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Clinical Features of Patients with Concomitant Parkinson's Disease and Progressive Supranuclear Palsy Pathology

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Abstract: The pathologic changes of Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP) have been reported to coexist, but whether PSP pathology modifies the clinical course of those individuals is unknown. The aim of this study was to determine whether clinical features of pathologically confirmed PD subjects with concomitant PSP pathology differ from those with PD alone. Subjects enrolled in the Arizona Study of Aging and Neurodegenerative Disorders had annual movement and cognitive evaluations from enrollment until death/autopsy. All cases between 1997 and 2014 with a final clinicopathological diagnosis of PD with or without PSP at autopsy were analyzed. Overall, 12 of the 125 cases with pathologically confirmed PD had coexisting PSP pathology (9.6%). Those with PD-PSP had more-prominent postural instability, body bradykinesia, difficulty arising from a chair, and falls; asymmetric onset was less common in this group. Downgaze palsy and square wave jerks were infrequent in both groups. Gender, age at death, disease duration, rate of dementia, and presence of rest tremor did not differ between groups. Only 58% of subjects in the PD-PSP group were correctly given a final diagnosis in life of PD, compared to 91% of those with PD alone. The combination of PD and PSP pathology yields a heterogeneous clinical syndrome that often resembles PD, but may be more symmetric at onset and have more-prominent postural instability and falls. Our observations suggest that coexisting PSP pathology may be an important factor contributing to the clinical heterogeneity in PD and a potential confounder in diagnosis.

Despite advances in the field of biomarkers, Parkinson's disease (PD) remains a diagnosis made chiefly on clinical grounds. However, defining PD in such a way that allows it to be reliably distinguished from other parkinsonian syndromes based on clinical features alone has proved challenging.[1,2] Concomitant pathologies, frequently found at autopsy in PD patients, may contribute to clinical heterogeneity and further complicate efforts to assign accurate diagnoses in life.[3–5] Progressive Supranuclear Palsy (PSP), in particular, can coexist with PD at autopsy,[6,7] but little is known about the clinical features of those with this combination of pathology.

Clinicians making a diagnosis of PD rely on the identification of levodopa-responsive parkinsonism with a combination of cardinal motor signs and an absence of markers suggestive of other disease.[8] Large clinicopathological series estimate the accuracy of a clinical diagnosis of established idiopathic PD to be 76% to 90%.[1,9–11] However, in early PD, the motor symptoms may be less apparent and the diagnostic accuracy as low as 53%.[1] PSP is often misdiagnosed as PD, but is recognized as being distinct both clinically and pathologically. Classic PSP (also known as Steele-Richardson's syndrome) is characterized by early postural instability, supranuclear gaze palsy, progressive axial rigidity, and bulbar palsy, but other "atypical" variants have been described that are less distinct from PD.[12,13] Moreover, it is known that, in classic PSP, the clinical signs are specific, but not sensitive, for this disorder.[13] For both PD and PSP, a "definite" diagnosis requires postmortem neuropathological confirmation.

PD and PSP are distinct from each other pathologically by the abnormal accumulation of α-synuclein (α-Syn) and 4-repeat tau, respectively. In PSP, tau-positive "tufted astrocytes" and neurofibrillary tangles are found in a characteristic distribution.[12] α-Syn immunoreactive neuronal inclusions (Lewy bodies; LBs)

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and neuronal loss in the SNpc form the essential neuropathological diagnostic criteria of PD.[14] All types of LB disorders, including PD, dementia with LBs (DLB), and incidental LB disease, have been documented in association with PSP pathology in neuropathological studies in which the clinical details were not extensively discussed.[7,15] A more specific neuropathological association between PD and PSP was reported through the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), in which 9% of patients with pathologically confirmed PD had PSP pathology.[4] However, the literature detailing the clinical features of PD subjects with concomitant PSP pathology is limited to case reports.[6,16–19] Whether PSP pathology modifies the course of those with clinical PD is unknown. The aim of this study was to determine whether clinical features of pathologically confirmed PD subjects with concomitant PSP pathology differ from those with PD alone by performing a clinical analysis of patients in the AZSAND database.

Patients and Methods

The AZSAND enrolls volunteers from the community with PD and Alzheimer's disease (AD), as well as healthy controls, for annual standardized movement and cognitive evaluations until death/autopsy.[20] All subjects sign written informed consent for clinical assessment and autopsy through the Brain and Body Donation Program (www.brainandbodydonationprogram.org) approved by the Banner Sun Health Research Institute (Sun City, AZ) and Mayo Clinic (Scottsdale, AZ) Institutional Review Boards.

