

Clinical and neuropathologic features of progressive supranuclear palsy with severe pallido-nigro-luysial degeneration and axonal dystrophy

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Pallido-nigro-luysial atrophy (PNLA) is a rare disorder that in many cases has histopathological features similar to **progressive supranuclear palsy (PSP)**. In a pathological series of over 400 cases of **PSP**, eight cases were noted to have features similar to those described in **PNLA**, including severe atrophy and neuronal loss in the globus pallidus, substantia nigra and subthalamic nucleus, in addition to many axonal spheroids in the globus pallidus and substantia nigra. These eight cases of **PSP–PNLA** were compared to 11 typical **PSP** cases with quantitative neuropathologic indices and assessment of demographics, clinical features and the timing of clinical features. **PSP–PNLA** cases were younger, had longer disease duration and more often were not initially diagnosed with **PSP**; in the end, they did not differ from **PSP** with respect to any major clinical feature. The clinical course of **PSP–PNLA**, however, was different, with earlier gait abnormalities and difficulty with handwriting, but later falls, rigidity and dysphagia than **PSP**. Pathologically, the same types of lesions were detected in both **PSP** and **PSP–PNLA**, but there were differences in the distribution and density of tau-pathology, with less tau-pathology in motor cortex, striatum, pontine nuclei and cerebellum in **PSP–PNLA**. These clinical and pathological findings suggest that **PSP–PNLA** should be considered a variant of **PSP**.

Keywords: natural history; neuropathology; pallido-nigro-luysial atrophy; progressive supranuclear palsy; pure akinesia; tau

Abbreviations: CB = coiled-bodies; CN = caudate nucleus; DD = disease duration; DN = cerebellar dentate nucleus; GIF = gait ignition failure; GP = globus pallidus; MTR = motor cortex; NFT = neurofibrillary tangles and pre-tangles; NT = neuropil threads; PA = pure-akinesia; PAGF = pure akinesia with gait-freezing; PNLA = pallido-nigro-luysial atrophy; PPF = primary progressive freezing gait; PSP = progressive supranuclear palsy; PSP-P = PSP-Parkinsonism; RN = red nucleus; RS = Richardson's syndrome; SCP = superior cerebellar peduncle; SN = substantia nigra; STN = subthalamic nucleus; TA = tufted astrocytes; VGP = vertical gaze palsy

Received August 13, 2007. Revised November 15, 2007. Accepted November 20, 2007. Advance Access publication December 24, 2007

Introduction

Progressive supranuclear palsy (PSP) is one of the most common atypical Parkinsonian syndromes. Clinically, PSP is characterized by severe postural instability leading to falls, supranuclear gaze palsy, pseudobulbar palsy, axial rigidity, Parkinsonism and sometimes mild cognitive dysfunction (Steele *et al.*, 1964; Litvan *et al.*, 1996a). Pathologically, PSP is considered to be one of the tauopathies due to the presence of abnormally phosphorylated tau-protein in neurons and glia in subcortical and cortical structures. Of these regions, the globus pallidus (GP), substantia nigra (SN) and subthalamic nucleus (STN) consistently contain tau-pathology and are

vulnerable to neuronal loss (Hauw *et al.*, 1994). Although consensus criteria for the clinical and pathological diagnosis of PSP have been formulated, PSP is heterogeneous on both accounts (Hauw *et al.*, 1994; Litvan *et al.*, 1996a, b). Recent clinical and pathological studies have identified a number of variants of PSP (Josephs *et al.*, 2002, 2005, 2006a; Williams *et al.*, 2005, 2007a, b).

In 1977, Takahashi and coworkers described two patients who clinically resembled PSP, but pathologically had severe neuronal loss in the GP, SN and STN similar to pallido-nigro-luysial atrophy (PNLA) (Takahashi *et al.*, 1977). Due to selective loss of neurons and subsequent atrophy in these

regions, the preferred diagnosis was PNLA, a pathological entity described by Contamin and co-workers in 1971 (Contamin *et al.*, 1971). A link between PSP and PNLA was bolstered by a case report describing pathological features of both PSP and PNLA in the same individual, suggesting that PSP and PNLA were part of a disease spectrum (Yamamoto *et al.*, 1991). A recent case report highlighted the overlap in tau-pathology and severe neuronal loss in PNLA and PSP, yet the authors felt a pathological diagnosis of PNLA was more fitting (Konishi *et al.*, 2005). Collectively, these case reports suggest a link between PSP and PNLA; however, the pathological classification of such cases is still subject to individual interpretation.

Cases with pathological features of both PSP and PNLA are rare. Although clinical and pathological features are well documented in case reports, there has not been a report of a series of PNLA cases studied with reference to findings in pathologically confirmed PSP. In addition, many of the case reports were published before the routine use of tau-immunohistochemistry, which is more sensitive than commonly used silver stains at detecting the tau-related pathology seen in PSP and other tauopathies. In the present study, we performed a systematic and comparative analysis of clinical and pathological features of PSP cases with and without features consistent with PNLA.

Material and Methods

Case material

All brains were obtained from the Society for PSP Brain Bank at the Mayo Clinic in Jacksonville, Florida and accessioned between 2001 and 2007. From over 400 pathologically confirmed PSP cases evaluated in this time frame, eight cases were noted to have pathology consistent with PNLA (Contamin *et al.*, 1971; Takahashi *et al.*, 1977), in particular severe atrophy, neuronal loss and gliosis in the GP, SN and STN, along with many axonal spheroids in the GP and SN. These cases are referred to as PSP–PNLA. For comparison, we selected 11 cases of pure PSP from a consecutive series of PSP cases collected in 2006–07. During this time period, the laboratory processed 59 cases of PSP. The pure PSP cases lacked Alzheimer pathology, Lewy bodies, argyrophilic grains or other pathological processes, such as infections, trauma, infarcts or acute encephalopathy. From a total of 16 pure cases, 11 were chosen at random for this study. The PSP–PNLA and pure PSP cases were subsequently evaluated blinded to any clinical or specific pathological attributes. All cases of PSP–PNLA and pure PSP met neuropathological criteria for PSP (Hauw *et al.*, 1994; Litvan *et al.*, 1996b).

All available clinical documentation was reviewed, including formal neurological assessments and a standard next-of-kin questionnaire, to extract clinical variables such as age at onset, age at death and disease duration (DD). As with any retrospective clinical series, the quality of medical records was variable from case to case; therefore, an index for the quality of medical records was recorded for each case: 1 = poor; 2 = acceptable; 3 = good. There was no difference in this index between the two groups. The medical records were reviewed for presence and timing of a range of clinical features and neurological signs. If a particular

sign or symptom was not mentioned, it was so noted and not considered to be absent.

The definitions used for clinical features are similar to those used previously (Williams *et al.*, 2005) with minor modifications: tremor—resting tremor, only; balance problems—also described as postural instability; nuchal or axial rigidity—rigidity or dystonia of trunk and neck; rigidity—rigidity not affecting the neck or trunk without respect to whether or not it was described as cog-wheel in type; response to levodopa—the degree of response was difficult to assess, therefore response was recorded as present or absent. When clearly documented, the time that the clinical feature was first noted was recorded (i.e. the number of years from disease onset to appearance of a specific feature). The timing was analysed by assigning a chronological score: 0 = initial or presenting; 1 = early (within first year); 2 = middle (2–7 years from onset); 3 = late (8 or more years after onset); 4 = symptoms specifically noted to be absent, 8 or more years after onset). All patients had an initial diagnosis of Parkinsonism; however, particular attention was paid to other clinical diagnoses throughout the disease course and the final clinical diagnosis before death.

