Long-Duration Progressive Supranuclear Palsy: Clinical Course and Pathological Underpinnings

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Objectives: To identify the clinical characteristics of the subgroup of benign progressive supranuclear palsy with particularly long disease duration; to define neuropathological determinants underlying variability in disease duration in progressive supranuclear palsy.
Methods: Clinical and pathological features were compared among 186 autopsy-confirmed cases with progressive supranuclear palsy with ≥10 years and shorter survival times.
Results: The 45 cases (24.2%) had a disease duration of ≥10 years. The absence of ocular motor abnormalities within the first 3 years from disease onset was the only significant independent clinical predictor of longer survival. Histopathologically, the neurodegeneration parameters in each survival group were paralleled anatomically by the distribution of neuronal cytoplasmic inclusions, whereas the tufted astrocytes displayed anatomically an opposite severity pattern. Most interestingly, we found significantly less coiled bodies in those who survive longer, in contrast to patients with less favorable course.
Interpretation: A considerable proportion of patients had a more "benign" disease course with ≥10 years survival. They had a distinct pattern and evolution of core symptoms compared to patients with short survival. The inverted anatomical patterns of astrocytic tau distribution suggest distinct implications of these cell types in trans-cellular propagation. The tempo of disease progression appeared to be determined mostly by oligodendroglial tau, where the high degree of oligodendroglial tau pathology might affect neuronal integrity and function on top of neuronal tau pathology. The relative contribution of glial tau should be further explored in cellular and animal models.

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Additional supporting information can be found in the online version of this article.

Progressive supranuclear palsy (PSP) is a rapidly progressive neurodegenerative disease characterized by a specific four-repeat (4R) tau neuropathology affecting neurons, astrocytes, and oligodendrocytes.[1–3] The progression of PSP is thought to be driven by cell-to-cell and region-to-region spreading of tau pathology, analogous to the prion-like spreading mechanism observed in many neurodegenerative diseases.[4,5] Recently, significant progress has been made in the understanding of the clinical heterogeneity within this entity, comprising variable combinations of akinetic-rigid, cognitive, behavioral, speech/language, and ocular motor symptoms.[2]

The prognosis of PSP is generally poor with a mean survival of 7 to 8 years.[2,5] However, several studies reported individual cases of autopsy-confirmed PSP that survived longer than 10 years,[2,6,7] which further speaks in favor of the surprisingly vast variability within this entity.

So far, there are no systematic studies dealing with clinico-pathological determinants of long-duration PSP (LD-PSP). We addressed this issue by exploring the characteristics of PSP subgroups with different disease duration, aiming to define biological determinants underlying the variability in disease duration and prognostic factors, which would allow risk stratification in PSP. At the same time, we explored neuropathological underpinnings associated with the heterogeneity in disease duration.

Methods

Patient Consent and Collection of Data

This study included 186 pathologically confirmed patients with PSP, collected from five brain banks: Center for Neuropathology and Prion Research, Ludwig-Maximilians-University, Munich, Germany; MRC London Neurodegenerative Diseases Brain Bank, King's College, London, UK; Netherlands Brain Bank, Amsterdam in collaboration with the Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands; Neurological Tissue Bank of the Biobanc–Hospital Clinic–IDIBAPS, Barcelona, Spain in collaboration with the Neurology Department of the Hospital Clínic Barcelona, Spain; Brain Bank of the Royal University Hospital, University of Saskatchewan, Canada. The brain samples, which were available for further detailed pathological analysis, were sent to the Center for Neuropathology and Prion Research, Munich (the German national reference center for neurodegenerative disorders and the coordinating center of the BrainNet Europe), where standardized central verification of the pathological diagnosis of PSP and further neuropathological assessments were performed. The neuropathological diagnosis of PSP was confirmed according to the National Institute of Neurological Disorders and Stroke neuropathological criteria[8] with the specifications in Dickson and colleagues.[9] For this study, the major criterion for the neuropathological diagnosis of PSP was the presence of tufted astrocytes in the anterior striatum (preferably in the head of the caudate nucleus) and/ or in the cortex of the anterior medial frontal gyrus. All cases were previously published.[2,5,10–12] However, these studies did not analyze the research question of the current manuscript, i.e., the pathological and clinical features in different survival groups.

Written informed consent was obtained from all donors or their next of kin before death, according to the Declaration of Helsinki for the use of the brain tissue and clinical records for research purposes. The work was approved by local institutional review boards and ethics committees at each participating center.

Clinical Data

Detailed clinical information was extracted in standardized manner from the 186 patients' medical records. The clinical features listed in Supporting Information Table S1, which is available online,[3] were recorded and considered present if specifically mentioned in the clinical notes. They were considered absent if they were specifically mentioned as absent, or if they were not mentioned ("not available"). The onset of features relative to disease onset was recorded. If the onset of a symptom or sign could not be abstracted from the files, the year of onset was excluded from the analysis of their temporal evolution.

Pathological Evaluation and Immunohistochemistry

Detailed pathological examination was performed on 97 out of 186 brain samples. All immunohistochemical stainings for hyperphosphorylated microtubule-associated protein tau, using the mouse monoclonal AT-8 antibody, were performed as previously described.[11]

Neuropathological Assessment of Tau Inclusion Frequency and Neurodegenerative Changes

The tau pathology scores were determined in PSP samples using a semi-quantitative four-point severity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe), as it is previously described.

Scores were assessed separately for each of the following tau-lesion types: neuronal cytoplasmic inclusions (NCIs), pre-inclusions, neuropil threads (NTs), tufted astrocytes (TAs), and cytoplasmic oligodentroglial inclusions in the form of coiled bodies (CBs) together with threads in the white matter, as well as for spongiosis, gliosis and neuronal loss as parameters for neurodegenerative changes.

