Florid Nonmotor Manifestations of a Pathologically proven Progressive Supranuclear Palsy

Sir,

Progressive supranuclear palsy (PSP) is an atypical parkinsonism characterized by supranuclear gaze palsy and postural instability. After nonmotor symptoms (NMSs) were first recognized as constitutional features of those with Parkinson's disease, NMSs were also studied, revealing high frequency and great severity of NMSs such as a sleep problem, mood disturbance, gastrointestinal dysfunction, or urinary dysfunction in PSP.[1] Among various NMSs, psychosis is rare and less suggestive of PSP. Visual hallucination (VH) is also infrequently associated with the diagnosis of PSP.[2] However, NMS was not fully evaluated in the previous autopsied cases.

Here, we report an autopsy-proven case of PSP who presented with a lot of NMSs including psychosis and VH.

A 65-year-old female presented with cognitive decline and repeated falls 2.5 years before the visit. Cognitive impairment began at the age of 63 years, and cognitive function progressively deteriorated. Her family also complained about her psychotic problems such as delusion. The patient reported insomnia and urinary symptoms, including frequency, urgency, and nocturia. Parasomnia including rapid eye movement sleep behavior disorder was absent.

At the initial visit, the Seoul neuropsychological screening battery [Table 1] identified 8/30 in the Korean version of the mini–mental state examination (K-MMSE) and 49/144 in the caregiver-administered neuropsychiatric inventory questionnaire [Supplementary Table 1]. Follow-up levels of K-MMSE at 3, 10, 13, and 24 months after the first evaluation were 19/30, 14/30, 7/30, and 11/30, respectively. The family reported that cognitive function was worse in the evening.

Neurological examination showed typical features of PSP [Supplementary Video 1]. Brain magnetic resonance imaging showed midbrain atrophy with the hummingbird sign and cortical atrophy [Figure 1a].

Treatment with levodopa was ineffective. The patient exhibited multiple NMSs on the Korean version of the NMSs scale [Supplementary Table 2] 2 years after the initial visit. The motor symptoms rapidly progressed, resulting in a wheelchair-bound state. The patient developed VH during treatment with levodopa, which was controlled with the addition of quetiapine. She became bedridden at the age of 68 years, was placed in a nursing home, and died of pneumonia at the age of 71 years. Autopsy was done 4 h after death, which was compatible with the pathologic diagnosis of PSP [Supplementary Table 3 and Figure 1b, c].[3]

Table 1: Detailed results of the Seoul Neuropsychological Screening Battery at the initial visit

Category	Test	Score	Z-score
Global cognitive function	K-MMSE	8	−14.26
Attention	Digit span forward	3	−2.04
	Digit span backward	3	−0.81
Language	Fluency	Fluent	
	Contents	Normal	
	Comprehension	Abnormal	
	Repetition	10	
	Reading	Normal	
	Writing	Abnormal	
	Right–left orientation	Abnormal	
	Body part identification	Abnormal	
	Calculation	0	
Naming	K-BNT	19	−3.65
Visuospatial	RCFT copy	3	−10.02
	RCFT time	45	1.85
Memory	SVLT recall	3	−4.05
	SVLT delayed recall	0	−3.35
	SVLT recognition	13	−3.39
	RCFT recall	1.5	−2.57
	RCFT delayed recall	0	−3.36
	RCFT recognition	12	−4.61
Frontal/executive function	COWAT animal	2	−3.75
	COWAT supermarket	2	−3.32
	K-CWST time per item	2.03	−5.57
Other	B-ADL	8	
	CDR	3	
	CDR-SOB	15	

K-MMSE=Korean version of the mini–mental state examination, K-BNT=Korean Boston naming test, RCFT=Rey complex figure test, SVLT=Seoul verbal learning test, COWAT=Controlled oral word association test, K-CWST=Korean color word Stroop test, B-ADL=Barthel activities of daily living, CDR=Clinical dementia rating, SOB=Sum of boxes

She had presented with a plethora of psychiatric symptoms. Although delusion was present in 3% of clinically diagnosed PSP,[4] only one case was reported to have schizophrenic symptoms as initial presentations in pathologically proven PSP.[5] Thus, this is the second pathologically proven PSP presenting with psychosis.