Tissue sampling and pathological assessment

One half of the brain was fixed in formalin for pathological assessment (four right and 15 left hemi-brains) and the other half was frozen for genetic and biochemical studies. Transverse sections of brainstem were made, with the plane defined by an initial cut from the posterior commissure to the interpeduncular fossa. Samples were taken of the midbrain at the level of the third nerve (Gibb and Lees, 1991), the rostral pons at the level of the isthmus and middle-to-caudal medulla at the level of the inferior olivary nucleus. The cerebellar dentate nucleus (DN) was taken from a transverse section perpendicular to the long axis of the brainstem. The sample from parasagittal pre- and post-central gyrus, including the primary motor (MTR) cortex, was taken prior to coronal sectioning of the brain. The caudate nucleus (CN), GP and STN were sampled from coronal sections of the cerebrum.

Tissue samples were embedded in paraffin and cut at 5 µm thickness for histological stains, including thioflavin-S and haematoxylin and eosin, of which the latter was used to assess neuronal loss and gliosis. Neuropathologic evaluation included assessment of other pathological processes, including Alzheimer type pathology, Lewy bodies and vascular pathology. One PNLA case had brainstem Lewy bodies and an infarct in occipital lobe, as well as minimal Alzheimer-related changes. All other cases were free of such pathology. To detect tau-pathology, sections were immunostained using a DAKO Autostainer and phospho-tau antibodies (CP13, 1:500, kind gift of Peter Davies, Albert Einstein College of Medicine, Bronx, NY, USA) and a monoclonal antibody specific to 3R tau (RD3, 1:3000, kind gift of Rohan de Silva, Reta Lila Weston Institute of Neurological Studies), as previously described (Uchikado *et al.*, 2006).

A semi-quantitative analysis (Supplementary Material I) was used to record the degree of atrophy and neuronal loss, according to the following scheme: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = almost complete. To do this, we first assessed the neuronal populations of age-matched neurologically normal individuals. Once familiar with these, we scanned the whole surface area of the SN, STN and DN in our PSP cohorts at a magnification of ×100 and related this to our semi-quantitative scheme. Although gliosis was not recorded, its presence was a supportive feature in assessing

the degree of neuronal loss. In large anatomical structures (i.e. MTR cortex, CN and GP) or in regions with minimal neuronal loss (i.e. pontine base and inferior olive), neuronal loss was not quantified.

A semi-quantitative scheme was used to describe the density of tau-related pathology, including neurofibrillary tangles and pre-tangles (NFT), tufted astrocytes (TA), coiled-bodies (CB) and neuropil threads (NT) as follows: 0 = none; 1 = sparse; 2 = moderate; 3 = frequent; 4 = severe. Tau-pathology was also assessed at $\times 100$, in a total of 11 brain regions. In regions with variable tau-pathology, an estimate of the whole region was made. The reliability of the semi-quantitative tau-scoring scheme was confirmed by performing quantitative image analysis for individual tau-lesions in a subset of 11 cases. Image analysis data showed a strong and significant correlation with respective tau-scores (Supplementary Material II).

The superior cerebellar peduncle (SCP) was assessed by examining macroscopic digital images of mid-pons taken from the fixed brain specimen and measuring the width to the nearest millimetre, similar to the method previously described (Tsuboi *et al.*, 2003).

Determination of tau-haplotypes was performed according to previously published methods from DNA isolated from frozen brain samples (Baker *et al.*, 1999).

Statistical analysis

Data were analysed with SigmaStat 3.0 (Systat Software, Inc., Point Richmond, CA, USA), and the significance level was set at $P < 0.05$. For continuous variables (age at onset, age at death, DD, SCP width) PSP and PSP–PNLA were compared with *t*-tests. The Fisher exact test was used for categorical variables (initial diagnosis, symptom presence and genetic analysis). Mann–Whitney rank sum test was used for ordinal variables (timing of clinical features, comparison of regional pathologic scores). Spearman Rank Order Correlation was used to assess correlation between DD and clinical or pathological variables. No adjustments for multiple comparisons were made in these exploratory analyses.

Results

Case demographics

Clinical demographics are summarized in Table 1. For all 19 cases (14 males, 5 females), the mean age at onset was 62 years (range 46–73) with mean DD of 9.2 years (range 4–19). All cases had a clinical diagnosis of PSP at the time of death, which on average was 71.2 years (range 59–83). Age at onset and DD were significantly different between PSP

and PSP–PNLA. The age at onset was significantly higher in the PSP group, whereas DD was longer in the PSP–PNLA group (Supplementary material III). The majority of PSP–PNLA cases were males (88%), although this was not statistically different from the PSP cases (54%). For our purposes, initial diagnosis was defined as a specific movement disorder diagnosis other than Parkinsonism. All PSP cases had an initial diagnosis of PSP, in contrast to 33% in the PSP–PNLA group; other clinical considerations were multiple system atrophy (two cases), ‘basal ganglionic degeneration’ (one case) and atypical-Parkinson’s disease (one case); these diagnoses were not given at the time of disease onset. A family history of neurodegenerative disease was noted in three cases. One case from each group had a family history of Alzheimer’s disease, and PSP was noted in the father of a PSP–PNLA case. All cases were H1/H1 homozygote except for one PSP case that was H1/H2 heterozygote.

Clinical features in PSP and PSP–PNLA

The clinical features are summarized in Table 2. The cardinal features of PSP were frequent in both groups. These included balance problems (postural instability), falls and vertical gaze palsy (VGP). Less common features segregated with PSP or PSP–PNLA. Disequilibrium, often referred to as dizziness, was frequently mentioned in PSP (46%), but was not mentioned in PSP–PNLA ($P = 0.04$). On the other hand, gait-freezing, characterized by difficulty initiating movement or feeling that the feet are stuck to the ground, was more frequent in PSP–PNLA (62%) than PSP (18%), although this did not reach statistical significance ($P = 0.07$).

In both groups gait disturbance, visual problems (including VGP) and cognitive changes were frequently mentioned. Table 3 provides details on the specific clinical features. Gait abnormalities, which were reported as unsteady, wide-based and shorted stepped, were mentioned in PSP, while festinating gait, dragging feet or a slow type gait were noted in PSP–PNLA. With respect to visual problems, the direction of initial VGP was variable in both groups. Blurring of vision was only noted in the PSP and eye-lid apraxia was only noted in PSP–PNLA. The low frequency of these individual features precluded statistical analysis.

Table 1 Case demographics

	All (<i>n</i> = 19)	PSP (<i>n</i> = 11)	PSP–PNLA (<i>n</i> = 8)	<i>P</i> -value
Sex (male, %)	68.4	54.5 (7/11)	87.5 (7/8)	0.34*
Age at onset	62 (± 1.9)	65.5 (± 1.9)	57.1 (± 3.1)	0.03 [#]
Age at death	71.2 (± 1.5)	73.0 (± 2.0)	68.8 (± 2.2)	0.17 [#]
Disease duration	9.2 (± 0.8)	7.6 (± 0.5)	11.5 (± 1.6)	0.007 [#]
Initial PSP dx. (%)	72.2 (<i>n</i> = 18)	100	33.3 (<i>n</i> = 7)	0.006*
PSP dx. at death (%)	100 (<i>n</i> = 18)	100	100 (<i>n</i> = 7)	1.0*
H1 allele frequency	37/38	21/22	16/16	1.0*

\pm = standard error of the mean; * = Fisher’s exact test; [#] = Student’s *t*-test; dx. = diagnosis.

