital Neurologique, Lyon (one case), Columbia University, New York (two cases) and Kingston General Hospital, Ontario (one case). Review of medical records, professional or domestic videos, photographs, samples of hand writing, telephone calls and visits to the homes of the patients and relatives were undertaken by members of the research team when needed in order to evaluate secondary cases.

The diagnosis of PSP in a proband required either (i) pathology proven diagnosis according to international criteria (Hauw *et al*., 1994; Litvan *et al*., 1996*a*), (ii) the presence of the international clinical research criteria for the diagnosis of PSP (Litvan *et al*., 1996*b*) or (iii) in some cases, analysed retrospectively, with insufficient details in the available history to fulfil the international clinical research criteria, the diagnosis of PSP was accepted if the patients had at least five out of the seven most common clinical symptoms of the disease (bradykinesia, gait disturbance, supranuclear gaze palsy, dysphagia, dysarthria, axial dystonia or disabling mental changes with frontosubcortical characteristics) as described in a recent clinicopathological series (Daniel *et al*., 1995). The presence of these signs was determined clinically. Supranuclear gaze palsy was defined by saccades smaller than 15° in the vertical or horizontal plane. Whenever possible, in patients seen at Fundación Jiménez Díaz, supranuclear gaze palsy was confirmed by oculonystamographic analysis. Abnormal findings were defined by latency, velocity or accuracy of saccadic movements more than 2 SD away from the mean for that age group.

When the available information was insufficient to make a reliable diagnosis of PSP, but it was suggested by the relatives describing the phenotype as ‘similar’ or ‘the same’ as the proband, the individual was diagnosed as ‘likely PSP’. We respected the initial diagnosis of other neurological disorders including parkinsonism, dementia, etc. when there was not additional clinical information that allowed for reclassification.

We obtained information on all available or deceased first and second degree relatives (parents, brothers, sisters, uncles, cousins) of the probands when possible. Children of probands were excluded since they were too young to clinically express PSP.

Results

Description of the families

A brief description of the pedigrees is presented in Table 1 and Fig. 1 (relationship, age of onset, years of evolution, medical history and clinical diagnosis). Detailed clinical phenotypes and response to L-dopa therapy are described in Table 2.

Family 1

Proband, individual 1.III.12. This was a 57-year-old female who presented progressive difficulty in doing up buttons and turning in bed. She had a long history of smoking and hypercholesterolaemia. At the age of 60 her neurological examination revealed moderate axial and limb rigidity, and dystonia in the left arm. She was diagnosed as having Parkinson’s disease and treated with L-dopa, which improved her symptoms but induced akathisia and orolingual dyskinesias. She was then seen by one of us (J.G.Y.) at age 65. She complained of slowness, gait disturbance, speech problems with hypophonia and progressive dysphagia. A bruit was heard over the left carotid artery. Mental status and cranial nerves were normal with the exception of limitation of downgaze. She had dystonic posturing of the neck (anterocollis) and dystonic up-going toes. She showed severe, generalized akinesia and postural instability with a tendency to fall backwards. MRI of the brain was normal. She became unresponsive to L-dopa and pergolide and died at the age of 67.

The macroscopic examination of the brain revealed a pale substantia nigra. Light microscopy examination showed neuronal loss, gliosis and a high density of neurofibrillary tangles in the globus pallidus, putamen, subthalamic nucleus, substantia nigra and the inferior olivary nucleus. There were a moderate number of tangles in the neocortex (predominantly in anterior frontal and parietal regions), hippocampus, amygdala, nucleus basalis of Meynert and locus coeruleus. Tangles were also identified in both colliculi, peri-aqueductal region, red nucleus, dentate nucleus and oculomotor complex.

Individual 1.III.3. This was the first cousin of the proband, with a history of diabetes. His neurological disorder began with a progressive slowness of the left arm and leg when he was 68 years old. He was thought to have Parkinson’s disease and received treatment with L-dopa with improvement of his symptoms. At the age of 73 he was evaluated by one of us (J.G.Y.) and the neurological examination revealed slowness, clumsiness, severe dysphagia and diplopia. His physical examination revealed a bruit over the left internal carotid artery. Formal neuropsychological testing revealed bradyphrenia and abnormalities of executive memory and