The following anatomical regions were examined: cortex and subcortical white matter of (a) the medial frontal gyrus (level of nucleus accumbens), (b) the anterior

cingulate gyrus (GC), (c) the inferior parietal lobe, (d) the medial and superior temporal gyri, and (e) the striate and adjacent peristriate area, insular cortex at level of pallidum, amygdala, hippocampus region divided into 4 areas (CA1/2, CA3/4, dentate gyrus, and subiculum), (trans) entorhinal cortex, claustrum, putamen, globus pallidus (GP), caudate nucleus (CAU), nucleus basalis Meynert (NbM), nucleus accumbens, thalamus, subthalamic nucleus (STN), hypothalamus, cerebellum, substantia nigra (SN), superior colliculus, nucleus ruber, oculomotor nucleus, inferior colliculus, locus coeruleus (LC), pontine nuclei, dorsal raphe nucleus, dorsal nucleus nerve X, nucleus nerve XII, and medulla oblongata at obex level.

The Assessment of Co-Pathology

Diagnoses and stages of co-pathologies were established according to standardized criteria, as follows:

- *Alzheimer's disease-related pathology* (Thal phases of amyloid beta plaques;[13] Consortium to Establish a Registry for Alzheimer's Disease [CERAD] neuritic plaques frequency scores;[14] and Braak & Braak stages based on the localization and density of neuropil threads immunopositive for hyperphosphorylated tau visualized by clone AT-8 antibodies.[15] Braak & Braak stages were confirmed by the immunohistochemical detection of 3-repeat tau-isoform positive neurofibrillary tangles visualized by clone RD3 antibodies;
- *Argyrophilic grains* (Saito stages);[16]
- *Lewy-related pathology* (Braak stages);[17]
- Presence of *TDP-43* and fused in sarcoma (*FUS*)-positive inclusions;
- *Cerebral amyloid angiopathy* (Thal stages);[18]
- *Small vessel disease* (SVD stages).[19]

Details on the evaluation of co-pathology are given in previously published paper.[11]

Conceptual Approach and Statistical Analysis

Our investigation contained several steps:

1. Defining survival groups

LD-PSP was defined by the neuropathological diagnosis of PSP and a disease duration ≥10 years after onset of first PSP-related symptoms (considering any new onset neurological, cognitive, or behavioral deficit that subsequently progresses during the clinical course in absence of other identifiable causes).[3] This threshold was used as it represented the 75th percentile of normally distributed disease duration in our cohort. In addition to this, the 10-years disease duration threshold represents longer survival compared to the commonly reported average range of 7 to 8 years in the litterature.[2,5]

The LD-PSP survival group was compared to two additional survival groups, i.e., short-duration PSP (*SD-PSP*) with survival of <5 years (25th percentile), and intermediate PSP (*IM-PSP*) with disease duration of 5 to 10 years.

2. Clinical characteristics of LD-PSP

We analyzed the differences in frequency and temporal evolution of main clinical milestones in the defined survival groups. Therefore, we relied on clinically obvious and meaningful features, which were commonly documented in the available records.[2,3] These clinical features included clinical diagnoses (first and last *ante mortem* record), age at symptom onset, age at death, disease duration, postural instability with falls, abnormal saccades or pursuits, supranuclear gaze palsy (SNGP), frontal lobe dysfunction, cognitive dysfunction, dysarthria, dysphagia, bradykinesia, tremor, asymmetry at onset, and levodopa responsiveness. These features were considered present if specifically mentioned in the clinical notes. They were considered absent if they were specifically mentioned as absent or if they were not mentioned ("not available"). The onset of features relative to disease onset was recorded. If the onset of a symptom or sign could not be abstracted from the files, the year of onset was excluded from the analysis of their temporal evolution. The clinical predominance type for each patient was assigned using the operationalized Movement Disorders Society PSP diagnostic criteria (MDS-PSP criteria).[3,10]

The proportional distribution of categorical variables was analyzed with the chi-squared (χ^2) test or Fisher's exact test where applicable. To compare non-parametric or parametric data between two groups, Mann–Whitney-U test or t test (with Bonferroni correction) was used, respectively. If necessary, one-way analysis of covariance was used to control differences between groups while considering potential covariates. The associations between all clinical characteristics listed in Supporting Information Table S1 (present vs absent within the first 3 years) and respectively a long (≥10) and short (<5 years) disease duration were examined by binominal logistic regression models (multiple comparison problems in these models, were taken into account using Holm's approach; the models were adjusted for age at onset).

3. Neuropathological characteristics of LD-PSP

Patients were removed from neuropathological analysis if they had >50% missing data across defined neuroanatomical regions for the given tau pathology measure and/or neurodegenerative changes (see Supporting Information Figure S1: Flow chart of the study).

In order to perform regional distribution analyses, 34 investigated regions across the brain were further

grouped into the following *four brain regions*: (1) *Cortical*: the medial frontal gyrus (level of nucleus accumbens), GC, the inferior parietal lobe, the medial and superior temporal gyri, the striate and adjacent peristriate area, insular cortex at level of pallidum; (2) *Temporomesial*: amygdala, hippocampus divided into 4 areas (CA1/2, CA3/4, dentate gyrus, subiculum), (trans)entorhinal cortex; (3) *Subcortical*: claustrum, putamen, GP, CAU, NbM, nucleus accumbens, thalamus, STN, hypothalamus; and (4) *Brainstem/cerebellum*: cerebellum, SN, superior colliculus, nucleus ruber, oculomotor nucleus, inferior colliculus, LC, pontine nuclei, dorsal raphe nucleus, dorsal nucleus nerve X, nucleus nerve XII and medulla oblongata at obex level.

The semiquantitative scores of each of the cellular tau lesion types and each of the neurodegenerative lesions in those four brain regions were compared: (1) *within the survival group*: if the average score for a certain lesion in one region was significantly higher than for the other, we displayed that with different color coded heatmaps (Kruskal-Wallis test, with posthoc pairwise comparison between anatomical brain regions, p values adjusted for multiple comparisons, $p < 0.05$); and (2) *between two survival groups*: the differences of average severity score in 4 anatomical regions were investigated by Mann–Whitney *U* test, $p < 0.05$.

Nonparametric Spearman correlation was used to analyze correlations between disease duration and each investigated pathological lesions (the significance of p set as $p < 0.01$).

All data were analyzed using the IBM SPSS statistical software package (version 23.0; IBM Corp., Armonk, NY).

