

Phenotypic Variants of Patients with Progressive Supranuclear Palsy

Progresif Supranükleer Palsili Hastalarda Fenotipik Varyantlar

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ABSTRACT

Introduction: Progressive supranuclear palsy (PSP) is a commonly observed disease among Parkinson plus syndromes, and its early and accurate diagnosis is usually not possible. PSP is currently reported to have eight different subtypes. This study aims to determine the phenotypic subtypes of PSP and reveal their accompanying characteristics.

Methods: Eighteen patients who were diagnosed as having PSP according to the National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) criteria were included in the study. Initial symptoms of the patients, their initial diagnosis, course of the disease with time, cranial images, and predominant clinical features were assessed with regard to the subtypes of PSP.

Results: The mean age of the patients was 65.83 years. According to the NINDS-SPSP criteria, all patients were diagnosed as having probable PSP. An evaluation of the patients with respect to the subtypes showed that five different subtypes had predominant characteristics. Richardson's syndrome was found to be the most common subtype.

Conclusion: Classifying PSP with regard to its phenotypes may be useful for informing clinicians about the diverse clinical presentations of PSP, thereby possibly improving the diagnostic sensitivity of the disease.

Keywords: Progressive supranuclear palsy, phenotype, variant

ÖZ

Amaç: Progresif supranükleer palsi (PSP) Parkinson plus sendromları içinde sık görülen hastalıktır ve doğru tanı alması geç olmaktadır. Günümüzde PSP'nin sekiz farklı alt tipi olduğu bildirilmektedir. Bu çalışmanın amacı; PSP'li hastaların fenotipik alt tiplerini belirlemek ve eşlik eden özelliklerini ortaya koymaktır.

Yöntem: Çalışmaya NINDS-SPSP kriterlerine göre tanı almış PSP hastaları alındı. Hastaların başlangıç semptomları, aldıkları ilk tanı, hastalığın zaman içindeki seyri, kraniyal görüntülemeleri ve predominant klinik özelliklerinin hangi alt tip ile uyumlu olduğu yönünden değerlendirildi.

Bulgular: Çalışmaya 18 PSP hastası dahil edildi. Hastaların yarısı erkekti, yaş ortalaması 65,83 bulundu. NINDS-SPSP kriterlerine göre tüm hastalar 'Muhtemel PSP' olarak kabul edildi. PSP hastaları alt tiplerine göre incelendiğinde; hastaların kliniğinde beş farklı alt tipin predominant özellik olduğu belirlendi. En sık görülen alt tipin Richardson's syndrome (PSP-RS) olduğu saptandı.

Sonuç: PSP'nin fenotiplere göre sınıflandırılması, klinik sunum çeşitliliğinin farkındalığını ve buna bağlı olarak klinik tanı hassasiyetini artırabilir.

Anahtar kelimeler: Progresif supranükleer palsi, fenotip, varyant

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease. Progressive supranuclear palsy (PSP) is the most commonly observed disease among Parkinson plus syndromes (1). From its onset, PSP cannot usually be accurately diagnosed, especially by inexperienced neurologists (2). The NINDS-SPSP criteria are used for the clinical diagnosis of PSP (3). Clinical characteristics include early onset postural instability, vertical gaze palsy, symmetrical parkinsonism with serious axial symptoms and non-responsive to L-dopa, pseudobulbar dysarthria, dysphagia, and frontal dysfunction. The majority of cases are sporadic (4). The incidence of PSP is 4%–6% among all parkinsonisms (5). PSP is a tauopathy disorder, and neuropathology is needed for its definite diagnosis. Neurofibrillary tangles are present in several subcortical areas such as the substantia nigra, subthalamic nucleus, and midbrain.

Data regarding the subtypes of PSP is increasing in the literature (6,7). According to the data present in the literature, there are eight different subtypes of PSP, namely PSP with Richardson's syndrome (PSP-RS), PSP with predominant parkinsonism (PSP-P), PSP with pure akinesia with gait freezing (PSP-PAGF), PSP with corticobasal syndrome (PSP-CBS), PSP with predominant language and speech dysfunction (PSP-PNFA and PSP-AOS), PSP with predominant frontotemporal dysfunction (PSP-FTD), PSP with cerebellar ataxia (PSP-C), and PSP with primary lateral sclerosis (PSP-PLS) (8). The most significant challenge regarding the diagnosis of PSP-P arises owing to the phenotype. This is not usually possible to diagnose PSP type until the later stages of the disease due to lack of decisive biomarkers.