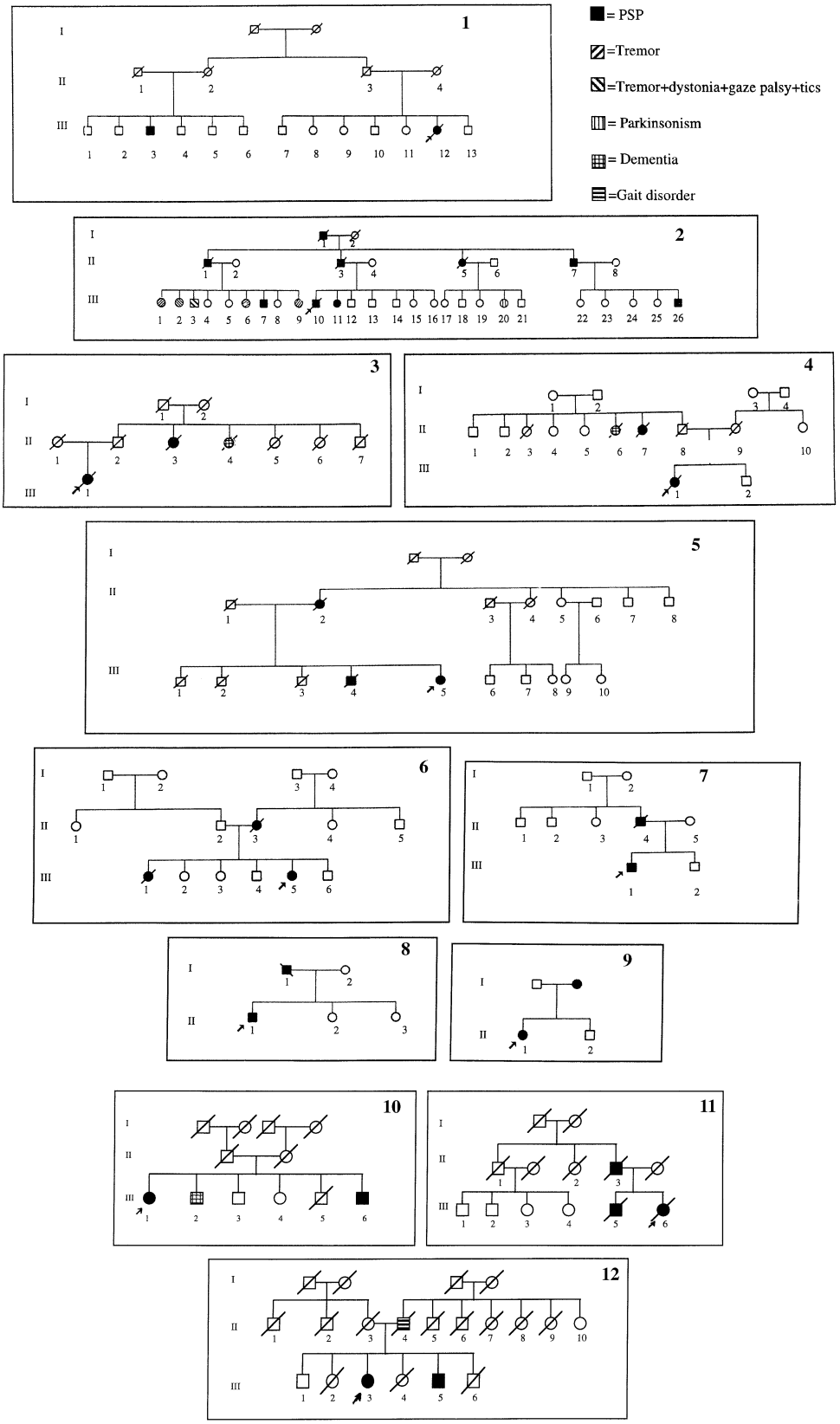

Fig. 1 Familial trees of families 1–12. Arrows point to probands.

Table 1 *Epidemiological data*

Family	Number		Sex	Age at onset (years)	Actual age (years)	Age at death	Actual diagnosis
1	III.12	Proband*	F	57	–	67	PSP
	III.3	Cousin	M	68	73	–	PSP
2	III.10	Proband*	M	53	–	59	PSP
	I.1	Grandfather	M	NA	–	NA	Likely PSP
	II.1	Uncle	M	NA	–	81	PSP
	II.3	Father	M	62	–	71	Likely PSP
	II.5	Aunt	F	70	–	84	PSP
	II.7	Uncle	M	NA	–	77	PSP
	III.1	Cousin	F	NA	73	–	Tremor
	III.2	Cousin	F	NA	72	–	Dystonia, tremor, gaze palsy, tics
	III.3	Cousin	M	NA	71	–	Dystonia, tremor, gaze palsy, tics
	III.6	Cousin	F	NA	63	–	Tremor
	III.7	Cousin	M	NA	60	–	Likely PSP
	III.9	Cousin	F	NA	52	–	Tremor
	III.11	Sister	F	53	59	–	PSP
	III.20	Cousin	F	63	71	–	Parkinsonism
	III.26	Cousin	M	59	NA	–	Likely PSP
3	III.1	Proband*	F	60	–	72	PSP
	II.3	Aunt	F	70	–	86	Likely PSP
	II.4	Aunt	F	70	–	74	Dementia
4	III.1	Proband*	F	62	–	71	PSP
	II.6	Aunt	F	91	–	96	Dementia
	II.7	Aunt	F	73	–	78	Likely PSP
5	III.5	Proband	F	75	86	–	PSP
	III.4	Brother	M	75	–	86	PSP
	II.2	Mother	F	73	–	83	Likely PSP
6	III.5	Proband	F	37	41	–	PSP
	II.3	Mother	F	41	–	45	PSP
	III.1	Sister	F	37	–	41	Likely PSP
7	III.1	Proband	M	55	59	–	PSP
	II.4	Father	M	70	–	83	PSP
8	II.1	Proband	M	49	68	–	PSP
	I.1	Father	M	NA	–	80	Likely PSP
9	II.1	Proband	F	67	69	–	PSP
	I.2	Mother	F	75	–	83	Likely PSP
10	III.1	Proband	F	70	77	–	PSP
	III.2	Brother	M	70	76	–	Dementia
	III.6	Brother	M	60	64	–	PSP
11	III.6	Proband	F	43	–	48	PSP
	II.3	Father	M	40	–	47	Likely PSP
	III.5	Brother	M	48	–	53	PSP
12	III.3	Proband	F	71	72	–	Likely PSP
	III.5	Brother	M	63	68	–	PSP
	II.4	Father	M	NA	–	49	Gait disorder

M = male; F = female; NA = not available; PSP = progressive supranuclear palsy. *Pathological confirmation.

learning suggestive of abnormal frontal function. He had limitation of voluntary eye movements in all directions, limb rigidity, hypokinesia and gait disturbance which was greater when turning. The retropulsion test was negative but he had bilateral Babinski signs. The patient was thought to have PSP. He informed us that two of his brothers had diplopia, but they have not been examined yet.

Family 2

Clinical data from the proband and other family relatives (individuals 2.III.10, 2.I.1, 2.II.1, 2.II.3, 2.II.5) have been reported elsewhere (de Yébenes *et al*., 1995). More recently we have personally examined 25 additional family members. The most important new findings are described below.