Results

Demographic Features

The demographic features are shown in Table. Of 186 PSP patients with sufficient clinical data, 45 (24.2%) had a long disease duration of ≥10 years (mean: 13.8 [10–27] years) and are referred to as LD-PSP group. On average, LD-PSP were younger at disease onset, when compared to those with SD-PSP, and significantly older at the time of death when compared to both groups with less favorable disease course. More than 2/3 of cases died after 2000, with a similar proportion of such cases in all survival groups. Only 4 of the 186 cases included in this study died in the 1970s and 1980s, all in the SD-PSP group. No differences were found in sex distribution between the groups.

Frequency of Clinical Milestones

The frequency of important clinical milestones in the different survival groups of the 186 definitive PSP cases are presented in Figure 1 and Supporting Information Table S2.

When analyzing the entire clinical course, patients with LD-PSP more often had asymmetric onset, L-dopa responsiveness, bradykinesia and falls, in comparison to SD-PSP patients. On the other hand, in contrast to IM-PSP, SNGP and dysphagia were less prevalent in the overall disease course of LD-PSP, while levodopa responsiveness consistently occurred more frequently in LD-PSP, when compared to both groups with less favorable disease course.

When analyzing only the first 3 years of the clinical course, LD-PSP showed the lowest prevalence of the majority of investigated clinical features (ocular motor abnormalities, frontal/cognitive dysfunction, dysarthria, and dysphagia), but there were no differences between the prevalence of falls, tremor, and bradykinesia, even when compared to the most progressive group of SD-PSP.

Temporal Evolution of Clinical Milestones

The typical clinical disease course differed markedly between LD-PSP and both groups with less favorable disease course (SD-PSP, IM-PSP), whereas the latter 2 did not differ from one another (Fig 2, Table S2).

The time to reach essential clinical milestones were significantly prolonged in LD-PSP, compared to those with less favorable disease course, while the latency to onset of tremor, did not differ significantly between survival groups.

The earliest milestones in LD-PSP were tremor, followed by bradykinesia, while clinical hallmarks of PSP, such as onset of falls, cognitive and frontal dysfunction, bulbar dysfunction, and SNGP, occurred after more than 5 years from the disease onset, on average. In contrast, both groups with shorter survival presented with identical sequencing of clinical features in their timelines: falls were the earliest clinical manifestation and all clinical milestones developed within 4 years from disease onset. Additionally, we observed close temporal association of the occurrence of dysphagia and SNGP, which preceded the onset of death in all investigated groups (Fig 2).

The distribution of the first and last *ante mortem* recorded PSP predominance types in LD-PSP according to the MDS-PSP criteria, differed significantly from both groups with poorer survival (Supporting Information Table S3, Fischer's exact test, $p \leq 0.05$). PSP with Richardson's syndrome (PSP-RS) and PSP-postural instability (PSP-PI) were the most common phenotypes at initial record in SD-PSP and IM-PSP, while LD-PSP patients mainly had PSP-PI and PSP-parkinsonism (PSP-P) variants as initial presentation. At final record, the most prevalent phenotype was PSP-RS in all survival groups, but PSP-P, PSP-speech/language disorder (PSP-SL) and PSP-corticobasal syndrome were more frequent in LD-PSP. On the other hand, pure PSP-frontal cognitive/behavioral presentation (PSP-F) was observed only in SD-PSP and IM-PSP.

TABLE. Demographic Data of the Clinical Analysis Cohort of Autopsy-Confirmed Patients with Progressive Supranuclear Palsy, Subclassified by Their Survival Times

	Data				*p* Values [95% Confidence Interval for Difference][a]		
	All PSP	LD-PSP	IM-PSP	SD-PSP	LD Versus IM	LD Versus SD	IM Versus SD
Patients, N (%)	186	45 (24.2)	101 (54.3)	40 (21.5)			
Female: male	93:93	25:20	48:53	20:20	0.370[1]	0.609[1]	0.791[1]
Age at disease onset	66.2 ± 8.6	63.9 ± 8.0	66.3 ± 8.2	68.6 ± 9.6	0.093[2]	**0.014**[2]	0.154[2]
	[41–91]	[41–78]	[47–87]	[51–91]	[−0.414, 5.334]	**[0.973, −8.554]**	[−0.877, 5.474]
Age at death	74.0 ± 8.6	77.6 ± 8.0	73.2 ± 9.4	71.9 ± 9.4	**<0.003**[2]	**0.004**[2]	0.433[2]
	[54–94]	[59–92]	[54–94]	[55–93]	**[−7.341,-1.591]**	**[−9.460,-1.979]**	[−4.402, 1.895]
Disease duration	7.8 ± 4.5	13.8 ± 4.6	6.9 ± 1.4	3.3 ± 0.8	**<0.001**[3]	**<0.001**[3]	**<0.001**[3]
	[1–27]	[10–27]	[5–9]	[1–4]	**[−7.915,-5.938]**	**[−11,937, −9.018]**	**[−4.024,-3.079]**
Initial clinical diagnosis							
Correct, N (%)	32 (17.2)	2 (4.4)	23 (22.7)	7 (17.5)	**0.013**[1]	0.110[1]	0.644[1]
Not correct, N (%)	77 (41.4)	26 (57.8)	37 (36.7)	14 (35.0)	**0.027**[1]	0.059[1]	0.990[1]
Not reported, N (%)	77 (41.4)	17 (37.8)	41 (40.6)	19 (47.5)	0.890[1]	0.492[1]	0.273[1]
Final clinical diagnosis							
Correct, N (%)	110 (59.2)	21 (46.7)	67 (66.3)	22 (55.0)	**0.039**[1]	0.302[1]	0.287[1]
Not correct, N (%)	51 (27.4)	18 (40.0)	19 (18.8)	14 (35.0)	**0.012**[1]	0.802[1]	0.067[1]
Not reported, N (%)	25 (13.4)	6 (13.3)	15 (14.9)	4 (10.0)	0.988[1]	0.889[1]	0.626[1]
Cause of death							
PSP-related, N (%)	164 (88.2)	43 (95.5)	88 (87.1)	33 (82.5)	0.210[1]	0.110[1]	0.658[1]
PSP-unrelated, N (%)	22 (11.8)	2 (4.5)	13 (12.9)	7 (17.5)			

Note: Values are presented in years, as means ± standard deviations [range], unless noted otherwise. IM, intermediate duration (survival ≥5 and <10 years); LD, long duration (survival ≥10 years); PSP, progressive supranuclear palsy; SD, short duration (survival <5 years). *p* values: [1] $\chi 2$ test, [2]Two-sample *t*-test, [3]Mann-Whitney-*U*-test.