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In a recent article published by the PSP Study Group of Movement Disorder Society, four clinical areas (ocular dysfunction, postural imbalance, akinesia, and cognitive function impairment) are recommended for the clinical differential diagnosis of PSP. In addition, three clinical features contribute to the diagnostic accuracy at different stages. Accordingly, specific combinations of these characteristics describe the diagnosis criteria with under three subtypes (probable PSP, possible PSP, and suggestive PSP). Imaging features (midbrain atrophy or hypometabolism and/or postsynaptic striatal dopaminergic degeneration) and clinical features are among the supporting characteristics (9). Thus, there is needed to optimize for the accurate, early, and specific diagnosis of PSP.

This study aimed to determine the phenotypic subtypes of PSP and reveal their accompanying characteristics.

METHODS

Patients who were diagnosed as having PSP at Erciyes University School of Medicine between June 2014 and December 2016 were included in this study. The approval of the local ethics committee and the consent of the patients were obtained.

Medical records of the patients who were followed up owing to the diagnosis of PSP were retrospectively assessed, and the latest clinical characteristics were noted. The NINDS-SPSP criteria were considered for the diagnosis of PSP (3). Clinical characteristics included the onset of disease at an age of ≥ 40 years, slower vertical eye movements or vertical gaze palsy, significant postural instability or falls during the first year, and accompanying symmetrical parkinsonism. In addition, cranial magnetic resonance (MR) images of all patients were examined. Conventional 1.5-Tesla MR imaging (MRI) sections were collected. The patients with evident rostral midbrain atrophy and hummingbird sign on MRI were included in this study (10). The criterion for the midbrain-to-pons ratio was $< 0.124 \text{ mm}^2$ (11). Patients with PSP who met the abovementioned characteristics were included in the study.

Each patient was extensively examined by a neurologist who had experience with movement disorders. Initial symptoms of the patients, their initial diagnosis, treatment responses, course of the disease with time, additional symptoms, cranial images, disabling symptoms, and predominant clinical characteristics were assessed according to the subtypes of PSP.

Statistics Analysis

Demographical and clinical data of the participants that were obtained within the scope of the study were evaluated using descriptive statistics. Mean \pm SD and median 25 and 75 percentile values are presented. Results of frequency analysis applied to certain data are given in Table 1, 2. The Statistical Package for the Social Sciences 15.0 (SPSS Inc.; Chicago, IL, USA) was used for analysis.

RESULTS

We included 18 patients with PSP in this study. The mean age of the patients was 65.83 years. The mean age at onset was 61.78 (51–70) years. Furthermore, the mean disease duration was 4.06 (3–8) years. According to the NINDS-SPSP criteria, all patients were diagnosed as having probable PSP. All patients had postural instability that was characterized by falls within the first year. Subsequently, in the next years, they developed supranuclear gaze palsy and slowness in vertical saccades.

Considering the clinical characteristics of the 18 patients with PSP, only two patients were accurately diagnosed as having PSP diagnosis on the basis of the onset characteristics. Thirteen patients were followed

Table 1. Clinical features of patients with PSP

First diagnosis	N	%
PSP	2	11.1
PD	13	72.2
Ataxia	3	16.7
L-Dopa response		
Yes (temporary)	4	22.2
No	14	72.8
Tremor		
No	10	55.6
Unilateral	2	11.1
Bilateral	6	33.3
Cervical dystonia		
Yes	4	22.8
No	14	77.2
Vertical gaze palsy		
Yes	18	100
No	0	0
Difficulty with eye opening		
No	5	27.8
Apraxia	8	44.4
Dystonia	5	27.8
RBD		
Yes	12	66.7
No	6	33.3

PSP: progressive supranuclear palsy; PD: parkinson's disease; RBD: REM sleep behavior disorder

Table 2. Subtypes of PSP

PSP subtypes	N	%
PSP-RS	7	38.9
PSP-P	3	16.7
PSP-PAGF	2	11.1
PSP-FTD	4	22.2
PSP-AOS and PSP-PNFA	2	11.1