Individual 2.II.7. He died at the age of 77. His relatives said that he had 'the same' neurological syndrome as his brothers. He had parkinsonism, proven by pictures, and micrographia as shown by samples of his handwriting.

Individual 2.III.1. The 73-year-old female was a cousin of the proband, who suffered from postural hand and head

Table 2 *Clinical features*

No.	Akinesia	Gait	Gaze	Dysp.	Dysa.	Axial dystonia	Dementia	Other	Response to L-dopa	Initial diagnosis	Actual diagnosis
Family 1											
II.12	+	+	+	+	+	+	–	6	+	Parkinsonism	PSP*
III.3	+	–	+	+	+	–	+	.	+	Parkinsonism	PSP
Family 2											
III.10	+	+	+	+	+	+	+	.	+	PSP	PSP*
I.1	+	+	+	–	–	–	–	.	NA	NA	Likely PSP
II.3	–	+	+	+	–	–	–	.	NA	NA	Likely PSP
II.1	+	+	+	+	–	–	+	.	NA	NA	PSP
II.5	+	+	+	+	+	–	+	.	NA	NA	PSP
II.7	+	+	–	–	–	–	–	.	NA	NA	PSP
III.1	+	–	–	–	–	–	–	1	NA	Tremor	Tremor
III.2	–	–	+	–	–	–	–	1, 2, 3	NA	Dystonia	Dystonia, tremor gaze palsy, tics
III.3	–	–	+	–	–	–	–	1, 2, 3	NA	Tremor, dystonia	Dystonia, tremor gaze palsy, tics
III.6	–	–	–	–	–	–	–	1, 4	NA	Tremor	Tremor
III.7	+	+	+	–	–	–	–	1	NA	Tremor	Likely PSP
III.9	–	–	–	–	–	–	–	1	NA	Tremor	Tremor
III.11	+	+	+	+	–	+	–	6	+	Parkinsonism	PSP
III.20	+	+	–	+	–	–	–	1	NA	NA	PK
III.26	+	–	+	–	+	–	–	1	NA	NA	Likely PSP
Family 3											
III.1	+	+	+	+	+	+	+	2, 5, 6	+	Binswanger	PSP*
II.3	+	+	–	–	+	–	–	1	NA	Parkinsonism	Likely PSP
II.4	–	+	–	–	–	–	+	.	NA	Dementia	Dementia
Family 4											
III.1	+	+	+	–	+	–	–	.	–	Parkinsonism	PSP*
II.6	–	+	–	–	–	–	+	.	NA	Dementia	Dementia
II.7	+	+	–	+	+	–	–	.	NA	Parkinsonism	Likely PSP
Family 5											
III.5	+	+	+	–	+	+	+	6, 7	NA	PSP	PSP
III.4	+	+	+	+	+	–	+	2	–	PSP	PSP
II.2	+	+	–	+	–	–	–	.	NA	NA	Likely PSP
Family 6											
III.5	+	+	+	+	+	+	+	5, 6	–	PSP	PSP
II.3	+	+	+	+	+	–	–	1	NA	Parkinsonism	PSP
III.1	+	+	+	–	+	–	–	5	–	Parkinsonism	Likely PSP
Family 7											
III.1	+	+	+	+	–	+	+	5	NA	PSP	PSP
II.4	+	+	+	+	–	+	+	1, 5	–	Parkinsonism	PSP
Family 8											
II.1	+	+	+	+	+	+	+	1	+	Parkinsonism	PSP
I.1	+	+	–	+	–	–	+	.	NA	Dementia	Likely PSP
Family 9											
II.1	+	+	+	–	+	+	–	6	NA	PSP	PSP
I.2	–	+	–	+	+	–	+	1	+	Parkinsonism	Likely PSP
III.1	+	+	+	+	+	+	–	5, 6	–	PSP	PSP
Family 10											
1 III.2	–	–	–	–	–	–	+	.	NA	Dementia	Dementia
III.6	+	+	+	–	+	–	–	2	–	Gait disorder	PSP
Family 11											
III.6	+	+	+	+	+	–	–	.	NA	PSP	PSP
II.3	–	+	+	–	–	–	–	.	NA	CJD	Likely PSP
III.5	+	+	+	+	+	–	–	.	NA	PSP	PSP
Family 12											
III.3	+	+	+	–	–	–	–	.	–	NA	Likely PSP
III.5	+	+	+	+	+	+	+	1, 6	–	Neurodeg. dis.	PSP
II.4	–	+	–	–	–	–	–	.	NA	NA	Gait disorder

Gait = gait disturbance; gaze = supranuclear gaze palsy; dysp. = dysphagia; dysa. = dysarthria; + = present ; – = absent; 1 = tremor; 2 = cranial dystonia; 3 = tics; 4 = orofacial dyskinesia; 5 = apraxia of eyelid opening; 6 = limb dystonia; 7 = myoclonic jerks; PSP = progressive supranuclear palsy; CJD: Creutzfeldt–Jacob disease; neurodeg. dis. = neorodegenerative disease; NA = not available. *Pathological confirmation.

tremor, compatible with essential tremor and mild bradykinesia. At present she is considered not to have PSP.

Individual 2.III.2. The 72-year-old female had cranial dystonia (blepharospasm and dystonia in the lower half of the face), postural tremor, facial tics and vertical supranuclear gaze palsy. Her neuropsychological examination was normal.

Individual 2.III.3. The 71-year-old male had blepharospasm and oromandibular dystonia, facial and phonic tics, vertical upward gaze palsy, predominantly axial rigidity and postural tremor in the right arm. His oculo-nystagmographic examination revealed slow vertical saccades, with a marked decrease in range and precision, both with predictable and random stimuli, and breakdown of optokinetic nystagmus in the vertical plane. His neuropsychological testing was normal.