[a]95% Confidence intervals for difference are presented in the table, except for $\chi 2$ test.

Predictors of Survival

Data from binominal logistic regression models are presented in Supporting Information Table S4. The absences of SNGP and of abnormal saccades or pursuits in the first 3 years from disease onset were the only significant independent predictors of LD-PSP. On the other hand, presence of ocular motor dysfunction and of frontal dysfunction in the first 3 years from disease onset, highly predicted poor survival of less than 5 years. Patients presenting frontal lobe dysfunction in the first 3 years from

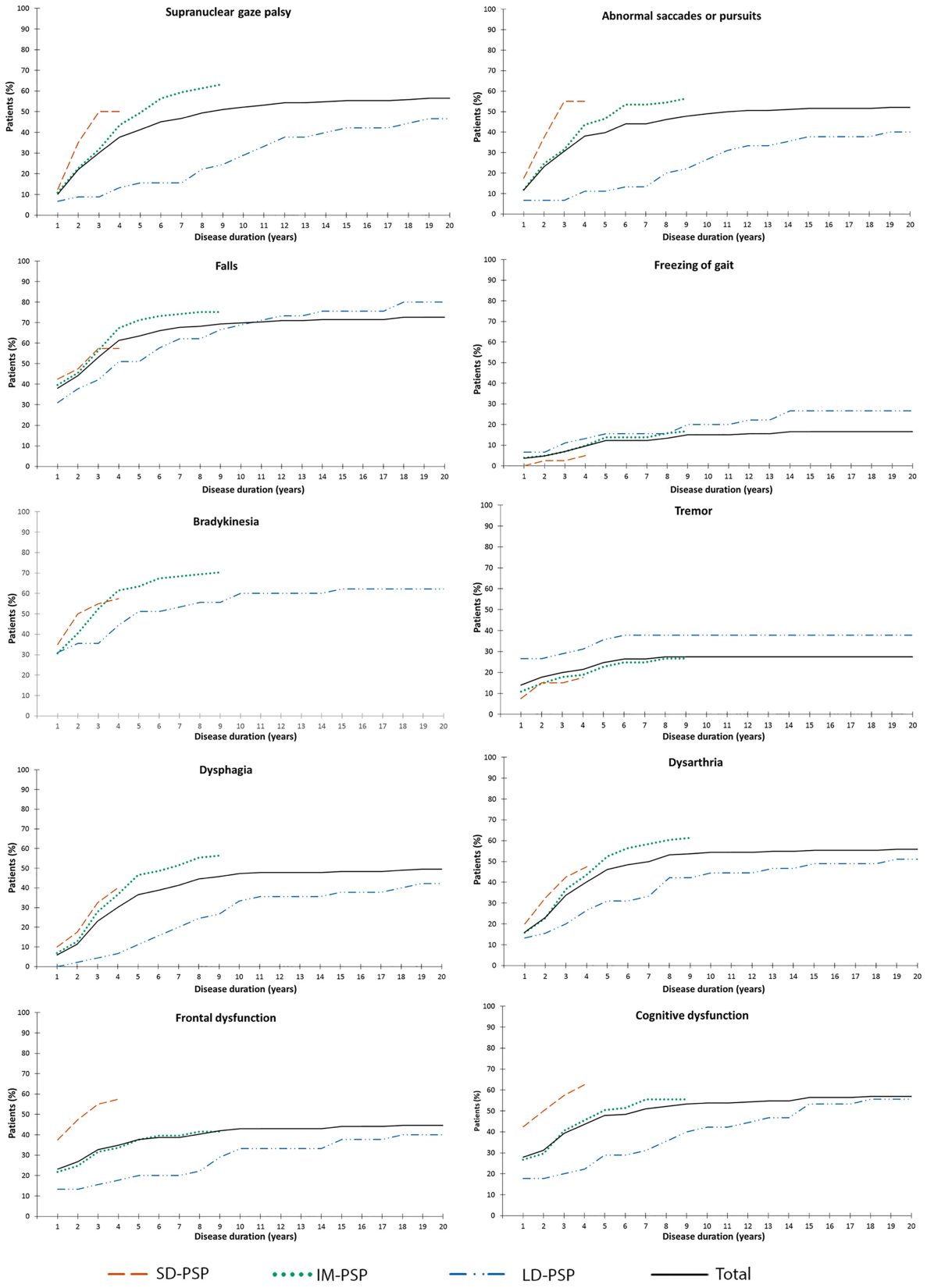


FIGURE 1: Cumulative risk of acquiring important disease milestones in the clinical analysis cohort of autopsy-confirmed patients with progressive supranuclear palsy, subclassified by their survival times. Abbrevations: IM, intermediate duration (survival ≥5 and <10 years); LD, long duration (survival ≥10 years); PSP, progressive supranuclear palsy; SD, short duration (survival <5 years). [Color figure can be viewed at www.annalsofneurology.org]

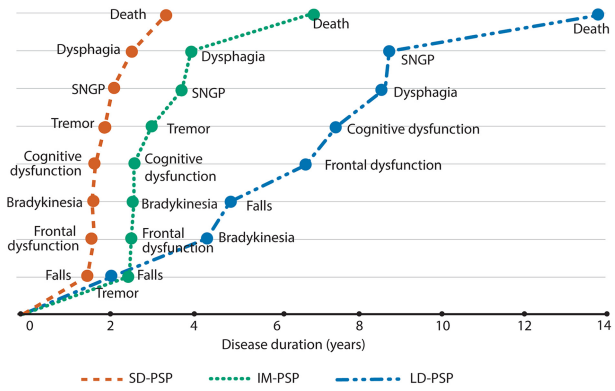


FIGURE 2: Average sequence of reaching disease milestones in the clinical analysis cohort of 186 autopsy-confirmed patients with progressive supranuclear palsy, subclassified by their survival times. Abbreviations: IM, intermediate duration (survival ≥5 and <10 years); LD, long duration (survival ≥10 years); PSP, progressive supranuclear palsy; SD, short duration (survival <5 years); SNGP, supranuclear gaze palsy [Color figure can be viewed at www.annalsofneurology.org]

the disease onset had over 250% higher odds to get into the group of SD-PSP.