Table 2 Clinical features in PSP and PSP-PNLA

Clinical feature	PSP (n = 11)				PSP-PNLA (n = 8)				P-value*
	P	A	NR	% P	P	A	NR	% P	
Asymmetry	2	5	4	18	0	3	5	0	0.48
Resting tremor	0	9	2	0	0	7	1	0	1.0
Disequilibrium	5	0	6	46	0	0	8	0	0.04
Balance problems	10	0	1	91	7	0	1	88	1.0
Falls	11	0	0	100	7	0	1	88	0.42
Hypomimia	10	0	1	91	7	0	1	88	1.0
Speech problems	10	0	1	91	8	0	0	100	1.0
Changes in handwriting	8	0	3	73	5	0	3	62	1.0
Gait disturbance	11	0	0	100	7	0	1	88	0.42
Difficulty walking	9	0	2	82	7	0	1	88	1.0
Freezing gait	2	0	9	18	5	0	3	62	0.07
Vertical gaze palsy	11	0	0	100	8	0	0	100	1.0
Other visual problems	8	0	3	73	5	0	3	62	1.0
Dysphagia	10	0	1	91	5	1	2	62	0.26
Bradykinesia	11	0	0	100	6	0	2	75	0.16
Limb rigidity	9	0	2	82	7	1	0	88	1.0
Nuchal/axial rigidity	8	0	3	73	7	1	0	62	0.60
Cognitive changes	9	1	1	82	6	1	1	75	1.0
^a Levodopa response	6	4	1	54	4	1	3	50	1.0

* = Fisher's exact test; P = present; A = absent; NR = not recorded; % P = percentage present in total number of cases; ^a = Response not sustained.

Table 3 Details of cardinal clinical features in PSP and PSP-PNLA

Specific feature	PSP	PSP-PNLA
Initial gait disturbance		
Shuffling	1	1
Slow ^a	0	2
Festinating ^a	0	4
Drags feet ^a	0	2
Narrow base	1	2
Wide base ^a	3	0
Short steps ^a	1	0
Unsteady ^a	5	0
Initial direction of vertical gaze palsy		
Upward	5	3
Downward	3	2
Not specified	3	3
Other visual problems		
Reduced blinking	4	2
Blurring ^a	3	0
Diplopia	6	3
Blepharospasm	1	2
Ptosis	2	1
Eye lid apraxia ^a	0	2
Cognitive changes		
Slow mentation	2	3
Memory problem	4	5
Personality change	6	2
Depression	5	1

Numbers represent the frequency of the specific features in PSP and PSP-PNLA.

^a = only present in one of the groups.

Clinical course

For those cases in which sufficient information was available, the timing of clinical features was recorded on a 4-point scale. For features present in both groups, the mean and median scores for each feature are shown in Table 4. The mean score for the timing of clinical features is ranked (lowest to highest) for PSP and PSP-PNLA in Fig. 1. In PSP, balance problems were the presenting symptom, followed by falls within the first year and later by progressive gait disturbance, changes in handwriting and hypomimia. Difficulty walking, speech problems and bradykinesia preceded VGP. A diagnosis of PSP was most often made at the time that dysarthria and rigidity were noted. Axial or nuchal rigidity and dysphagia were, on average, the last clinical manifestations, as was gait-freezing in two patients. All these features were present within 7 years of onset.

In PSP-PNLA, the order of clinical features differed from PSP. Changes in handwriting preceded gait disturbance. Balance problems were followed by gait-freezing and falls. Speech problems and hypomimia presented before axial or nuchal rigidity. Bradykinesia as well as dysarthria, limb rigidity and VGP contributed to a diagnosis of PSP at this time. Again, dysphagia was last.

In the PSP group, there was considerable variation from case to case as indicated by large whisker caps in Fig. 1A. In contrast, there was less variation between cases in the PSP-PNLA group as shown in Fig. 1B.

Table 4 Clinical feature chronologic score in PSP and PSP–PNLA

Clinical feature	PSP		PSP–PNLA		P-value*
	Mean	Median	Mean	Median	
Axial/Nuchal rigidity	2.0 ± 0.0	2.0	2.0 ± 0.0	2.0	1.0
Balance problems	0.2 ± 0.2	0.0	0.9 ± 0.3	1.0	0.08
Bradykinesia	1.8 ± 0.1	2.0	2.3 ± 0.2	2.0	0.05
Changes in handwriting	1.4 ± 0.3	1.5	0.2 ± 0.2	0.0	0.02
Difficulty walking	1.6 ± 0.2	2.0	0.7 ± 0.2	1.0	0.01
Dysarthria	1.9 ± 0.3	2.0	2.4 ± 0.2	2.0	0.27
Dysphagia	2.0 ± 0.0	2.0	2.8 ± 0.3	3.0	0.005
Falls	0.5 ± 0.2	0.0	1.4 ± 0.2	1.0	0.03
Freezing gait	2.0 ± 0.0	2.0	1.2 ± 0.4	1.0	0.38
Gait disturbance	1.4 ± 0.3	2.0	0.4 ± 0.2	0.0	0.04
Hypomimia	1.5 ± 0.2	2.0	1.7 ± 0.2	2.0	0.75
Limb rigidity	1.9 ± 0.1	2.0	2.5 ± 0.2	2.5	0.03
PSP diagnosed	1.9 ± 0.1	2.0	2.4 ± 0.2	2.0	0.06
Speech problems	1.7 ± 0.2	2.0	1.6 ± 0.4	2.0	1.0
Vertical gaze palsy	1.8 ± 0.2	2.0	2.5 ± 0.2	2.5	0.01

The timing was analysed by assigning a chronological score: 0 = initial or presenting; 1 = early (within first year); 2 = middle (2–7 years from onset); 3 = late (8 or more years after onset); 4 = symptoms specifically noted to be absent, 8 or more years after onset.

*=Mann–Whitney U-test; ± = standard error of the mean.

The onset of certain clinical symptoms was significantly earlier in PSP: falls ($P=0.03$), VGP ($P=0.01$), limb rigidity ($P=0.03$) and dysphagia ($P=0.002$). The onset of other symptoms was earlier in PSP–PNLA: gait disturbance ($P=0.04$), difficulty walking ($P=0.01$) and changes in handwriting ($P=0.02$).

Clinical correlations

Within the PSP group, case histories that had reports of possible improvement with levodopa therapy ($n=6$) had significantly longer DD ($P=0.01$) than cases with no reported improvement ($n=4$). Response to levodopa, however, was minimal, transient and usually subjectively reported by the patient without objective confirmation on neurological examination. Missing data for levodopa response in PSP–PNLA limited the ability to compare this feature. PSP–PNLA cases with gait-freezing ($n=5$) showed a significant negative correlation between age at death and the onset of gait freezing ($r=-0.95$, $P=0.017$), which suggests that gait-freezing occurred earlier in older patients. The onset of gait freezing also showed a significant positive correlation ($r=0.91$, $P=0.017$) with the onset of VGP. Only 2 of 11 PSP cases had gait freezing, thereby limiting the ability for comparison of this feature.

Pathologic findings

Macroscopic features

The SCP (Tsuboi *et al.*, 2003) and the STN (Hardman *et al.*, 1997) are known to be vulnerable to macroscopic atrophy in PSP. In comparison to neurologically normal cases, the SCP and STN were atrophic to varying degrees in both groups (Fig. 2A–C). The SCP width was significantly less in PSP than in PSP–PNLA ($P<0.001$) (Fig. 2D).