Individual 2.III.6. The 63-year-old female had orofacial dyskinesia, increased blink rate, postural tremor in the left arm, and axial and right arm rigidity. Her mental status and gaze were normal.

Individual 2.III.7. The 60-year-old male had bruxism, akinesia and rigidity predominantly in the left arm and leg and postural tremor in the arms. He also had exophoria and failure of convergence. His mental status was normal.

Individual 2.III.9. The 52-year-old female had postural tremor for several years in the upper limbs and a diminished left arm swing. Neuropsychological testing and oculonystagmographic analysis were normal.

Individual 2.III.11. This was a sister of the proband who was diagnosed as having Parkinson's disease at age 53 when she required medical attention for a slowly progressive akinetic rigid syndrome without tremor. She was treated with small doses of L-dopa and her symptoms improved greatly, although she developed visual hallucinations. At the age of 57 she developed typical wearing off fluctuations and at age 59 she complained of swallowing problems which were accompanied by severe weight loss. On examination she had generalized slowness, difficulty in convergence, anterocollis and limb dystonia in the four extremities, a persistent glabellar tap reflex, brisk sustained palmomental responses, hyperreflexia and extensor plantar reflexes. She developed increasing gait difficulty with frequent freezing.

Individual 2.III.20. This patient complained of head tremor at age 63 and progressive slowness and tremor in her right arm. At age 71 she is still active, but with moderate right side akinesia and rigidity, mild walking difficulty, dysphagia and urinary incontinence.

Individual 2.III.26. At age 59 he complained of tremor at rest in the right hand, hypophonia and excessive sweating. During the following year he developed an akinetic syndrome with gait disturbance, hypomimia, generalized rigidity, dystonia in the lower face and supranuclear gaze palsy with slowing of horizontal and vertical saccades in the oculonystagmographic study. Cognitive testing was normal.

Family 3

Proband, individual 3.III.1. This 72-year-old female developed a lack of initiative, lack of social interest and apathy at age 60. One year later she had speech abnormalities and gait disturbance with frequent falls. She had hypertension and a history of smoking. Her neurological examination at age 64 revealed hypomimia, bradykinesia, hyperreflexia and gait disturbance and she was diagnosed as having Binswanger's disease. Her symptoms worsened slowly over the following years, her walking became progressively worse and she developed limitation of downgaze. Two years later she complained of dysphagia and urinary incontinence. At age 69 she was treated with L-dopa, which produced a mild, transient improvement, and with dopamine agonists, without improvement. She was examined at age 70 when there was evidence of frontal lobe dysfunction, severe dysarthria and dysphagia, facial dystonia and apraxia of eyelid opening. The oculomotor examination revealed limitation of downgaze, difficulty in convergence and slowing of horizontal and vertical saccades. Her neurological examination revealed rigidity and akinesia predominantly in her left limbs, retrocollis and left lower limb dystonia. Her stretch reflexes were exaggerated and she had left foot dystonia. Investigation of her regional cerebral blood flow by HMPAO-SPECT (single photon emission tomography) revealed a deficit of perfusion in the frontal region. A cerebral MRI showed midbrain and subcortical atrophy which was more severe in frontal region. During the ensuing months she became wheelchair bound, unable to read because of complete vertical and horizontal gaze palsy and she developed severe dysphagia and oromandibular dystonia but she declined gastrostomy. She died of pneumonia at age 72. Macroscopic examination of the brain was normal except for pallidal atrophy with brownish discoloration and loss of pigment in the substantia nigra. Light microscopy revealed neuronal loss, gliosis and high density of neurofibrillary tangles and neuropilic threads with positive immunoreactivity to tau and PHF-1 (paired helical filaments) in globus pallidus, subthalamic nucleus, substantia nigra, peri-aqueductal region and oculomotor complex. There was a moderate number of tangles in caudate, putamen, locus coeruleus, pontine nuclei, inferior olive, nucleus ambiguus, raphe nuclei and dentate nucleus.

Individual 3.II.3. This was the proband's aunt on whom we only have retrospective information from relatives. Photographs of the patient taken during her youth and early adult life did not reveal any neurological disease. She developed a parkinsonian syndrome around age 70 with tremor in her hands, early gait disturbance with frequent falls

and speech difficulties. She developed progressive and severe deterioration of her gait and speech and became bedridden and virtually mute for the last few years before her death at age 86.

Individual 3.II.4. This was the proband's aunt on whom we only have reports from relatives. In the last years of her life she developed dementia with frequent hallucinations and severe gait disturbance and she died at age 74.

Family 4

Proband, individual 4.III.1. This was a 62-year-old woman with a history of hypertension, diabetes and smoking who developed progressive gait disturbance and speech difficulty. One year later her neurological examination revealed dysarthria with orolingual apraxia, and persistent glabellar tap and palmomental reflexes. Her mental status was normal. She had ocular dysmetria, slowing of saccades and breakdown of vertical opticokinetic nystagmus. Standing and tandem walking were difficult. She was treated with L-dopa without improvement and at age 65 she lost vertical gaze (up and down) with abolition of vertical optokinetic nystagmus. She had axial and limb rigidity, facial dystonia, bradykinesia and loss of balance and gait difficulty. A cerebral MRI revealed corticosubcortical and brainstem atrophy, mostly in the mesencephalic tegmentum. She died at age 71 and had a post-mortem examination. Light microscopy revealed neuronal loss, gliosis and presence of neurofibrillary tangles and neuropil threads in neurons and glia in globus pallidus (more severe in the medial segment), frontal cortex, subthalamic nucleus, substantia nigra, red nucleus, oculomotor complex, locus coeruleus, dentate and inferior olivary nucleus. Tangles were also identified in Meynert's nucleus, hippocampus, subiculum and pons.