Neuropathological Features of LD-PSP

Detailed histopathological analysis was performed in 97 patients out of 186 PSP cases. No differences were found between PSP cases included in clinical and PSP included in neuropathological analysis, in terms of baseline demographic characteristics (Supporting Information Table S5).

Given that patients with SD-PSP and those with IM-PSP showed remarkably similar clinical patterns (see the Results, *Temporal evolution of clinical milestones* section), these two groups were merged into one (labeled SD/IM-PSP) in order to analyze the pathological characteristics of this shared phenotype in contrast to the clinically distinct LD-PSP group. Therefore, pathological characteristics of 23 LD-PSP patients were further compared with 74 SD/IM-PSP patients (Table S6). The average disease duration in LD-PSP and SD/IM-PSP was 13.1 and 5.8, respectively. There were no significant differences between LD-PSP and SD/IM-PSP in age at onset, age at death, nor in the sex distribution. Non-PSP-related causes of death were similar between groups.

The distribution of PSP phenotypes in the pathological analysis cohort, according to the MDS-PSP criteria, did not differ between LD-PSP and SD/IM-PSP (Supporting Information Table S7, Fischer's exact test, $p > 0.05$).

Since different clinical syndromes of PSP are closely associated with the distribution and severity of underlying pathology,[5] we aimed to analyze differences in regional severity of neurodegenerative changes and tau specific lesions, which could account for different clinical pattern in two survival groups (LD-PSP and SD/IM-PSP) (Fig 3).

Neuronal Tau Inclusions

The regional distribution analysis of *pre-inclusions* scores revealed the same pattern in both survival groups. Brainstem/cerebellum and temporomesial areas were equally affected, followed by less prominent findings in cortical and subcortical areas (Fig 3A).

The pattern of *NCIs* findings was also consistent across two survival groups. Brainstem/cerebellum regions were found to be most affected, followed by subcortical and temporomesial areas, which were involved at similar extent (Fig 3A, B). Among these regions, the highest rates of NCIs were found in mesencephalic nuclei (including SN), cerebellum, STN, LC, NbM, GP, and CAU. The cortical lobar areas were less involved, with the highest score found in GC.

NTs had high densities in brainstem/cerebellum and subcortical regions, while cortical areas were relatively spared, in both survival groups (Fig 3A).

In summary, there was no difference in neuronal tau load between the survival groups.

Glial Tau Changes

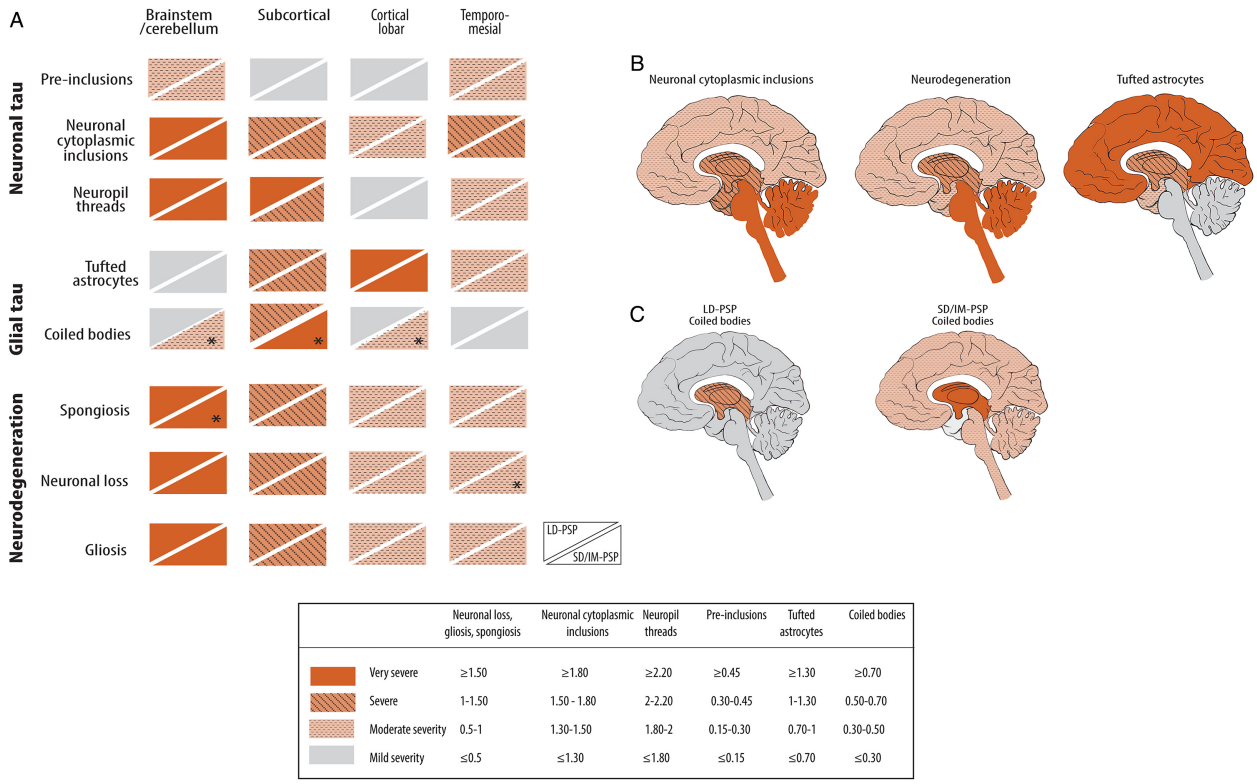
The regional pattern of TA revealed an opposite gradient of severity compared to neurodegenerative and neuronal tau changes, with a downward gradient from cortical to brainstem regions, with frontal cortex being most affected (Fig 3A, B).