In contrast, atrophy of the STN was more in PSP–PNLA than in PSP ($P\leq 0.001$) (Fig. 2E).

Microscopic features

Neuronal loss in regions such as the SN, STN and DN are common in PSP. Semi-quantitative scores of neuronal loss in PSP and PSP–PNLA showed differences between the two groups (Fig. 3). The SN can be divided into specific neuronal clusters described previously (Gibb and Lees, 1991). In the SN, neuronal loss was similar in the A10, ventrolateral and dorsolateral clusters of neurons in both groups; however, neuronal loss in the medial group (also known as intermediate group) of neurons was more severe in the PSP–PNLA cases ($P=0.002$). The STN was consistently and severely depleted of neurons in PSP–PNLA, while in PSP neuronal loss was rarely as severe ($P\leq 0.001$). Neuronal loss in the STN was the most striking feature of PSP–PNLA. In almost all cases, the normal lentiform shape of the STN was transformed into a slit-like gliotic structure, almost totally devoid of neurons. In the cerebellar DN, moderate neuronal loss was detected in PSP, but very little in PSP–PNLA ($P\leq 0.001$).

Subcortical regions such as the SN and GP frequently had axonal spheroids and extracellular iron pigment. There was no statistical difference in the density of axonal spheroids between the two groups, although the SN had a slightly higher density compared to the GP in both groups (Fig. 3). The spheroids were structurally pleomorphic even within the same region and case.

Tau-pathology

Regional tau severity scores are summarized in Table 5 and illustrated graphically in Fig. 3. Using the current neuropathologic criteria for PSP (Hauw *et al.*, 1994;

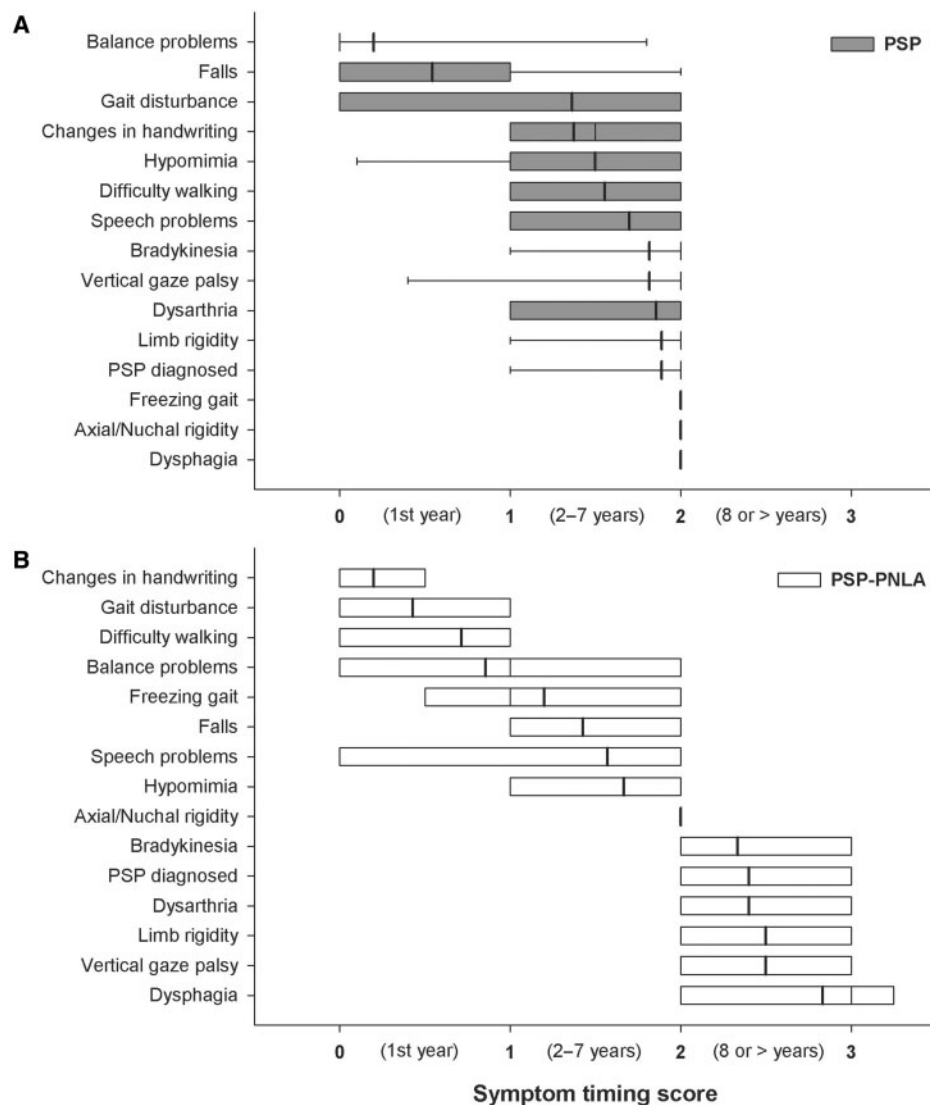


Fig. 1 Natural history of PSP (**A**, grey bars) and PSP-PNLA (**B**, white bars) indicated by the onset of clinical features. Median (thin vertical line), interquartile ranges and mean (bold vertical line) score values are shown for each feature; represented in order of the mean scores.

Litvan *et al.*, 1996b), which requires a high density of NFT and NT in at least three of the cardinal nuclei (SN, STN, GP and pons) and a low-to-high density of NFT and NT in at least three of secondary areas (striatum, oculomotor complex, medulla and DN), all cases in this study meet criteria for PSP. Tau-pathology detected using a phospho-specific antibody (CP13) was negative when using an antibody specific for 3-repeat forms of tau (RD3), indicating that all cases were 4-repeat tauopathies.

In some anatomical regions neuronal-tau pathology was similar in both groups, whereas glial-tau pathology (TA and CB) was significantly different. For instance, the median NFT and NT density in the SN was comparable in PSP and PSP-PNLA, in contrast to TA and CB that were significantly greater in PSP. A similar pattern was also observed in the red nucleus (RN) and CN where glial pathology was

significantly greater in PSP. The STN, on the other hand, showed significant differences in NFT and NT density, but not glial lesions. In regions such as the MTR cortex and pons, all pathological tau-profiles were greater in PSP, with PSP-PNLA cases having no or very little tau-pathology (Fig. 4). In the GP, only the density of TA was significantly different between the groups. It is important to point out that all cases had TA in the CN even though the density of lesions was significantly different between PSP and PNLA ($P=0.002$). TA are considered a characteristic feature of PSP (Nishimura *et al.*, 1992).