PSP: progressive supranuclear palsy; PSP-RS: PSP with Richardson's syndrome; PSP-P: PSP with predominant parkinsonism; PSP-PAGF: PSP with pure akinesia with gait freezing; PSP-AOS and PSP-PNFA: PSP with predominant speech and/or language dysfunction; PSP-FTD: PSP with predominant frontotemporal dysfunction

up owing to a diagnosis of PD, and the remaining three patients were followed up for a diagnosis of ataxia. Most of the patients did not have tremors and cervical dystonia. However, most patients had eye opening apraxia and eyelid dystonia. The majority of patients (14/18) were non-responsive to L-dopa, and postural instability was a major problem. The patients were not followed up at the same center and by the same doctor regularly from the onset of the disease until admission to our polyclinic. Three patients were followed up for a diagnosis of ataxia. Clinicians might have diagnosed the patients as having ataxia owing to postural instability and frequent falls. Despite this, no cerebellar atrophy was observed on the MR images of the patients. The clinical characteristics of the patients are given in Table 1.

An evaluation of patients with PSP with respect to subtypes showed that five different subtypes were predominant characteristics. It is necessary to

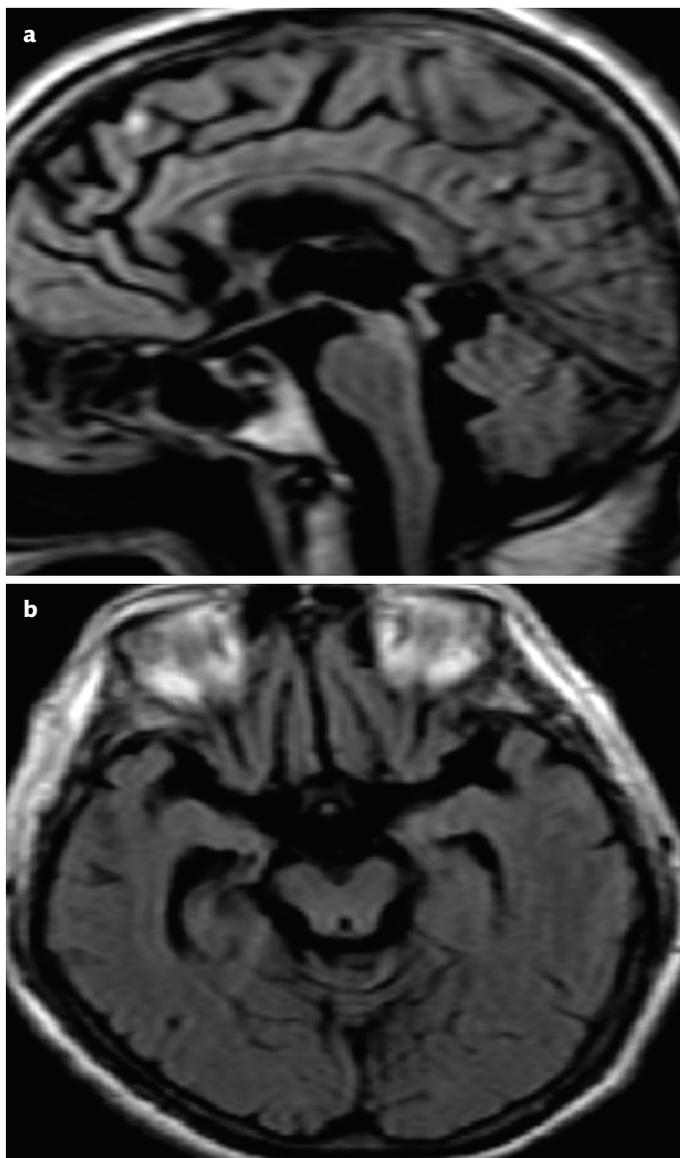


Figure 1. a, b. (a) The preservation of the pons constitutes a specific pattern that resembles a hummingbird sign or a penguin (sagittal section) is seen on MRI (b) Midbrain atrophy with the enlargement of the third ventricle (axial section) is seen on MRI

underline the fact that all patients had symmetrical parkinsonism, postural instability, and other clinical PSP characteristics together with predominant characteristics. However, the predominant subtypes were determined according to the major presentation during clinical examination and the course of the disease. PSP-RS was found to be the most common subtype. Atrophy of the midbrain with the preservation of the pons constitutes a specific pattern that resembles a hummingbird or penguin and is known as the hummingbird sign, which is sometimes also called the penguin silhouette sign, as observed on midsagittal sections. The hummingbird sign has a very high specificity (100%; sensitivity, 97.8%). Cranial MRI of a patient with PSP-RS is shown in Figure 1a and 1b. The predominant subtypes PSP-CBS, PSP-C, and PSP-PLS were not observed in our patients. The PSP subtypes of our patients are given in Table 2.