Individual 4.II.6. This was the proband's aunt for whom we only have reports from relatives. In the last years of her life she had a neurological syndrome characterized by dementia, gait disturbance and severe weight loss. She died aged 96 years.

Individual 4.II.7. This was the proband's aunt and a sister of 4.II.6 for whom we only have reports from relatives. She was said to have Parkinson's disease in her seventies. She moved slowly, had no tremor, had frequent falls backwards, developed severe dysphagia and dysarthria and died at age 78.

Family 5

Proband, individual 5.III.5. This 75-year-old female had a progressive syndrome characterized by slowness, clumsiness and dementia. Her neurological examination at age 83 revealed facial dystonia, dysarthria, rigid-akinetic syndrome and gait disturbance. A cerebral MRI revealed corticosubcortical atrophy. During a visit to her home when she was 85 years old, a neurological examination revealed disorientation, abnormalities of memory, limitation of vertical gaze, generalized rigidity (predominantly axial), retrocollis, facial and upper limb dystonia. She was unable to walk and she had a spontaneous tendency to fall backwards. Occasionally she had myoclonic jerks in the arms. She is still alive at age 86.

Individual 5.III.4. This was the proband's brother and his neurological disorder began at age 75 with an akinetic rigid syndrome, dementia, dysphagia, dystonia (antero- and retrocollis) and blepharospasm. His neurological examination 10 years later revealed hypokinesia, upgaze abolition, reduction of the verbal fluency and axial and limb rigidity. A cerebral MRI revealed corticosubcortical and brainstem atrophy. He was unable to walk, developed severe dysphagia and he lost 12–15 kg. He died at the age of 86. During the last few months of his life he took L-dopa without apparent improvement.

Individual 5.II.2. This was the mother of the previous patients for whom we only have information from relatives. For several years she had a neurological syndrome similar to that suffered by her children before dying aged 83.

Family 6

Proband, individual 6.III.5. At age 37 she developed generalized slowness, gait disturbance with frequent falls and micrographia. Her neurological examination 1 year later revealed dysarthria, difficulty in convergence, abolition of upgaze and apraxia of eyelid opening. Stretch reflexes were exaggerated, the left plantar response was extensor and she had axial rigidity and right arm dystonia. She was treated for 3 months with L-dopa without improvement and in the following years she developed axial dystonia, vertical gaze palsy and slow horizontal saccades. Her dysphagia became so severe that she lost weight and required percutaneous gastrostomy. She became virtually mute only being able to express affirmation or negation with slow movements of her hand. Cognitive evaluation was difficult but she was suspected by her physicians to have frontal lobe dementia. She is now 41 years old.

Individual 6.II.3. This was the proband's mother whose neurological disorder began at age 41 with tremor in the left arm and progressive slowness. She was diagnosed with Parkinson's disease 2 years later. When she was 44 years old she had hypophonia, dysphagia and gait disturbance with frequent falls. Neurological examination revealed rigidity, exaggerated stretch reflex, left extensor plantar response and micrographia. A right thalamotomy was performed without improvement. One year later her left arm was fixed in flexion and pronation, she had severe generalized bradykinesia and extensor plantar responses. A few months later there was evidence of voluntary upgaze paralysis and she died at age 45.

Individual 6.III.1. This was the proband's sister who developed a progressive akinetic syndrome when she was 37 years old. Two years later she had a gait disturbance with frequent falls and micrographia and neurological examination revealed hypophonia, a reduced range of vertical gaze movements, difficulty for ocular convergence, apraxia of eyelid opening, exaggerated stretch reflexes and axial rigidity. She was treated with bromocriptine without improvement and died aged 41.

Family 7

Proband, individual 7.III.1. A 55-year-old male presented with loss of memory and progressive gait disturbance, frequent backwards falls and dysphagia, and neurological examination 3 years later revealed downgaze limitation. He is now 59 years old and has an akinetic rigid syndrome with severe gait disturbance, retrocollis, apraxia of eyelid opening and downgaze limitation with occasional diplopia.

Individual 7.II.4. This was the proband's father who, during the last 13 years of his life, had an akinetic rigid syndrome with postural tremor in the left arm, dementia with apathy, gait disturbance, dysphagia and significant weight loss. Neurological examination revealed retrocollis, apraxia of eyelid opening and micrographia. He was treated with L-dopa without improvement. Later he lost vertical downgaze and developed diplopia. He died at age 83.

Family 8

Proband, individual 8.II.1. This was a 49-year-old male who developed bradykinesia in his left arm. He was diagnosed with Parkinson's disease and was treated with L-dopa and bromocriptine with clear improvement for many years. When we saw him for the first time at age 63 he was hallucinating and examination revealed hypokinesia, bilateral rest and postural tremor, somnolence and fatigue. Two years later he had frequent falls, dysarthria and memory loss and at age 66 the akinetic syndrome had progressed and he had horizontal gaze limitation, difficulties in convergence and 'frontal dementia'. After 15 years of L-dopa therapy his akinesia was still improved but now at age 68 he has dysphagia, facial dystonia, retrocollis, supranuclear gaze palsy affecting all directions and gait disturbance.

Individual 8.I.1. This was the proband's father on whom we only have reports from relatives. He had an akinetic rigid syndrome without tremor with frequent falls and dementia. During the last years of his life he had dysphagia with weight loss and he died at age 80.

Family 9

Proband, individual 9.II.1. At the age of 67 this woman had a predominantly right-sided akinetic rigid syndrome. Two years later she developed dysarthria, palilalia, facial dystonia and axial and right arm dystonia. Vertical ocular movements were abolished and horizontal ones were slow. She developed urinary incontinence and loss of balance with frequent backwards falls.