The DN and inferior olive are vulnerable mainly to NFT and NT pathology. In these regions, only the density of NT pathology was significantly different between PSP and PSP-PNLA. The cerebellar white matter and the cerebral peduncle (CP) were consistently affected by NT and CB

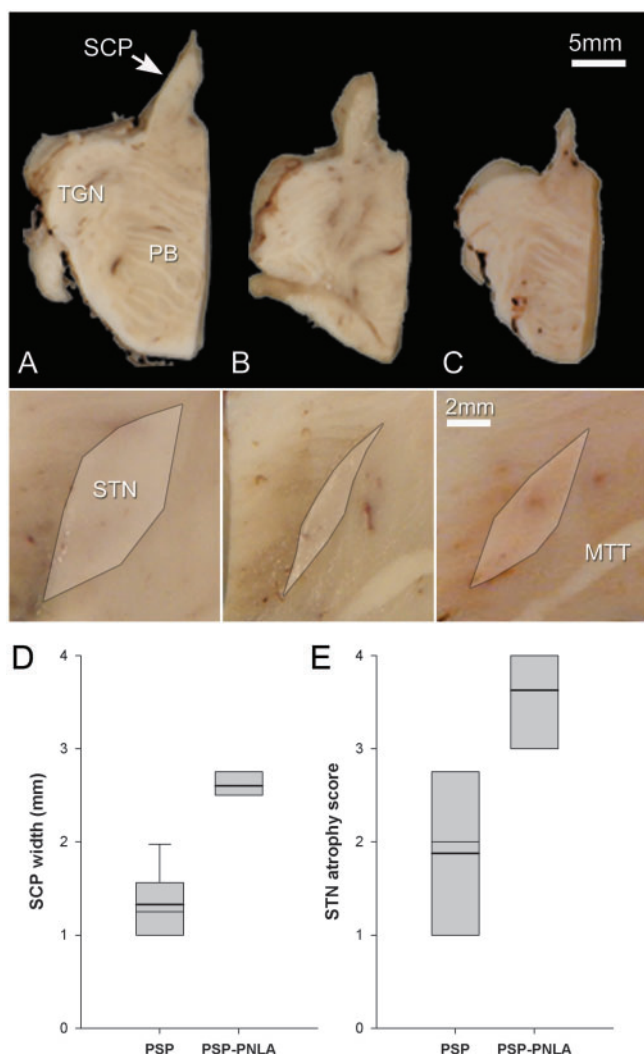


Fig. 2 SCP and STN atrophy in PSP and PSP-PNLA. Representative images of SCP and STN from a neurologically normal case (A) compared to a PSP-PNLA (B) and PSP (C) cases. Quantitative measurements of the SCP (D) and STN (E) identified significant differences (Mann–Whitney U-test, $P < 0.001$) between PSP and PSP-PNLA. Median (thin vertical line), interquartile ranges and mean (bold vertical line) are shown. TGN = Trigeminal nerve; PB = Pontine base; MTT = Mammillothalamic tract.

pathology in PSP, but were almost totally devoid of such pathology in PSP-PNLA.

Severe neuronal loss in the SN and STN was a confounding factor when analysing density of NFT. If there were any remaining neurons in SN or STN in PSP-PNLA cases, almost all of them harboured NFT. In contrast, in PSP a similar density of NFT was accompanied by neurons not affected by tau-pathology. Such differences can only be detected by determining a ratio of NFT to neurons, which highlights the importance of some assessment of neuronal loss in these nuclei.

An overall comparison of PSP and PSP-PNLA revealed that the tau-burden on a whole was greater in PSP.

In no region was the tau-pathology significantly greater in PSP-PNLA than in PSP. The MTR cortex tau-scores provide a good example of this, with scores in PSP ranging from 1 to 3 in comparison to 0–0.5 in PSP-PNLA.

Clinicopathological correlations

Recent studies have attempted to find correlations between neuropathology and DD in PSP (Henderson *et al.*, 2000; Josephs *et al.*, 2006b; Williams *et al.*, 2007a). Clinicopathological correlations with DD are summarized and discussed in Supplementary Material IV. In brief, no pathological feature showed a significant correlation with DD in both groups; however the density of NT in the STN did show a negative correlation with DD in PSP-PNLA ($r = -0.86$) and PSP ($r = -0.55$), but the latter did not reach statistical significance. For some lesions, the correlations were in opposite directions. For example, NFT in the pons showed a positive ($r = 0.92$) correlation with DD in the PSP-PNLA, but a negative correlation ($r = -0.42$) in PSP, although the latter did not reach statistical significance. Interestingly, the majority of correlations of lesions with DD were negative. The only significant positive correlation in the PSP group was between the density of spheroids in the GP and DD ($r = 0.75$), which was absent ($r = 0.22$) in the PSP-PNLA group.

Discussion

In this study, we provide a detailed clinical and pathological description of PSP cases with features similar to PNLA. We have determined the frequency of clinical symptoms and highlighted differences in the natural history of PSP and PSP-PNLA by analysing the chronological order of clinical features. We describe microscopic pathological differences, such as neuronal loss and tau-pathology, and highlight macroscopic features that help differentiate PSP-PNLA from typical PSP.

Clinical features and natural history

A cursory analysis of clinical features in PSP and PSP-PNLA might indicate that they are the same clinical syndrome, which fits with the fact that all cases had a clinical diagnosis of PSP at the time of death. The major differences between PSP and PSP-PNLA were not the presence or absence of any particular clinical feature, but rather the timing of the features. Initial signs of PSP-PNLA were usually impairment in handwriting and gait problems. Falls occurred later in the disease course and were not an initial symptom. In contrast, PSP presented with balance problems and had significantly earlier falls, often as the initial sign of the disease. Due to the retrospective nature of clinical assessment, variability in the quality of medical records and the rarity of PSP-PNLA, clinical features in the present study should be interpreted with caution.