CBs were most prominent in subcortical structures in both survival groups. However, we found that patients with LD-PSP had lower CB-load in subcortical, cortical, and infratentorial regions, when compared to SD/IM-PSP (Fig 3A, C). Moreover, GP, which is found to be one of the regions of interest deemed most specific to CBs, was significantly less affected in LD-PSP ($p = 0.013$, Mann–Whitney U test).

Neurodegenerative Changes

The highest scores of neuronal loss, gliosis, and spongiosis were found in the brainstem/cerebellum areas, followed by the subcortical areas. Cortical lobar and temporomesial areas were affected at similar extent (Fig 3A, B). The most severe scores were found in GP, STN, SN, mesencephalic nuclei, and cerebellum.

Both survival groups had a similar pattern of neurodegeneration throughout the brain, except that LD-PSP had higher rate of spongiosis in the brainstem/cerebellum and higher rate of neuronal loss in the temporomesial region.



	Neuronal loss, gliosis, spongiosis	Neuronal cytoplasmic inclusions	Neuropil threads	Pre-inclusions	Tufted astrocytes	Coiled bodies
Very severe	≥1.50	≥1.80	≥2.20	≥0.45	≥1.30	≥0.70
Severe	1-1.50	1.50 - 1.80	2-2.20	0.30-0.45	1-1.30	0.50-0.70
Moderate severity	0.5-1	1.30-1.50	1.80-2	0.15-0.30	0.70-1	0.30-0.50
Mild severity	≤0.5	≤1.30	≤1.80	≤0.15	≤0.70	≤0.30

FIGURE 3: Heat mapping of different cellular tau pathologies in PSP, subclassified by their survival times. (A) Severity of specific lesion is coded by a heat map, according to the presented legend. Different graphical/color tones also indicate the presence of significant differences between average scores of observed pathology in predefined 4 brain regions, *within the survival groups* (Kruskal-Wallis test, with posthoc pairwise comparison between regions, *p* values adjusted for multiple comparisons, for more details please see Supporting Information Table S8). *Significant differences were found for certain subregions *between survival groups* (Mann–Whitney U test, $p < 0.05$, Table S8). (B) Pseudo-colored brain diagrams: the opposite pattern of neurodegeneration and tufted astrocytes, observed in both survival groups. (C) Pseudo-colored brain diagrams: the pattern of coiled bodies in patients with progressive supranuclear palsy, subclassified by their survival times. Note that the only significant differences between survival groups were found in coiled bodies pathology, whereas cases with long disease duration had lower scores. Abbreviations: LD, long-duration PSP, progressive supranuclear palsy; SD/IM, short duration/intermediate duration. [Color figure can be viewed at www.annalsofneurology.org]

Correlation of Disease Duration and Pathological Findings

Among all investigated tau-lesion types across 4 different brain regions, only neuronal loss (Spearman's rho = 0.293, $p = 0.004$) and CBs (Spearman's rho = −0.259, $p = 0.009$) in cortical lobar areas (Supporting Information Figure S2) correlated significantly with disease duration.

Co-Pathology Findings in Different Survival Groups

The severity and prevalence of co-pathology findings were similar among survival groups, except that CERAD positive findings were more frequent in LD-PSP (39.1% vs 16.2%, χ^2 test, $p = 0.02$), without differences in the severity scores (Supporting Information Figure S3).

Discussion

The present study is first to summarize the detailed clinicopathological characteristics of patients with autopsy-confirmed PSP with regard to disease duration. As many as 24.2% of PSP patients had an unexpectedly long disease duration of ≥10 years (LD-PSP), presenting with a distinctive pattern and timeline of core clinical features. The absence of ocular motor abnormalities in the first 3 years from disease onset was the only significant independent predictor of longer survival. We observed no significant difference in neuronal loss between the LD and SD/ID subgroups, indicating that – at time of death – both groups were equally affected by neurodegeneration. The neurodegeneration parameters were paralleled anatomically by the distribution of neuronal tau deposits (specifically NCIs), but not TAs and CBs, suggesting that neuronal more than glial tau deposits relate to neurodegeneration. Interestingly, there were no differences in the severity of TAs between the LD and SD/ID, but TAs displayed an opposite anatomical severity pattern than NCIs, indicating distinct implications of these cell types in trans-cellular propagation. CBs, in contrast, displayed a similar anatomical severity pattern as NCIs, pointing that oligodendroglial and neuronal tau

spreading may be linked via joint mechanisms and follow similar propagation pathways. Most interestingly, we found significantly more CBs in SD/ID than in LD patients, suggesting that patients with less oligodendroglial tau pathology appear to survive longer.

Clinical Background of LD-PSP

Disease duration of PSP ranges in the literature between 7 and 8 years on average.[2,20] However, these and other clinico-pathological studies on PSP reported a high variability of disease duration, with individuals who survived considerably longer than 10 years.[2,6,21–24] In our cohort, 21.5% of PSP patients died within 5 years, increasing to 75.8% within 10 years, whereas 24.2% of patients survived ≥10 years from symptom onset. The high percentage of LD-PSP found here is higher than expected by prior clinical studies and might be explained by the inclusion of only pathologically confirmed cases.

The more favourable disease course of LD-PSP was highlighted by the lower prevalence of clinical milestones reached in the first 3 years of the disease, different sequencing of clinical features over time, and by the prolonged latency to onset of clinical milestones. Interestingly, by the time patients with both median and short survival had developed all debilitating clinical milestones (4 and 3 years on average, respectively), PSP-specific clinical features had not even started to appear in LD-PSP. These results are consistent with other studies,[25–27] showing us that the tempo of accumulation of clinical features in the early phase of PSP plays an important role in determining the further disease course.