Individual 9.I.2. This was the proband's mother who, at age 75, developed loss of balance, gait disturbance, postural tremor, dementia, dysarthria and severe dysphagia with weight loss. She received treatment with L-dopa with clear improvement, but she had hallucinations. She died at age 83.

Family 10

Proband, individual 10.III.1. At the age of 70 this lady developed unexplained falls. Her balance progressively deteriorated with frequent falls and she also had micrographia and general slowness of movement. By the time we examined her 7 years after symptom onset, she was unable to stand unaided but was able to walk with the aid of two people, with a tendency to fall backwards. Her neck was fixed in an anteroverted position and she had a complete vertical supranuclear palsy with slow and hypometric lateral saccades, blepharospasm and apraxia of eye lid opening. She had a low pitched dysarthria and mild symmetrical distal bradykinesia and rigidity. There was intermittent dystonic posturing of the right leg with extension at the knee and plantar flexion at the ankle.

Individual 10.III.2. At the age of 70 this man developed nocturnal restlessness and was frequently found by his wife wandering around the house. He developed urinary frequency and mild short-term and remote memory loss. At the age of 76 he was unable to answer any questions or follow commands but he had dressing apraxia and required assistance for feeding. He walked unaided with steady balance as he turned and his eye movements were normal. Although he could not be formally examined there was no obvious bradykinesia, but there was mild symmetrical cogwheel rigidity, together with mild axial rigidity and turning and sitting *en bloc*. There were small amplitude irregular, stimulus sensitive finger movements indicating cortical myoclonus. He developed marked bradykinesia and rigidity following a depot injection of anti-psychotic medication.

Individual 10.III.6. At the age of 60 this man developed difficulty walking with unsteadiness and backwards falls while pushing a wheelbarrow. Over the following year he noted that he had difficulty in starting to walk with his feet 'glued to the floor' and had difficulty in turning, particularly in confined spaces, although he walked with normal step size. He also developed mild micrographia. At this time he had no bulbar symptoms and examination of his extraocular movements was normal. His cranial MRI showed no vascular changes and the diagnosis was of a frontal gait disorder. Four years after symptom onset he developed mild dysarthria

and difficulty with reading. Examination showed that he had developed mild slowing of vertical saccadic eye movements and blepharospasm.

Family 11

Proband, individual 11.III.6. At the age of 43 this lady developed a lack of interest in day-to-day events and chronic insomnia. She had slowing of her speech, difficulty in shifting her gaze and she became obsessional about performing particular tasks. Two years after symptom onset she had impairment of postural reflexes and a complete absence of vertical saccadic eye movements to command but well preserved smooth pursuit eye movements. The mini-mental test score was 30/30 but there was impaired verbal fluency. Over the next few years she developed increasingly severe dysarthria and dysphagia and died of a respiratory infection 5 years after symptom onset.

Individual 11.II.3. In his forties this man developed 'problems with his eyes', gait unsteadiness and frequent falls, some of them quite serious. He also found it hard to judge distances and frequently bumped into people, and he is recalled by his family as having had staring eyes. He deteriorated quite rapidly, was transferred to a nursing home and then to a hospital where he died in 1954 at the age of 47 years. The death certificate diagnosis was of Creutzfeldt–Jacob disease but no pathological report has been ever found. Both his children are now dead and we have never obtained medical records or the post-mortem details on him. However, from accounts given by his daughter and members of the broader family that this patient had the same staring eyes and other neurological features observed in his children we feel that there is sufficient grounds to be suspicious of PSP.

Individual 11.III.5. He was a professor of economic geography who, in his forties, was noted by his work colleagues to become obsessive and worried about small details. At the age of 48 he developed difficulty in focusing and then in reading and started to have frequent falls and memory loss, particularly for recent events. When seen by a neurologist in 1989 he had symmetric akinetic–rigid syndrome with severe supranuclear downgaze palsy, slurring of speech, marked hypomimia, diffuse pyramidal signs, a brisk jaw jerk and bilateral grasp reflexes. At the age of 52 he had a severe supranuclear gaze palsy and was profoundly bradykinetic and dysarthric with marked postural instability. There were no sensory or cerebellar signs and he scored 25/30 on the Mini-Mental State Examination. All laboratory tests were normal and L-dopa was tried without benefit. He became mute and increasingly immobile and died at the age of 53.

Family 12

Proband, individual 12.III.3. This right-handed woman started to fall at 71 and she also complained of unsteady gait and had difficulty looking down, particularly when going down stairs or eating . Anti-parkinsonian therapy was initiated but with no benefit. On examination she had a 'dystonic, pseudobulbar' face, markedly impaired vertical gaze (supranuclear), impaired vertical pursuit, hypometric saccades and square wave jerks. On motor examination there was bradykinesia, tone was normal and there was no cogwheeling. Stretch reflexes were exaggerated but the plantar responses were down going. Her gait was narrow-based and unsteady with unpredictable falls and there was limited arm-swing and she turned en bloc. She is still alive.

Individual 12.III.5. This man began having symptoms at the age of 63 with personality changes and increasing irritability. He subsequently developed dysarthria followed by falls and an unsteady gait. One year later a 'wide-eyed' stare was evident and he later developed coarse rhythmical activity and posturing in his right hand. The family noted rigidity and dysphagia as well as cognitive changes (poor memory and judgement) but he did not benefit from L-dopa. On examination he had typical PSP facies and there was also hypophonia and fluctuating dysarthria. He had impaired vertical gaze and pursuit with a normal oculocephalic reflex. There was left facial weakness. On motor examination there was bradykinesia, axial dystonia and dystonic posturing of his right hand. There was also a coarse, intermittent tremor of his right hand and gegenhalten was present in the legs. He had a persistent glabellar tap and grasp reflex, rapid alternating movements were severely impaired, there was axial dystonia and his gait was unsteady. He is still alive.