Subjects are given a movement disorder diagnosis in life after each evaluation. A diagnosis of PD requires two of three cardinal signs (rest tremor, bradykinesia, or cogwheel rigidity) without apparent symptomatic cause; the designation of probable PD is given if there is L-dopa responsiveness and possible PD if an adequate trial of dopaminergic medication had not been tried in those with a disease duration ≤5 years. A diagnosis of parkinsonism not otherwise specified (NOS) is given to those subjects who have parkinsonism (1) without response to an adequate trial of dopaminergic medication or (2) have not been given an adequate trial of dopaminergic medication after 5 years of symptomatic disease or (3) are suspected to have another etiology for their parkinsonism.[1] The National Institute of Neurological Disorders and Stroke (NINDS)-PSP clinical criteria are used for PSP.[21]

Postmortem clinicopathological diagnoses of PD and/or PSP are assigned based on standardized neuropathological criteria.[1] A clinicopathological diagnosis of PD requires the presence of LBs (Fig. 1A) and pigmented neuron loss in the SN as well as clinically documented parkinsonism.[14,22] A diagnosis of PSP is made if the subject has tufted astrocytes (Fig. 1B) and neurofibrillary tangles present in several of the following areas: frontal cortex; putamen; pallidum; STN; SN; dentate nucleus; inferior olivary nucleus; or pontine nuclei.[12,21] Semiquantitative Lewy-type α-synucleinopathy (LTS) densities (none = 0, mild = 1, moderate = 2, severe = 3, and very severe = 4) are determined according to guidelines set by the third report of the Dementia with Lewy Body Consortium[23] in 10 standard brain regions: olfactory bulb and tract; medulla; pons; SN; amygdala; transentorhinal cortex; cingulate gyrus; middle temporal gyrus; middle frontal gyrus; and inferior parietal lobule. The AZSAND tissue-processing methods, including immunohistochemistry (IHC) stains for LBs and tau, have previously been reported on.[4,24] In brief, formaldehyde-fixed, paraffin-embedded sections are subject to IHC with an antibody against phosphorylated α-Syn peptide (1:10,000; rabbit polyclonal anti-human phosphoserine 129; gift of Dr. Akiyama),[25,26] whereas large-format, 40- to 80-μm-thick formaldehyde-fixed sections are subject to Gallyas silver staining to reveal abnormal tau pathology.

Screening for G2019S mutation in the gene encoding leucine-rich repeat kinase 2 (Lrrk2) G2019S was performed on all PD cases.

The AZSAND database was queried for cases that had come to autopsy between 1997 and 2014 with a final clinicopathological diagnosis of PD with or without PSP. Movement scores more than 1.5 years preceding death were excluded.

Comparisons of demographic details, final clinical diagnoses, concomitant AD pathology, LTS scores, Unified Staging System (USS) for Lewy Body Disorders,[22] symptoms at disease onset, H & Y scores, and UPDRS total and individual item scores

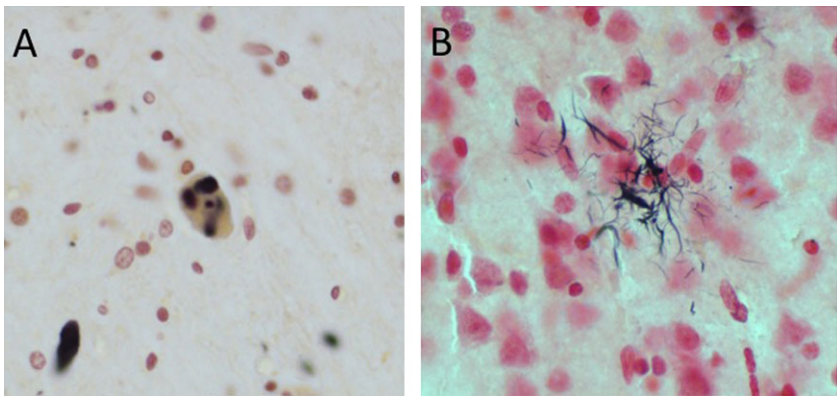

Figure 1 (A) Photomicrograph of multiple LBs in a noradrenergic cell of the pons on a 5-μm paraffin section that was subject to IHC for α-Syn. (B) Photomicrograph of a tufted astrocyte in the superior frontal gyrus in the same case on an 80-μm section that was subject to Gallyas silver staining.

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were made between the PD and PD-PSP groups using the two-sample *t* and Pearson's chi-square tests. Fisher's exact test was used instead of Pearson's chi-square test if the minimum expected cell count was less than 5. The positive predictive value of a final clinical diagnosis of PD was calculated for each group.