Previous studies trying to assess the likelihood of survival, have used very heterogenous methodologies and have identified different clinical parameters as possible determinants of short disease duration: occurrence of falls,[28,29] speech and swallowing problems,[27,28,29] SNGP,[27,30,31,32] PSP-RS phenotype,[25,27] older age of onset,[25,29] male gender,[25] a short interval from disease onset to reaching the first clinical milestone,[25,26] early insertion of the percutaneous gastrostomy,[29] motor severity score,[33] and early cognitive symptoms.[27,34] We were able to control for the majority of these factors in our study. However, in our PSP cohort the only significant predictor of survival was the early presence or absence of ocular motor abnormalities, which were important in the further dichotomy of survival groups. Several studies have already suggested our main finding, i.e. the predictive value of oculomotor dysfunction for life expectancy in PSP,[35,30,31,32] but the prior evidence for such an association was based on small case numbers and /or lack of autopsy confirmation.[27] The reason why absence or presence of ocular motor dysfunction in PSP is so decisive about the prognosis and future rate of disease progression remains elusive so far. In light of recent evidence suggesting that tau pathology is spreading along neuronal pathways,[36] the affection of brainstem ocular motor centers might facilitate the spread of PSP pathology into vital brainstem centers, e.g., such leading to dysphagia, which we found to occur in close temporal association with SNGP in our study and which is marked as a poor prognostic sign in PSP, preceding the death.[26,27,37] Delayed onset of dysphagia in benign PSP could be responsible, at least to some degree, for longer disease duration in this particular group.

In addition to SNGP, early presence of frontal dysfunction also predicts poor outcome in PSP, which is in line with previous findings,[27,34] probably reflecting the presence of widespread pathological changes, from brainstem to the frontal cortex, in the early stages of the disease.

We were unable to identify falls as an important determinant of disease duration in our study. However, our data showed that falls emerged significantly later in patients who survived longer.

Although the timeline and pattern of symptoms in LD-PSP observed in this study, highly resemble the course of the PSP-P phenotype, only one-third of LD-PSP presented with PSP-P at initial presentation, and even less (21%) at final record.[2,3,38] High diversity of phenotypes observed in all survival groups, both at initial and final records, demonstrates that differences in survival could not be explained by the PSP-P phenotype alone, despite the fact that this is the most common initial manifestation of LD-PSP, together with PSP-PI. In support of this, initial absence of oculomotor abnormalities, which is found to be the only significant determinant of longer survival in our cohort, is not exclusively characteristic of PSP-P phenotype, but has been described in other phenotypes, such as PSP-PGF, PSP-SL, and PSP-PI (ref).[3,39,40,41] Moreover, asymmetric onset, bradykinesia, and tremor, which belong to the core clinical features of PSP-P,[38] were not useful in distinguishing different survival groups in our study.

Neuropathological Background and Pathophysiological Implications of LD-PSP

Several significant observations emerged from our neuropathological analysis of LD-PSP.

In our series, the parameters of neurodegeneration followed the expected pattern (subcortical > brainstem/cerebellum > temporomesial > cortical),[42] and at the same time paralleled the distribution and density of neuronal tau inclusions (Fig 3A, B). Again, no major differences were found between 2 survival groups in neurodegeneration and neuronal tau inclusions, except that LD-PSP had more spongiosis in brainstem/cerebellum regions and more neuronal loss in temporomesial area. However, our

results indicated that the speed of the pathological process differed between investigated survival groups, because a similar pathologic endpoint was reached in both groups, despite differing disease duration. Analogous conclusions were reached in previous studies which correlated clinical progression with pathologic findings in PSP and other neurodegenerative disorders.[38,43]

The most interesting findings of our analysis are related to glial tau changes between survival groups, despite the lack of obvious differences in neuronal tau and neurodegeneration. It has been shown recently that the phenotypes in PSP are primarily conditioned by the dynamics of neuron–glia tau changes in brain regions, with oligodendrocytic tau showing highest variability between subtypes.[5] In that regard, our neuropathological analysis also revealed that survival variability is mainly influenced by pathology of oligodendrocytes, in the sense that LD-PSP had less CBs (Fig 3A, C). This finding was further confirmed by the negative correlation found between disease duration and the amount of CBs on the cortical level (Supporting Information Figure S2). Moreover, GP, which is found to be one of the regions of interest deemed most specific to CBs, was significantly less affected in LD-PSP.

Our findings on significance of CBs in the progression and clinical heterogeneity in PSP had already been suggested in prior clinico-pathological series. Josephs et al. pointed to the inverse relationship of disease duration and CBs burden in PSP.[44] Additionally, the PSP-tau score proposed by Williams and colleagues, which actually reflects the severity of CBs and threads throughout the brain, was found to be lower in PSP-P patients which generally shows a slower disease progression than PSP-RS.[34]

The question remains whether oligodendrocytic tau precedes, parallels, or follows neuronal tau in the process of neurodegeneration in PSP. Two possible hypotheses regarding the role of oligodendrocytes in PSP, which we pictured in Figure 4, emerge from our study.

The first hypothesis could be that *neuronal tau pathology is likely to be primary in PSP*, since tau expression is much higher in neurons than glial cells.[45] One may speculate that *oligodendrocytes are removing toxic tau from neurons and dictate the speed of axonal dysfunction and ultimately neuronal loss*. At that moment, when tau spreading also affects oligodendrocytes, consequent axonal dysfunction likely complicates neuronal dysfunction, leading to earlier onset of clinical symptoms and earlier death, observed in PSP patients with higher CB load (might be linked to oligodendrocyte-affine tau strains or an oligodendrocyte-intrinsic capacity to clear tau aggregates).

The second hypothesis starts from the assumption that *oligodendrocytes could be a starting point and determinant of progression of tau-related neurodegeneration*, which was proposed as possible scenario in glial-tau animal models.[46] These models suggest in the initial disease stages a *primary oligodendrocyte-phenotype* responsible for the onset and initiation of functional deficits. At later time points, through the influence of oligodendrocytic tau on neuronal integrity, a *secondary neuronal degenerative phenotype* may evolve.[46] Accordingly, PSP might be considered as primary oligodendrogliopathy. Although there is only rare evidence to support the relevance and extent of oligodentdrocytic contributions to the seeding and spreading of tau pathology,[46,47] our data firmly suggest that the tempo of progression of PSP is strongly related to CB pathology.