Individual 12.II.4. This man died at the age of 49 years from liver disease. He had gait problems with frequent falls.

Clinical genetics

In these families we have found 22 secondary PSP cases among 133 first and second degree relatives from whom there was available information. All the patients with 'likely PSP' ($n = 12$) had supranuclear gaze palsy and/or frequent falls or gait disturbance early in the course of the disease. Other individual members of these families presented with other neurological disorders including isolated tremor ($n = 3$), dementia ($n = 3$), parkinsonism ($n = 1$), gait disturbance ($n = 1$), and tremor, dystonia, gaze palsy and tics ($n = 2$).

In these families we found 34 individuals with clinical or pathological criteria of PSP (12 probands and 22 familial cases). Seventeen were male and 17 female and the mean age at onset of symptoms was 59.9 $\pm$ 12.4 years ($n = 28$). In 17 of these patients there was information available about vascular risk factors: five (29.41 %) were heavy smokers, two had high blood pressure (11.76 %) and two diabetes (11.76%). The duration of the disease from clinical onset to death was 8.81 $\pm$ 3.76 years ($n = 16$). Bradykinesia was the presenting feature in 15 patients, gait disturbance in five

Table 3 *Clinical features in 34 individuals with PSP*

	n	%
Bradykinesia	31	91
Gait disturbance	32	94
Supranuclear gaze palsy	29	85
Dysphagia	22	65
Dysarthria	21	62
Axial dystonia	12	35
Dementia	14	41
Tremor	8	23
Apraxia of eyelid opening	6	18
Blepharospasm	2	6
Limb dystonia	8	23
Myoclonic jerks	1	3
Response to L-dopa	7	44*

*Percentage of 16 patients who received L-dopa.

and change in personality in three. In nine patients it was not possible to determine the initial clinical symptom.

The frequency of the different clinical symptoms is summarized in Table 3. Gait disturbance was the most frequent alteration during the progression of disease (94% of the patients). Seven out of 16 patients treated with L-dopa improved initially (three out of the four cases confirmed by pathology) and in three of them this response was sustained for more than 3 years. In one patient, L-dopa therapy was thought to be of marginal efficacy, but its discontinuation because of paralytic ileus produced a malignant catatonic syndrome that caused his death in spite of intravenous administration of lisuride.

In order to evaluate if there were any differences between familial and sporadic PSP we compared clinical features of the five probands from the families seen in Fundación Jiménez Díaz with the last five cases of sporadic PSP seen by us in the same hospital (Table 4). We did not find clinical differences between familial and sporadic PSP in terms of age at onset and initial clinical findings. Patients with familial PSP more frequently had dystonia which may have reflected the more prolonged follow-up.

Discussion

This study presents a set of clinical data and clinical genetics of familial PSP. In 12 families from Europe and North America we found 22 secondary cases compatible with PSP in addition to the 12 probands, all with typical clinical features. Four of the probands had neuropathological confirmation of the diagnosis of PSP. In these families there were relatives with other neurological disorders including tremor (three patients), adult onset focal dystonia, tremor, gaze palsy and tics (two patients), dementia (three patients), parkinsonism (one patient) and gait disorder (one patient). Most of these disorders are frequent in the general population and, therefore, it is not possible to conclude whether these disorders appeared in these families by chance or as oligosymptomatic manifestation of PSP.

The recognition of familial cases of PSP requires (i) intensive investigation of the families including field trips and home visits of apparently healthy family relatives and (ii) long-term care and follow-up of the proband and relatives by specialized neurologists. These methods of evaluation and long-term follow-up are not common in our health care systems. For example, patient 1.III.12 was thought to be a sporadic case of PSP during her lifetime, although an intensive search for other cases in the family was performed. However, 4 years after the proband's death a secondary case appeared in her family. Patient 2.III.10 was thought to have sporadic PSP during his lifetime. He had a sister who at first was considered to have idiopathic, L-dopa responsive, Parkinson's disease but 1 year after the proband's death, his sister developed severe dysphagia, weight loss and opthalmoplegia. Four years later a first cousin developed akinesia, apathy, cranial dystonia and gaze palsy. After interviewing around 30 family relatives we concluded that five deceased ancestors considered, during their lives, to have 'parkinsonism', 'dementia', 'senility' or 'cerebrovascular disease' in fact had PSP. Patient 7.III.1 was thought to have idiopathic Parkinson's disease. His attending neurologist was not told that the patient's father died of 'parkinsonism'. Interviews with the patient's mother and brother, in addition to a review of the records and family pictures, provided convincing evidence of PSP.

The pattern of inheritance is compatible with autosomal dominance with reduced penetrance. Lack of evidence for vertical transmission in three or more generations, except in one family, could be related to insufficient information about grandparents of elderly patients, most of them with some kind of cognitive impairment. There are, however, other explanations. The disease was only described 3 decades ago (Steele *et al*., 1964) and people lose contacts with their place of origin because of the strong migratory movements that have taken place in many parts of the world, and the increased life expectancy of around 25 years that has occurred during this century. Since the prevalence of PSP is age related (Daniel *et al*., 1995) the chances of developing the disease in gene carriers is now much greater than at the beginning of the century.

The proportion of affected individuals in different generations increases with age. The number of secondary cases in the generation of the probands (6 out of 37 siblings and 3 out of 34 cousins, i.e. 9 out of 71) was smaller than the number of secondary cases in the previous generation (7 out of 24 parents and 5 out of 37 uncles and aunts, i.e. 12 out of 61) (Table 3). This is not surprising since the mean age of the siblings is 53 years and the age adjusted annual incidence of PSP increases from 1.4 at age 50 to 14.2 per 100 000 inhabitants at an age higher than 80 years (Bower *et al*., 1997). Therefore, it is likely that some living relatives will develop the disease in the future.