TABLE 1 Accuracy of final clinical diagnosis before death

	Clinicopathologic Diagnosis (%) PD (n = 113)	Clinicopathologic Diagnosis (%) PD-PSP (n = 12)
Final clinical diagnosis PSP	3 (3)	2 (17)
Final clinical diagnosis PD	103 (91)	7 (58)
Final clinical diagnosis parkinsonism NOS	7 (6)	3 (25)

TABLE 2 Demographic and clinical history comparisons based on final clinicopathologic diagnosis

	PD	PD-PSP	*P* Value
Age at death (years)	80.4 (6.7), 113	83.1 (8.2), 12	0.19
Female (%)	38/113 (34)	5/12 (42)	0.75
Disease duration (yr)	14.3 (7.6), 113	11.6 (7.1), 12	0.23
Tremor at onset (%)	44/86 (51)	4/9 (44)	0.74
Gait disturbance at onset (%)	1/86 (1)	1/9 (11)	0.18
Asymmetry at onset (%)	71/93 (76)	4/9 (44)	0.05

Data are presented as mean (standard deviation), N, or as N (%).

Results

One hundred twenty-nine subjects had a final clinicopathological diagnosis of PD. Four subjects with brain cancer were excluded. Among the remaining 125 subjects, 113 had PD without PSP and 12 had combined PD and PSP.

A final diagnosis of dementia was present in 64% of those with PD and 67% of those with PD-PSP. Pathologic criteria for AD were met in 43 of 125 (34%) subjects and did not differ significantly between those with PD (40 of 113; 35%) and those with PD-PSP (3 of 12; 25%).

The accuracy of final clinical diagnoses is provided in Table 1. Those with combined PD-PSP pathology were more commonly given a final diagnosis in life of PD (58%; all 7 designated probable PD) than PSP (17%). Those with PD-PSP were more likely than the PD group to be labeled parkinsonism NOS at the end of life (n = 3; 25%). Of those given a postmortem clinicopathological diagnosis of PD without PSP, 91% were given a final diagnosis of PD in life (suspected, n = 1; possible, n = 3; probable, n = 99).

TABLE 3 Function and movement examination comparisons

	PD	PD-PSP	*P* Value
H & Y	**3.46 (1.03), 80**	**4.27 (0.79), 11**	**0.03**
Total UPDRS II	22.8 (8.8), 79	25.6 (7.6), 11	0.31
Speech	2.3 (1.1), 79	2.0 (1.2), 11	0.37
Salivation	1.7 (1.3), 79	2.1 (1.2), 11	0.41
Swallowing	0.00 (0.00 to 1.00), 79	1.00 (0.00 to 2.50), 11	0.10
Handwriting	3.2 (1.0), 79	3.4 (1.0), 11	0.55
Cutting food	1.8 (1.3), 79	2.2 (1.4), 11	0.37
Dressing	2.3 (1.2), 79	2.7 (1.0), 11	0.27
Hygiene	2.3 (1.2), 79	2.5 (1.1), 11	0.58
Turning in bed	2.37 (1.52), 79	2.64 (0.92), 11	0.57
Falling	**0.0 (0.0 to 1.0), 79**	**2.0 (0.0 to 2.0), 11**	**0.03**
Freezing	1.3 (1.4), 79	1.5 (1.6), 11	0.67
Walking	2.5 (1.1), 79	2.7 (1.3), 11	0.53
Tremor	0.96 (0.90), 79	0.55 (0.69), 11	0.14
Sensory complaints	0.43 (0.98), 79	0.27 (0.90), 11	0.62
Total UPDRS III	42 (18), 85	46 (13), 11	0.41
Speech	1.95 (1.22), 85	2.36 (0.92), 11	0.28
Facial expression	1.82 (0.96), 85	2.09 (1.04), 11	0.38
Rest tremor	1.2 (2.0), 85	1.0 (1.8), 11	0.78
Action tremor	**1.1 (1.5), 85**	**0.0 (0.0), 11**	**0.02**
Total rigidity	7.7 (6.0), 85	5.7 (5.8), 11	0.31
Neck rigidity	1.8 (1.6), 85	1.9 (1.7), 11	0.85
Limb rigidity	5.9 (4.7), 85	3.8 (4.8), 11	0.18
Finger taps	3.9 (2.2), 85	5.0 (1.6), 11	0.12
Hand movement	4.0 (2.1), 85	4.8 (1.9), 11	0.20
RAM of hands	3.9 (2.2), 85	4.6 (2.3), 11	0.30
Leg agility	4.2 (2.4), 85	4.8 (2.1), 11	0.43
Arising from chair	2.3 (1.4), 85	3.3 (1.1), 11	0.02
Posture	2.7 (1.2), 85	3.0 (1.3), 11	0.43
Gait	2.2 (1.3), 85	2.8 (1.1), 11	0.15
Postural stability	**2.51 (1.12), 85**	**3.59 (0.58), 11**	**0.002**
Body bradykinesia	**2.40 (1.18), 85**	**3.36 (0.67), 11**	**0.009**
Downgaze palsy at any time (%)	7/113 (6)	2/12 (17)	0.21
Square wave jerks at any time (%)	7/113 (6)	2/12 (17)	0.21
Rest tremor at any time (%)	63/113 (57)	7/12 (58)	0.86