This patient seemed to share some clinical features with dementia with Lewy bodies (DLBs): VH and a nonlinear pattern of cognitive deterioration (serial MMSEs). However, some patients with PSP could have VH (5%–13%), albeit the

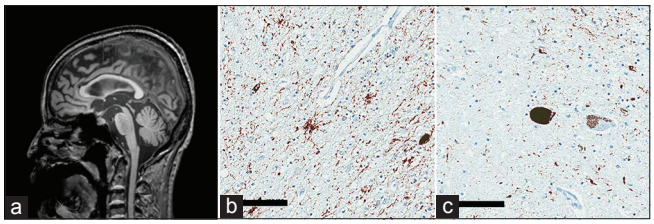

Figure 1: Brain magnetic resonance imaging and pathologic findings. (a) Brain magnetic resonance imaging showing prominent midbrain atrophy. (b) Immunohistochemical staining with antiphosphorylated tau antibody shows diffuse neutrophil threads and tufted astrocytes in the globus pallidus. (c) Globose tangles are seen in the substantia nigra. Immunohistochemical staining using antibodies against α-synuclein and transactive response DNA-binding protein 43 kDa (TDP-43) was negative. Braak neurofibrillary tangle stage = 1. Thal phase (amyloid plaques) = 2. *Calibration bar* = 100 μm

correlation between VH and medications was unclear in the majority of the cases.[2] Moreover, MMSEs are insensitive to capture disease-specific domains such as frontal function.

Although florid NMSs, especially constipation and change in ability to taste or smell, are also reminiscent of PD or DLB, pathologic basis of some NMSs such as gastrointestinal symptoms is not firmly established in PSP, whereas α-synuclein pathologies are found outside the central nervous system, providing a better understanding of NMSs.

In conclusion, this is a pathologically proven PSP presenting with a variety of NMSs. Further studies are needed to investigate clinicopathologic correlation between tau pathologies and NMSs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Detailed results of the caregiver-administered neuropsychiatric inventory at the initial visit

Item	Frequency (*F*)	Severity (*S*)	Total score (*F*×*S*)	Caregivers' distress
Delusions	3	2	6	4
Hallucinations	0			
Agitation/aggression	3	3	9	4
Depression/dysphoria	3	2	6	4
Anxiety	3	2	6	4
Euphoria/elation	0			
Apathy/indifference	3	2	6	4
Disinhibition	0			
Irritability/lability	2	2	4	4
Aberrant motor behavior	4	1	4	0
Night-time behavior	4	2	8	4
Appetite/eating change	0			

Supplementary Table 2: Detailed results of the Korean version of the nonmotor symptoms scale 2 years after the initial visit

Item	Score
Domain 1 (cardiovascular)	4
Dizziness	4
Falling due to fainting	0
Domain 2 (sleep/fatigue)	18
Daytime sleep	0
Fatigue	9
Difficulty falling asleep	9
Restless legs	0
Domain 3 (mood/cognition)	31
Loss of interest in surroundings	6
Lack of motivation	12
Nervous feeling	0
Depression	4
Flat mood	0
Lack of pleasure	9
Domain 4 (perceptual/hallucination)	0
Hallucinations	0
Delusions	0
Double vision	0
Domain 5 (attention/memory)	29
Poor concentration	8
Forgetfulness to past events	12
Forgetfulness to make plan	9
Domain 6 (gastrointestinal tract)	18
Drooling	0
Dysphagia	9
Constipation	9
Domain 7 (urinary)	33
Urgency	12
Frequency	12
Nocturia	9
Domain 8 (sexual)	28
Altered interest in sex	12
Sexual problems	16
Domain 9 (miscellaneous)	9
Unexplained pain	0
Change in ability to taste or smell	9
Weight change	0
Excessive sweating	0

The nonmotor symptoms scale is rated by both patient and caregiver

Supplementary Table 3: Regional immunohistochemistry staining of phosphorylated Tau

Anatomical area	Neuronal	Threads	Coiled bodies	Tufted astrocytes
Temporal cortex	+	+	+	+
Frontoparietal cortex	++	++	++	+++
Motor cortex	++	++	+ +	+++
Striatum	++	++	+/++	+++
Pallidum	++	++	+++	+
Basal nucleus	+++	++	+	+
Ventral thalamus	++	+++	+++	+/++
Thalamic fasciculus	N/A	+++	+++	0
Subthalamic nucleus	++/+++	+++	++/+++	+/++
Hypothalamus	++/+++	++	+	+
Tectum	++	+++	++/+++	++/+++
Red nucleus	++	++/+++	++/+++	+/++
Substantia nigra	++/+++	++	+/++	+
Locus coeruleus	+++	++	+	0
Pontine tegmentum	++/+++	++/+++	++	+
Pontine nuclei (base)	++/+++	++	+	+
Medullary tegmentum	+++	+++	+/++	+
Inferior olive	++	++/+++	+	+
Dentate nucleus	++/+++	++	+	+
Cerebellar white matter	N/A	+/++	++	0

The immunostaining results were semiquantitatively graded into 0, +, ++, or +++. N/A: Not available