The diagnosis of PSP is difficult in patients with atypical clinical phenotypes. Confirmed cases of PSP by autopsy have been diagnosed in life as Parkinson's disease, corticobasal

Table 4 *Clinical features in sporadic and familial PSP*

	Sporadic ($n = 5$)	Familial ($n = 5$)
Age of onset*	59.2 ± 6.8	60.2 ± 6.2
Smoking	2	4
High blood pressure	2	1
Other	1 diabetes mellitus	1 high cholesterol levels
Presenting feature	4 gait disorder, 1 cognitive changes	3 bradykynesia, 1 gait disorder, 1 cognitive changes
Bradykinesia	5	5
Gait disturbance	5	5
Supranuclear gaze palsy	5	5
Dysphagia	3	4
Dysarthria	4	5
Axial dystonia	1	5
Dementia	4	3
Tremor	1	1
Apraxia of eyelid opening	1	1
Blepharospasm	1	0
Limb dystonia	0	3

*Mean ± SE.

degeneration, multisystemic atrophy or Alzheimer's disease (Jackson *et al*., 1983; Boller *et al*., 1989; Rajput *et al*., 1991; Hughes *et al*., 1992). The pathology of PSP is characterized by a variable combination of neuronal loss, gliosis and neurofibrillary tangles in many brain areas including the cerebral cortex, basal ganglia and the brainstem (Hauw *et al*., 1994; Daniel *et al*., 1995). Although typical cases are characterized by akinesia, supranuclear gaze palsy, rigidity, axial dystonia, gait disturbance and dementia, there are patients with atypical symptoms and typical pathology (Daniel *et al*., 1995). In some of these patients the diagnosis of PSP could be easily missed.

Improvement with L-dopa is considered typical of Parkinson's disease and rare in PSP to the point that lack of response is considered support criteria for the diagnosis of PSP (Jellinger, 1995). However, 35–50% of the patients improve their bradykinesia or rigidity with L-dopa (Nieforth and Golbe 1993; Litvan *et al*., 1997). In the present study we found that 7 out of 16, 44% of the treated patients, improved with this treatment. Furthermore, three out of the four cases confirmed by pathology responded to L-dopa. In most of the patients the response was modest and transient, but in three individuals (1.III.3, 2.II.11 and 8.II.1) the benefit was maintained for several years. These patients were considered to have Parkinson's disease before they developed the complete typical syndrome of PSP. The possibility that some of these patients had Lewy body pathology cannot be ruled out in spite of the lack of Lewy bodies in the three patients with pathological confirmation of PSP and response to L-dopa. Unfortunately, we could not obtain post-mortem evaluation of some of the relatives of the probands with atypical clinical findings but [^{18}F]dopa and deoxyglucose-PET scans have revealed abnormal data compatible with PSP in members of these families with atypical phenotypes or who are clinically asymptomatic (Piccini *et al*., 1998).

Genetic risk factors for PSP are uncertain. In a case-control study by means of questionnaires answered by 50 patients it was found that parkinsonism (odds ratio 5.0) and dementia (odds ratio 3.6) were more common among first degree relatives of PSP patients (Davis *et al*., 1988) but, due to the small size of the cohort, the difference was not significant. Recent reports of familial PSP have raised the possibility of a genetic factor in the cause of this disease (David *et al*., 1968; Mata *et al*., 1983; Ohara *et al*., 1992; Brown *et al*., 1993; Gazely and Maguire, 1994; Tetrud *et al*., 1994; de Yébenes *et al*., 1995; Golbe *et al*., 1995; Lanotte *et al*., 1996; Tetrud *et al*., 1996). The pattern of inheritance in these previous reports was variable. Four of these families had affected members in two or more generations, suggesting autosomal dominant transmission, while five families had affected individuals in the same generation and consanguinity was observed in one. So far, familial clustering PSP has been reported in 20 families including those in the present study. There is evidence for vertical transmission in 10 families, consanguinity in one and horizontal aggregation in 13 families. Considering the difficulties in the diagnosis it is likely that the number of familial aggregates of PSP is greater than previously thought, suggesting that PSP could be a hereditary disorder, at least in some families.

Recent reports (Conrad *et al*., 1997; Lazzarini *et al*., 1997) have described a higher prevalence of the A_o polymorphism of the gene for tau in patients with sporadic PSP than in the general population. Higgins and colleagues (Higgins *et al*., 1998) confirmed these data and suggested that familial PSP could be inherited as an autosomal recessive disorder linked to the tau gene. These observations are interesting since the pathological lesions found in the brain of patients with PSP are tau containing neurofibrillary tangles. The significance of this finding, however, is very difficult to interpret since homozygosity for the A_o polymorphism occurs in around 55% of the population while the prevalence of PSP, even in aged individuals, is only 70 out of 100 000 inhabitants.

Furthermore, no linkage has been found (J. Hoenicka, M. Pérez, J. Pérez-Tur, A. Barabash, M. Godoy, R. Astarloa, J. Avila, T. Nyggard, J. G. de Yébenes, unpublished results) in the region 17q 21–22 where the gene for tau is localized, during a genomic search performed in families 2 and 7 of this study. In addition, we found that the polymorphism A_0 has a similar distribution in affected and non-affected members of families 2 and 6 of this study (Hoenicka *et al*., manuscript in preparation), and no evidence of linkage was found between the PSP phenotype and the gene for tau after analysing the data for both a pattern of autosomal dominant and recessive inheritance in these families.

It is very important that the familial character of PSP is recognized in order to look for additional families that could be included in a genetic search. Finding a gene responsible for PSP could be a great step forward towards finding a valuable treatment for this disease.

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