Data from last movement assessment unless otherwise stated. RAM, rapid alternating movement.
Bold indicates Mean and $P < 0.05$.

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TABLE 4 Comparison of LTS scores

	PD	PD-PSP	*P* Value
Total Score (0–40)	**25.3 (7.5), 96**	**19.8 (11), 9**	**0.04**
Olfactory bulb and tract	2.8 (1.2), 107	2.7 (1.6), 11	0.88
Medulla	3.26 (0.90), 109	2.73 (1.35), 11	0.08
Pons	3.19 (0.90), 110	2.75 (1.36), 12	0.13
SN	**2.7 (1.0), 109**	**1.8 (1.5), 11**	**0.01**
Amygdala	3.47 (0.85), 112	3.08 (1.24), 12	0.15
Transentorhinal cortex	2.8 (1.1), 108	2.3 (1.1), 12	0.12
Cingulate gyrus	**2.5 (1.1), 113**	**1.6 (1.2), 12**	**0.006**
Middle temporal gyrus	1.6 (1.1), 113	1.0 (1.3), 12	0.09
Middle frontal gyrus	**1.25 (0.91), 113**	**0.64 (1.21), 11**	**0.04**
Inferior parietal lobule	1.21 (0.92), 112	0.75 (0.97), 12	0.10

Data are presented as mean (standard deviation), N.
Bold indicates Mean and $P < 0.05$.

TABLE 5 Comparison of the USS for LB disorders

	PD (%)	PD-PSP (%)
Stage 0: No LTS	0/112	0/12
Stage I: Olfactory bulb only	0/112	0/12
Stage IIa: Brainstem predominant	9/112 (8)	3/12 (25)
Stage IIb: Limbic predominant	4/112 (4)	3/12 (25)
Stage III: Brainstem and limbic	52/112 (46)	2/12 (17)
Stage IV: Neocortical	47/112 (42)	4/12 (33)

Demographic and clinical history comparisons are provided in Table 2. Those with PD alone more commonly had asymmetric clinical manifestations at onset than those with PD-PSP. Gender, age at death, disease duration, and presence of tremor and gait disturbance at onset, for cases with data available, did not differ between the two groups.

Motor function and examination findings are outlined in Table 3. Scores on the total UPDRS parts II (Activities of Daily Living) and III (Motor Examination) did not differ between the groups. Patients in the PD-PSP group had a higher mean H & Y score. On individual items of the UPDRS parts II and III, those with PD-PSP had more-prominent postural instability, body bradykinesia, difficulty arising from a chair, and falls; action tremor was less severe in this group. The presence of downgaze palsy and square wave jerks was infrequent in both groups.

Total LTS scores were significantly higher in the PD group, as were regional scores in the SN, cingulate gyrus, and middle frontal gyrus (Table 4). A greater proportion of PD cases without PSP progressed to a higher USS stage, with 88% in stage III or IV versus only 50% of those with a combined diagnosis (Table 5).

Lrrk2 G2019S mutations were present in 3 of 113 in the PD group and 0 of 12 in the PD-PSP group.

Discussion

Nearly 10% of our PD cohort had concomitant PSP pathology, suggesting that PSP pathology coexists with PD in a substantial proportion of patients. In a large series by Uchikado et al., in which LBs were found in 11% of 290 autopsy-confirmed PSP cases, molecular diagnostic observations led to the conclusion that these are independent disease processes and that tau pathology does not influence α-Syn accumulation and vice versa.[7] Another study of PSP cases found that LBs were not increased in PSP subjects, compared to normal controls, suggesting that this combination of pathology is not more frequent than would be expected by chance.[27] Therefore, the present data are in agreement with these studies. Though Lrrk2 G2019S mutations have been associated with both tau and LB pathology,[28,29] none of the patients in our PD-PSP group were positive for this mutation. However, more data are needed to determine whether there is an increased rate of Lrrk2 mutations in subjects with combined pathology.