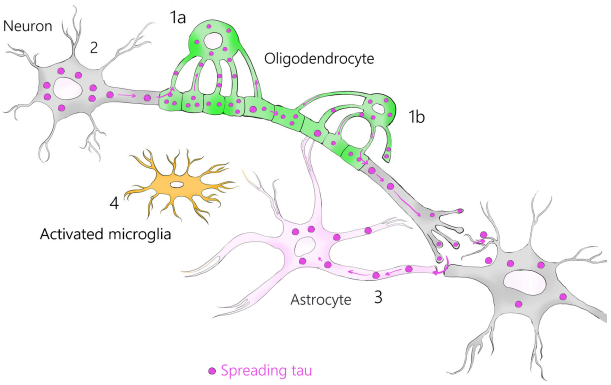


FIGURE 4: Hypotheses of neuron–glia interactions in tau spreading to explain the pathological patterns observed in the current study in progressive supranuclear palsy. (1) Oligodendrocytes, 2 hypotheses: (A) oligodendrocytes may remove spreading tau originated in neurons; higher oligodendrocytic tau degradation capacity may, thus, reduce the tempo of neuronal degeneration, or (B) oligodendrocytes may be targeted by tau-pathology; higher tau burden in oligodendrocytes may lead to dysfunction of oligodendrocytes and thus accelerate the tempo of neuronal degeneration; (2) Alterations of the microtubule-associated protein tau and axonal transport in neurons. Neurons are excreting the spreading-competent tau into extracellular space to spread it to neighboring cells; (3) Astrocytes may play a functional role in modulating extracellular tau spreading by inhibiting the propagation of spreading-competent tau; (4) Inflammatory response, including microglial activation, resulting in gliosis and neurodegeneration. [Color figure can be viewed at www.annalsofneurology.org]

Another important observation that arises from our neuropathological analysis is the inverse gradient of TAs density in contrast to neuronal tau pathology and neurodegenerative changes, above all to the severity of reactive gliosis. These results suggest two possible mechanisms of pathogenesis. First, the inverse gradient of TAs and gliosis tells us that these 2 processes appear not to be directly connected to one another. These findings are in line with previous analysis in a smaller PSP cohort, confirming the notion that astrocytic-tau accumulation does not seem to contribute directly to reactive gliosis.[48] Second, the inverse

gradient between neuronal and astrocytic tau pathology observed in the selected regions, suggests there may be transmission of pathological tau from neurons to neighboring astrocytes. One may speculate that astrocytes have a protective role by scavenging the toxic tau released from neurons in a region-specific manner within the brain in all PSP patients. Thus, *astrocytes could potentially have the ability to inhibit tau spreading and delay disease progression*. A simplified hypothesis could be that neurons remain preserved as long as astrocytes can protect them; at some point, the astrocytes are overloaded and do not longer have clearing capacity; this results in neuronal-tau accumulation, inflammatory responses, neuronal loss, including microglial activation (Fig 4). Therefore, in the areas with the lowest density of TAs (brainstem/cerebellum region), gliosis and neuronal loss are the predominant lesion types in advanced disease. The direct neuron-to-astrocyte transfer of aggregation-prone protein species has already been demonstrated in the metabolism of alpha-synuclein, tau, and beta-amyloid, with consequent inflammatory response and glial activation.[49,50,51,52] Moreover, a recent study suggested that astrocytes may play a functional role in modulating extracellular tau and the propagation of neuronal tau pathology in tauopathies such as Alzheimer disease.[53] Future studies on the possible interplay between astrocytic and neuronal tau changes are needed to explain these opposite severity patterns. Divergent brain gene expression patterns for neuronal and astroglial tau have already been described in PSP.[54]

Given that PSP typically manifests later in life and has the highest prevalence of additional neurodegenerative disease-related proteins among tauopathies,[55] the influence of co-pathology to the progression rate of such disease needs to be addressed as well. Analysis of comorbid pathology in this PSP cohort showed no significant differences in prevalence and severity of concomitant neurodegenerative protein aggregations and cerebral vessel co-pathologies between survival groups, suggesting that *co-pathology was not contributory to survival in PSP*. Our previous study has also confirmed that, despite the high prevalence, the co-pathologies in PSP do not have major impact on disease progression.[11]

The important limitation of this study lies in the retrospective collection of data from clinical charts. To limit this, we relied on robust disease milestones, which are commonly reported by patients, caregivers, and/or documented by treating physicians. At the same time, it is important to emphasize that, due to the assimilation of the clinical picture at final record, histopathological differences accounting for clinical heterogeneity in different survival groups in the earlier clinical course might be abolished at post-mortem examination. In other words, the results must be interpreted with caution, since we are making the conclusions about disease progression based on a single and terminal snapshot of this dynamic condition. Therefore, the missing puzzles of the disease progression in PSP are the cases in their earliest stages, including presymptomatic, incidental cases. No less important, the type of care, the availability of aids and other technological advances, as well as family support, certainly affect the disease duration, and these parameters should be included in the design of future prospective studies considering survival.

In conclusion, our data demonstrate that PSP can run a relatively benign course in a considerable proportion of patients, although we are accustomed to think of PSP as a rapidly progressive disorder with a very short life expectancy. In clinical practice, the type of first symptoms and the tempo of their onset in the initial disease stages allow us to predict long-term disease progression and make risk stratification in terms of survival. Our study also underlines that initiation of the neurodegenerative process and the tempo of disease progression may be determined by oligodendroglial rather than neuronal tau in PSP. Yet, future studies will have to address the functional impact of oligodendroglial tau and options to specifically attempt to target oligodendroglial tau therapeutically.

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Author Contributions

M.J.L., G.R., C.K., T.A., and G.H. contributed to the conception and design of the study.

M.J.L., G.R., C.K., Y.C., E.G., C.T., J.S., A.G., S.R., J.H., T.A., and G.H. (all authors) contributed to the acquisition and analysis of data.

M.J.L., G.R., T.A., and G.H. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

The authors report no competing interests.

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