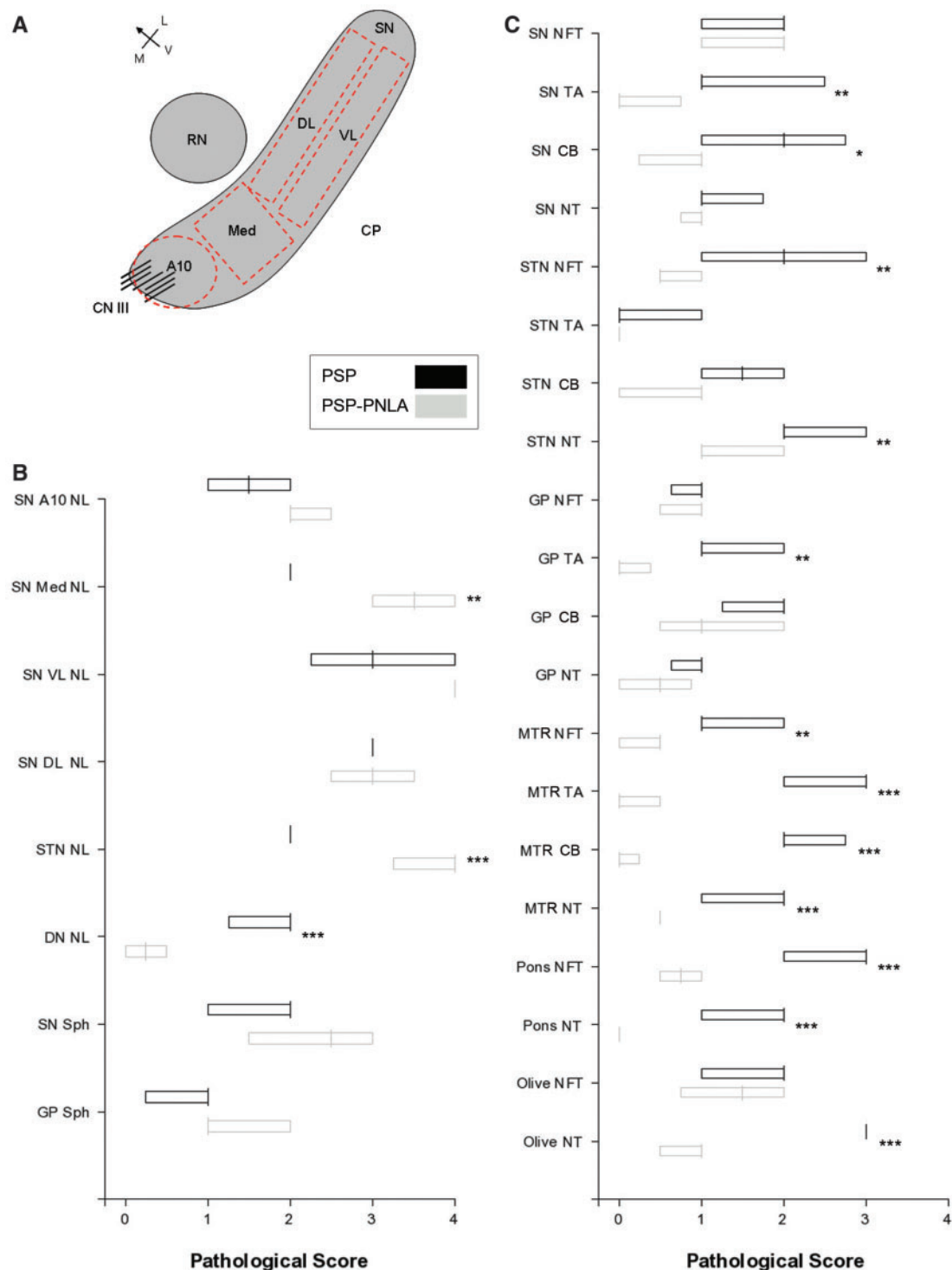


Fig. 3 Regional pathological changes in PSP and PSP-PNLA. When assessing neuronal loss, the SN was separated into four distinct neuronal groups (**A**). The median pathological score (thin vertical line) for neuronal loss and spheroids density (**B**) along with tau-related pathology (**C**) in PSP (black) and PSP-PNLA (grey) are shown with interquartile ranges. Med = medial; VL = ventro-lateral; DL = dorso-lateral; NL = neuronal loss; Sph = spheroids; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Although not specifically mentioned in all of the medical reports, the timing of falls as well as specific features of the gait disturbance (Table 3) suggests that the mechanism of the falls may be different in the two groups. In PSP-PNLA,

gait disturbance was characterized by festination and feet-dragging, in addition to gait freezing and troubles with initiating movement. In contrast, in PSP, disequilibrium, postural instability and a wide-based gait were

Table 5 Median and mean tau scores for different anatomical regions

Anatomical region	PSP					PSP–PNLA				P-value*
	Lesion	Median	0.25	0.75	Mean	Median	0.25	0.75	Mean	
Substantia nigra	NFT	2.0	1.0	2.0	1.6	2.0	1.0	2.0	1.6	1.0
	TA	1.0	1.0	2.5	1.5	0.0	0.0	0.8	0.3	0.001
	CB	2.0	1.0	2.8	2.0	1.0	0.3	1.0	0.8	0.01
	NT	1.0	1.0	1.8	1.3	1.0	0.8	1.0	1.0	0.16
<u>Red nucleus</u>	NFT	1.0	1.0	1.8	1.3	1.0	1.0	1.0	1.0	0.33
	TA	1.0	1.0	2.0	1.6	0.0	0.0	0.5	0.4	0.01
	CB	2.0	1.3	2.0	2.0	1.0	0.0	1.0	0.8	0.02
	NT	2.0	1.0	2.0	1.6	1.0	1.0	1.0	0.9	0.02
Subthalamic nucleus	NFT	2.0	1.0	3.0	1.9	0.5	0.5	1.0	0.7	0.004
	TA	0.0	0.0	1.0	0.4	0.0	0.0	0.0	0.0	0.18
	CB	1.5	1.0	2.0	1.7	1.0	0.0	1.0	0.8	0.07
	NT	2.0	2.0	3.0	2.3	1.0	1.0	2.0	1.3	0.007
Globus Pallidus	NFT	1.0	0.6	1.0	0.9	1.0	0.5	1.0	0.9	0.84
	TA	1.0	1.0	2.0	1.2	0.0	0.0	0.4	0.1	0.006
	CB	2.0	1.3	2.0	1.8	1.0	0.5	2.0	1.3	0.20
	NT	1.0	0.6	1.0	0.8	0.5	0.0	0.9	0.4	0.06
<u>Caudate</u>	NFT	1.0	1.0	1.0	1.1	1.0	1.0	1.0	1.0	0.46
	TA	3.0	2.0	3.8	2.8	1.3	1.0	2.0	1.4	0.002
Motor cortex	NFT	1.0	1.0	2.0	1.5	0.5	0.0	0.5	0.4	0.001
	TA	3.0	2.0	3.0	2.5	0.0	0.0	0.5	0.2	0.00
	CB	2.0	2.0	2.8	2.1	0.0	0.0	0.3	0.2	0.00
	NT	2.0	1.0	2.0	1.8	0.5	0.5	0.5	0.5	0.00
<u>Dentate nucleus</u>	NFT	2.0	2.0	3.0	2.2	1.5	1.0	2.0	1.5	0.05
	NT	1.0	1.0	2.0	1.5	1.0	0.8	1.0	0.9	0.01
Pontine base	NFT	3.0	2.0	3.0	2.7	0.8	0.5	1.0	0.7	0.00
	NT	2.0	1.0	2.0	1.5	0.0	0.0	0.0	0.1	0.00
Medullar olive	NFT	2.0	1.0	2.0	1.7	1.5	0.8	2.0	1.5	0.54
	NT	3.0	3.0	3.0	2.8	1.0	0.5	1.0	0.9	0.00
<u>Cerebellar white matter</u>	CB	2.0	1.0	2.8	1.8	0.0	0.0	0.3	0.1	0.00
<u>Cerebral peduncle</u>	CB	2.0	1.3	3.0	2.1	0.0	0.0	0.0	0.1	0.00

* = Mann–Whitney U-test; NFT = neurofibrillary tangles; TA = Tufted astrocytes; CB = coiled bodies; NT = threads. Regions underlined are not in Fig. 3.

more common. Early falls are important in the clinical identification and differential diagnosis of PSP (Litvan *et al.*, 1996a). The fact that falls were significantly later in PSP–PNLA may explain why the initial diagnosis was something other than PSP for many cases. In addition to falls, VGP is probably the second most important clinical feature for a clinical diagnosis of PSP (Litvan *et al.*, 1996a). In PSP–PNLA, VGP was significantly later than in PSP.

Dysphagia, which was often a terminal complication in both groups, was significantly later in PSP–PNLA. Given that dysphagia is an important factor leading to aspiration pneumonia, which is the most common cause of death in PSP (Litvan *et al.*, 1996c), the later onset of swallowing difficulties may be a factor in longevity of PSP–PNLA compared to PSP. It is worth noting that for two of the three PSP–PNLA cases with the shortest disease durations there were other serious medical problems, such as congestive heart failure and myocardial infarction, that could have shortened their survival.

Considering differences in disease duration alone, one would expect age at death to also be different; however,

the age at onset was substantially younger in the PSP–PNLA cases, on average by almost 10 years, explaining why there was no difference in the age at death. In other neurodegenerative disorders, earlier onset of disease is sometimes attributed to genetic risk factors or familial forms of disease. In the present series, only one of the PSP–PNLA had a family history of neurologic disease (PSP in the father). Familial history of neurologic disease has been reported in other cases of PNLA in the literature (Gray *et al.*, 1981, 1985; Kawai *et al.*, 1993). In addition, a missense mutation in the tau-gene has been identified in a Japanese patient with familial pallido-nigro-luysial degeneration (Yasuda *et al.*, 1999), but this patient had greater tau-pathology than PSP–PNLA cases in the present study. Tau-haplotype analysis was performed in both groups and was consistent with frequencies previously reported in PSP (Baker *et al.*, 1999).