The hummingbird sign was demonstrated on MR images of all patients. Moreover, frontoparietal atrophy was observed in patients with PSP-FTD. Frontal lobe dementia signs (behavior change, impairment in executive functions, inhibition, etc.) and parkinsonism were also observed. All patients considered postural instability to be a disabling symptom, which worsened over the years. Therefore, the patients used support devices such as a walking stick, walker, and wheelchair to walk.

DISCUSSION

In this study, other clinical characteristics of patients with PSP and their predominant clinical characteristics were examined. We showed that the characteristics of multiple clinical phenotypes may be present in a patient. The majority of patients (16/18) also did not receive an accurate diagnosis. In addition to initial clinical symptoms, the subtypes of PSP show differences with regard to the clinical course.

Accurately diagnosing PSP on the basis of its heterogeneous clinical course and predominant characteristics was difficult. Dugger et al. (12) assessed 64 patients who were diagnosed as having pathologically proven PSP and found that 36% of the patients had concomitant Alzheimer's dementia, 20% had PD, 1% had Lewy body dementia, 44% had argyrophilic grains, 52% had cerebral white matter rarefaction, and 25% had cerebral amyloid angiopathy. As can be observed in this study, the clinical presentation of PSP greatly differs. O'Sullivan et al. (13) examined 110 patients who were pathologically confirmed to have PSP. The authors also showed that frequent falls occurred 3.9 (± 2.5) years from the onset of the disorder. Also, they showed 4.2 (± 2.9) years for cognitive deterioration, 6 (± 2.5) years for speech defects to incomprehensibility, 6.4 (± 2.4) years for dysphagia, and 6.4 (± 2.7) for being wheelchair-bound.

Owing to the increasing number of studies in the literature, predominant characteristics of the subtypes of PSP are more clearly revealed (1). Akinetic rigid symptoms that are resistant to levodopa treatment are seen in PSP-RS. Axial muscles are affected and it leads to the tendency to fall back. Also, vertical gaze palsy is observed in the initial phase of the PSPRS. Apathy, pseudobulbar speech, aphasia, and deteriorations in executive functions are also observed (14). PSP-P is presented by parkinsonism with asymmetrical onset. Distinguishing PSP-P from PD until the onset of vertical gaze disorder is difficult (15). PSP-PAGF is characterized by sudden and temporary freezings that are observed without tremor and rigidity; this can be deemed typical for an underlying PSP neuropathology (16). Sometimes, the onset of the disease may be dominated by clinical symptoms that are suitable for the behavioral and language variants as in PSP-FTD or PSP-PNFA (17,18). The underlying pathologies of PSP-CBS are diverse, and 70% of patients present tauopathy. PSP-CBS accounts for only 4% of all cases with PSP (19,20). PSP-C is more commonly observed in Japan, and patients have neural loss in cerebellar dentate nucleus and gliosis (21). PSP-PLS is a progressive disorder that is accompanied by spastic gait with the degeneration of upper neuron motors and bulbar weakness. There may also be deterioration in vertical saccades; however, there is limited data regarding the same (22).

Among the subtypes of PSP, PSP-RS (40%) is the most common (23). PSPRS was also the most common subtype in our patient group (7/18), and it was followed by PSP-P (20%), PSP-FTD (15%), PSP-CBS (10%), PSP-AOS (5%), and PSP-PAGF (<5%) (6,14,24,25,26). In contrast, other subtypes of PSP are very rare (18,27,28). Although some studies suggest that the commonly used NINDS-SPSP criteria are very sensitive for PSP-RS, they are not very appropriate for detecting other clinical subtypes of PSP (23). Moreover, the existence of two or more PSP variants may be seen in a single case. The specificity of clinical syndromes depending on the underlying pathology cause contradictions for diagnosis. Thus, the determination of dominant clinical features and symptoms, which are specific and sensitive to an underlying PSP pathology, is significant to increase the clinical diagnostic precision in atypical phenotypes of PSP.

Our study has some limitations such as a relatively low number of patients, retrospective design, and lack of neuropathological examination of patients with PSP.

CONCLUSION

Conducting future clinicopathological studies with large samples and multiple centers on PSP subtypes will help better understand the etiology of PSP and its specific neurodegenerative mechanisms. Classifying PSP with respect to its phenotypes may be useful for informing clinicians about the diverse clinical presentations of PSP, thereby possibly improving the diagnostic sensitivity of the disease.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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