Although the occurrence of PD with PSP has been reported, there is little published literature regarding the clinical features during life of cases of combined PD and PSP, compared to PD alone. This study found that the presence and severity of clinical features in PD subjects with coexisting PSP pathology overall resemble those of PD alone, but with a few possibly important exceptions. Those with PD-PSP had less action tremor, whereas postural instability, difficulty arising from a chair, and falls were more prominent in this group. Well-described clinical features that help distinguish PSP from PD include relative symmetry of parkinsonism, earlier and more marked postural instability and falls, and supanuclear gaze palsy.[30] Our study shows that many of those important influences of PSP-tau pathology persist when the pathologies are combined. The presence of PSP-tau pathology in the combined group may be driving the early symmetry and severity of postural instability and falls. Downgaze palsy and/or square jerks were frequently absent in those with PD-PSP. However, these ocular features may never develop in those with PSP or appear years into the diagnosis.[13,31,32] Furthermore, there is a subset of PSP patients characterized by Williams et al. as PSP-parkinsonism (PSP-P) that have less-prominent eye findings postulated to reflect regional differences in tau deposition.[33]

Though those in the PD group without PSP were more likely to have progressed to a higher USS stage and have greater total LTS scores, many of the classic phenotypic characteristics of PD did not clearly differ between the groups. Tremor, both during action and rest, is classically more prominent in PD, but can be observed in PSP as well, particularly in the PSP-P variant.[33–35] In this study, rest tremor was found to be equally common and similar in severity in both groups, whereas action tremor was less prominent in the combined group. A number of studies have attempted to stratify PD into subtypes, and a distinction is often made between "tremor dominant" and "postural instability gait difficulty" types.[36,37] The latter has been found, in some studies, to have faster disease progression, greater functional impairment, and more-severe cognitive dysfunction.[36,38,39] Though the PD-PSP group in our study had greater postural instability and falls, it does not differ from the PD group with respect to gait dysfunction, rest tremor, disease duration, and functional or cognitive impairment and therefore does not clearly align with either subtype. In their descriptions of PSP-P, Williams et al. do not

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report any concomitant LB pathology, suggesting that the presence of tau alone can produce clinical features that resemble PD.[33,40]

Only 58% of subjects in the PD-PSP group in this study were correctly given a final diagnosis in life of PD, compared to 91% of those with PD alone at autopsy. Furthermore, all 12 of these patients were given a diagnosis of PD either before or after enrolling in the AZSAND program, but by final assessment, 25% had been reassigned as parkinsonism NOS. Though we cannot infer the temporal course of the PSP pathology in these cases, it is tempting to suggest that PSP pathology altered the clinical phenotype of these PD cases in particular. In 2012, Abhinav et al.[6] reported on a case of combined PSP and PD and reviewed the literature of 6 other published cases of either PD-PSP or DLB-PSP.[16–19] Among the 5 cases of PD-PSP, 2 received a final diagnosis of PD and 1 of PSP, further illustrating the difficulties in accurately diagnosing those with combined pathology.

The power to detect clinical differences between the two groups in this study is limited by the small number of subjects with combined PD and PSP pathology. Nevertheless, this is a significant contribution to the literature on this subject, which, up until this study, has been limited to case reports. A PSP comparison group could not be included because the AZSAND does not specifically recruit patients with PSP.

The combination of PD and PSP pathology yields a heterogeneous clinical syndrome that mostly resembles PD, but may be more symmetric at onset and have more-prominent postural instability and falls in late disease. Our observations underscore the possible importance of coexisting PSP pathology as a factor contributing to the clinical heterogeneity and a potential confounder in diagnosis. Clinical features alone are likely insufficient to identify PD patients with concomitant PSP pathology, but may be helpful in combination with biomarker data as it becomes available. Recognition of combined pathology is likely to have improved in recent years with the use of specific molecular postmortem diagnostic methods and may have been underappreciated in previous studies. Future data on concomitant pathologies from other large brain banks will be critical to better understanding their frequencies and impact on clinical phenotypes and diagnostic accuracy.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

H.B.R.: 1A, 1B, 1C, 3A, 3B
B.N.D.: 1A, 1B, 1C, 3B
J.G.H.: 2A, 2B, 3B
C.H.A.: 1C, 3B
T.G.B.: 1C, 3B
H.A.S.: 1C, 3B
E.D.-D.: 1C, 3B
M.N.S.: 1C, 3B
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