Gait freezing was a frequent feature in PSP–PNLA, but was also present in two cases of PSP. Although based upon a small sample size ($n=5$), cases of PSP–PNLA with early gait freezing also developed VGP earlier, indicating that the

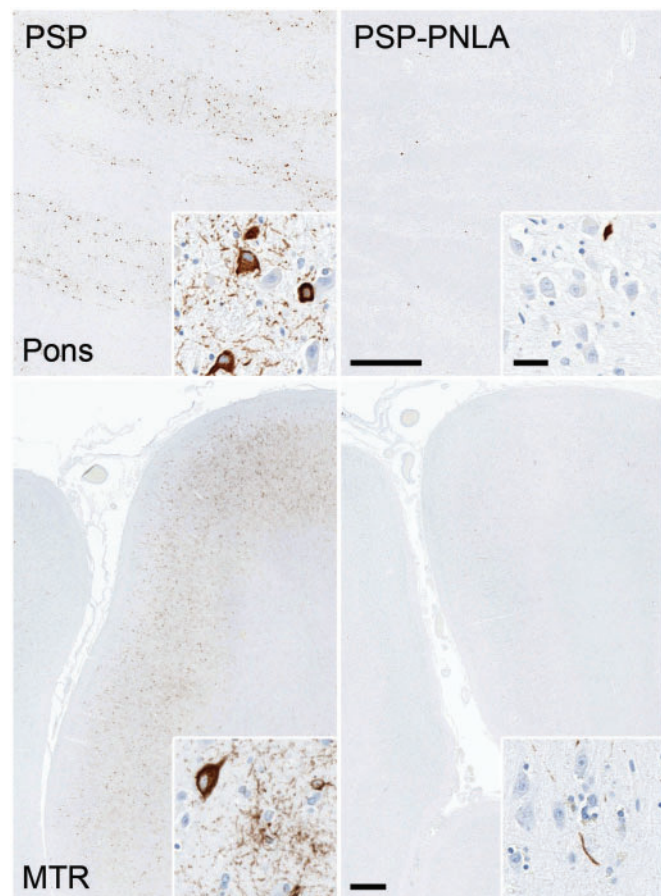


Fig. 4 Comparison of tau-pathology in the pons and MTR cortex in PSP and PSP–PNLA. In PSP, the pons has many NFT and NT in contrast to PSP–PNLA with very few. This pattern is also seen in the MTR cortex, which has NFT, TA, CB and NT in PSP cases yet only a few NFT in PSP–PNLA cases. Scale bars = 1 mm; Inset scale bars = 25 μ m.

neurodegenerative process leading to these symptoms was coincident. The onset of gait-freezing was also earlier in PSP–PNLA individuals who lived the longest.

Based on clinical research criteria for PSP (Litvan *et al.*, 1996b), the clinical diagnosis of PSP cases would be ‘clinically probable PSP’—onset at age 40 or more, postural instability (balance problems) and falls within the first year, and VGP. The clinical progression and demographics of PSP cases were also similar to those reported in clinical series of PSP (De Bruin and Lees, 1994; Collins *et al.*, 1995; Litvan *et al.*, 1996c). The demographics and clinical progression in PSP–PNLA cases, in contrast, departed from that reported in PSP. Most would not meet strict clinical research criteria for PSP. This is in part due to delayed onset of postural instability, falls and VGP. Interestingly, onset of falls after the first year has previously been reported as a prognostic indicator of good survival in PSP (Litvan *et al.*, 1996c), which was true for PSP–PNLA. PSP–PNLA cases eventually developed VGP as well as other clinical features of PSP consistent with the final clinical diagnosis of PSP in all cases.

Clinical features of PSP–PNLA compared to PA

The clinical features of our PSP–PNLA cases share some similarities to the syndrome of ‘pure-akinesia’ (PA), which was first described by Imai and co-workers (Imai and Narabayashi, 1974; Imai *et al.*, 1987, 1993; Imai, 1996). Riley and coworkers described clinical characteristics of five patients with PA who developed PSP-like symptoms later in life (Riley *et al.*, 1994). Micrographia, gait and speech problems were some of the initial features. All patients eventually developed speech problems, gait-freezing or festination and postural instability that resulted in falls. The case with the longest disease duration (14 years) developed bradykinesia, nuchal rigidity and VGP (Riley *et al.*, 1994). Imai also reported that many PA cases had VGP later in the disease course (Imai *et al.*, 1987, 1993). In most studies of PA, the term akinesia has been applied to not only gait problems (i.e. freezing or difficulty with initiation), but also to akinesia of speech (stuttering or stammering speech) and akinesia of writing (with micrographia) (Hoshino *et al.*, 1999). Interestingly, changes in handwriting were the earliest clinical feature in several PSP–PNLA cases.

No PSP or PSP–PNLA case had resting tremor or more than a minimal response to levodopa therapy. Even so, many of the patients in both groups remained on levodopa throughout the disease without suffering drug-induced dyskinesia. One should note that some cases referred to as PA have been reported to respond well to levodopa therapy, and one such case had postmortem evidence of Lewy body disease (Quinn *et al.*, 1989). A number of studies also describe a clinical syndrome similar to PA, with gait-freezing and falls occurring without other Parkinsonian features. These cases have been termed primary progressive freezing gait (PPFG) (Achiron *et al.*, 1993) or gait ignition failure (GIF) (Atchison *et al.*, 1993). Some cases of PPFG develop clinical features suggestive of PSP (e.g. VGP, postural instability and dysphagia) later in the disease course, as well as pathologic changes similar to PSP at autopsy (Compta *et al.*, 2007). In a study of nine cases, initially diagnosed as PPFG (Factor *et al.*, 2006), four evolved into a clinical syndrome resembling PSP or CBD. Autopsy studies of two of the nine cases revealed PNLA in one and diffuse Lewy body disease in another (Factor *et al.*, 2006). As in any diagnosis that is based upon a clinical syndrome, the pathology reflects distribution rather than underlying molecular pathology. For example, the pathologic substrate of the corticobasal syndrome includes several different pathologic processes, in addition to corticobasal degeneration (Boeve *et al.*, 1999). Thus, the neuropathology of PA and related clinical syndromes is likely to be heterogeneous.

Pathologic features of PSP–PNLA compared to PA

The pathologic findings of PA cases reported in the literature are summarized in Table 6. Not surprisingly, the pathologic

Table 6 Summary of pathological case reports of PA and PNLA in literature

Study	Takahashi 1977	Takahashi 1977	Homma 1987	Yamamoto 1991	Matsuo 1991	Matsuo 1991	Mizusawa 1993	Mizusawa 1993	Mizusawa 1993	Mizusawa 1993	Yoshikawa 1997	Konishi 2005
Sex	M	F	F	M	M	M	F	M	M	M	F	M
Onset	61	64	54	57	72	62	55	62	65	70	58	60
Disease duration	5	7	11	–	2	>5	21	>7	6	2	8	10
Path diagnosis	PNLA	PNLA	PSP	PSP/PNLA	PSP	PSP	PSP	PSP	PSP	PSP	PSP	PNLA
Gross atrophy	STN, GP	STN, GP	STN, GP	SN, STN	–	–	–	–	–	–	Normal	SN, STN, GP
SCP	–	–	–	Normal	–	–	–	–	–	–	–	–
SN NL	+++	+++	+++	+++	+++	+++	Y	Y	Y	Y	+++	+++
STN NL	+++	+++	Y	+++	++	++	Y	Y	Y	Y	+++	+++
GP NL	+++	+++	Y	+++	++	++	Y	Y	Y	Y	+++	+++
DN NL	N	N	Y	++	+	+	N	Y	Y	N	–	N
SN NFT	–	+	Y	–	+++	+++	+++	+++	+++	++	+++	+
STN NFT	–	–	Y	–	+	+	+++	+++	+++	++	+++	+
GP NFT	–	–	Y	–	+	+++	+++	+++	+++	++	+++	+
DN NFT	–	–	Y	+	–	+	+	–	–	+	–	+
Pons NFT	–	–	–	–	+	–	+	+	+	–	+	+
Olive NFT	–	–	–	–	–	–	+	+	+	–	+	+
MTR tau	–	–	–	–	–	–	–	–	–	–	–	–
Glial tau	–	–	–	–	–	–	–	–	–	–	–	Cb
Tau stain	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y
Silver stain	–	–	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

M = male; F = female; PNLA = pallido-nigro-luysial atrophy; PSP = progressive supranuclear palsy; Y = present; N = not present; + = Mild; ++ = Moderate; +++ = severe; – = not mentioned.

diagnoses that are most often given for PA are PSP (Takahashi *et al.*, 1987; Matsuo *et al.*, 1991; Mizusawa *et al.*, 1993; Yoshikawa *et al.*, 1997), PNLA (Takahashi *et al.*, 1977; Inagaki *et al.*, 1989; Konishi *et al.*, 2005) and in one case combined PSP and PNLA (Yamamoto *et al.*, 1991). Macroscopic atrophy accompanied by severe neuronal loss in the GP, SN and STN with relative sparing of the cerebellar DN and lower brainstem structures are consistent features in these reports. In addition, NFT pathology is described in many of these reports, mainly in regions (SN, STN, GP and DN) that are also vulnerable to PSP pathology. In comparison to silver stains, immunohistochemistry for tau is more specific and sensitive for neuronal (including pre-tangles) and glial tau-pathology. This may explain the discrepancy in frequency of glial pathology in reports of PA. The most recent case report by Konishi and co-workers reported glial tau-pathology with tau-immunohistochemistry (Konishi *et al.*, 2005). The presence of glial tau-pathology in PA supports a relationship to PSP. A major histopathological hallmark of PSP, tufted astrocytes (Nishimura *et al.*, 1992), was detected in all cases of PSP–PNLA. Biochemical data also supports a diagnosis of PSP in PNLA. Mori and coworkers reported results from immunoblot analysis of phosphorylated tau-protein in a patient with PNLA (Mori *et al.*, 2001). They identified major tau-bands at 64 and 68 kDa, which are biochemical characteristics of tau in PSP.

The preservation of hindbrain structures, such as the pontine nuclei and the cerebellar DN has been noted in reports of PA (Table 6). Our study also demonstrated less pathology in forebrain regions, such as the MTR cortex; in PSP–PNLA compared to PSP. In no region was the

tau-pathology in PSP–PNLA greater than PSP. Except for the cerebellar DN, neuronal loss was greater in all regions in PSP–PNLA compared to PSP and the SN and STN showed statistical significance. Collectively this data indicates that the differential distribution and severity of pathology in PSP and PSP–PNLA cannot be explained by obvious clinical variables and implies other environmental or genetic variables as driving factors in the two phenotypes.

Relationship of PSP–PNLA to PAGF

A detailed clinical study using pathologically confirmed PSP by Williams and co-workers suggested that PSP can be separated into two major clinical types, termed Richardson's syndrome (RS) and PSP–Parkinsonism (PSP–P) (Williams *et al.*, 2005). In the present study, PSP cases fit the syndrome of RS, with falls, balance problems or VGP within the first year. The same investigators reported the pathologic (Williams *et al.*, 2007a) and clinical features (Williams *et al.*, 2007b) of a group of patients with a clinical syndrome characterized by PA and gait-freezing (PAGF). Comparison of the clinical features of PAGF to the clinical features found retrospectively in PSP–PNLA reveals many similarities (Supplementary Material V). Unfortunately, pathological descriptions of PAGF had insufficient detail to know if they had severe pallido-nigro-luysial degeneration and axonal dystrophy (Williams *et al.*, 2007a, b). On the other hand, a regional tau severity score was used to characterize PAGF. This score was a summary measure of individual scores assigned for each of the lesion types (NFT, TA, CB and NT)

in a given region. The summary score eliminates the ability to detect differences related to a particular type of lesion, which we found helpful in differentiating PSP from PSP–PNLA, such as TA in the motor cortex and caudate (Table 5). While the median regional tau severity scores tended to be greater in RS than PAGF, statistical analyses showed relatively few differences (Williams *et al.*, 2007a). In particular, no differences were noted in tau severity score in the SN, STN or GP. Although there may be less severe tau-pathology overall in PAGF than RS, the results of the present study suggest that one should be cautious in concluding that pathological severity is less, since neuronal loss in the SN and STN might well have been as severe or worse than in RS, had this analysis been performed as in the present study of PSP–PNLA.

Differentiation of PSP and PSP–PNLA with imaging

In light of the possible differences in prognosis with respect to longevity, it would be useful to identify PSP–PNLA early in the disease course. Results of macroscopic findings in STN and SCP suggest that this might be possible with modern imaging techniques. We noted more severe atrophy of the STN in PSP–PNLA compared to PSP. Detailed imaging of the STN has significantly progressed in response to advances in deep brain stimulation therapy for PD patients (Elolf *et al.*, 2007). We also found that the width of the SCP was significantly smaller in PSP than PSP–PNLA, which has also been noted in PA (Yamamoto *et al.*, 1991). Several studies have highlighted the use of MRI techniques in assessing SCP atrophy in PSP to increase diagnostic accuracy (Paviour *et al.*, 2005, 2006). Differentiation of PSP from PSP–PNLA would theoretically be possible in a patient with atypical Parkinsonism with small STN and relatively normal SCP.

Summary

PSP–PNLA was characterized pathologically by severe degeneration and axonal dystrophy in a pallido-nigro-luysial distribution. The present study indicates that PSP–PNLA is a clinical and pathological variant of PSP. PSP–PNLA has the clinical and pathological hallmarks of typical PSP, yet the timing of clinical features, the age at onset, duration of disease, the density of pathology and the distribution of pathology make it distinct. The characteristic pattern of atrophy suggests that ante-mortem imaging might be able to differentiate PSP–PNLA from typical PSP.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgements

Z.A. is a Doctoral Candidate at the MRC Centre for Neurodegeneration Research, King's College London, Institute of Psychiatry, Department of Neuroscience, De Crespigny Park, London, SE5 8AF, UK. The authors acknowledge the valuable statistical support of Michael G. Heckman and Samuel Younkin; the assistance of Stacey Melquist and Mike L. Hutton in genetic analyses and the histological support of Monica Casey-Castanedes, Virginia Phillips and Linda Rousseau. Hiroshige Fujishiro helped with interpretation of original Japanese articles. The authors would like to thank the Society for Progressive Supranuclear Palsy and the generous brain donations from PSP patients and their families, without which these studies would be impossible. The article is funded by National Institute of Health (P50-NS40256, P01-AG17216 to D.W.D.), Society for Progressive Supranuclear Palsy (CurePSP, Inc.) and Mayo Foundation.

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