Freezing of gait is an early clinical feature of progressive supranuclear palsy

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Abstract

Background and Aim: Early clinical diagnosis of progressive supranuclear palsy (PSP) remains challenging.

Aim: We attempted to identify any sign or symptom to diagnose PSP earlier.

Methods: A total of 401 patients, 40 with PSP and 361 with other neurodegenerative disorders, were included. We followed these patients for at least 1 year since 2009. We reviewed the signs and symptoms of patients with PSP in a standardized manner, and observed four manifestations: “vertical supranuclear gaze abnormality,” “movement disorders,” “pseudobulbar palsy” and “dementia of frontal type.” Features, such as symmetric parkinsonism, freezing of gait, postural instability, dysarthria and/or dysphagia, or dementia of frontal type, were considered core clinical features.

Results: In patients with PSP, “movement disorders” was the most common manifestation, whereas “vertical supranuclear gaze abnormality” was uncommon during the early disease course. A total of 16 patients fulfilled the National Institute for Neurological Disorders and Stroke and Society for PSP criteria for possible PSP at their first clinic visit. Of the remaining 24 patients, 15 presented with one or more core clinical features before fulfilling the criteria for possible PSP; nine patients had a clinical diagnosis of PSP but never fulfilled the criteria. A total of 49 of the 361 patients with other neurodegenerative disorders had core clinical features. A comparison showed that freezing of gait differentiated the groups the best over the disease course.

Conclusion: Freezing of gait is an early feature that might improve the clinical diagnosis of PSP, whereas vertical supranuclear gaze abnormality is not.
each clinic visit. This enabled us to track the evolution of the patients’ clinical signs and symptoms. Next, we tried to determine if these signs and symptoms improved the diagnosis of PSP. Thus, patients that later or never fulfilled the NINDS-SPSP criteria for possible PSP were compared with patients that had other neurodegenerative disorders. Overlaps among any of these early clinical features with PSP were determined from the first clinic visit.

Methods
The present study depended on clinical diagnoses, and did not include pathologically confirmed cases. We enrolled a total of 401 patients from the Department of Neurology, Kochi Medical School Hospital, and the Department of Neurology of related hospitals. We followed these patients for at least 1 year, beginning in 2009. The ethics committee at the Faculty of Medicine, Kochi University, approved the study protocol. The study comprised two parts.

Part I began in January 2009. We enrolled 20 patients whose clinical phenotype included PSP-RS, PSP-parkinsonism (PSP-P), PSP-PAGF, PSP-progressive non-fluent aphasia (PSP-PNFA), PSP-corticobasal syndrome (PSP-CBS), PSP-cerebellum (PSP-C), or PSP-frontotemporal dementia (PSP-FTD). In terms of PSP-P, although the specific criteria has not been established, early pointers could indicate rapid progression, prominent axial symptoms or a poor response to levodopa. Falls and cognitive dysfunction occur later. In a few patients, abnormality of eye movements might never appear. Each patient may or may not have fulfilled the NINDS-SPSP criteria for possible PSP. We then followed up with the patients. We subsequently enrolled and prospectively followed an additional 20 patients. In sum, we included 40 patients whose clinical diagnosis was PSP and that were followed up for at least 1 year since 2009.

We reviewed all of the clinical signs and symptoms of each patient. The standardized assessment included the following: subjective onset of symptoms; objective signs at first clinic visit, such as eye movement, falls, freezing of gait, akinesia, rigidity, tremor, speech disturbance, swallowing disturbance and cognitive impairment; symmetric onset or asymmetric onset; presence or absence of midbrain and/or frontal lobe atrophy; and clinical phenotype. The onset date of each sign and symptom was recorded using the year and month. The patients were divided into three groups: those that fulfilled the NINDS-SPSP criteria for possible PSP at the first clinic visit; those that later fulfilled the NINDS-SPSP criteria for possible PSP; and those whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP. Then, we summarized the observed signs and symptoms into four manifestations: “vertical supranuclear gaze abnormality,” “movement disorders,” “pseudobulbar palsy” and “dementia of frontal type.” We reviewed the evolution of the signs and symptoms of each patient from the presenting stage to the late stage. During the analysis, we identified core clinical features of the early stage of PSP.

In part II, we collected an additional 361 patients with other neurodegenerative disorders, such as Parkinson’s disease, multiple system atrophy, dementia with Lewy bodies, corticobasal degeneration, frontotemporal lobar degeneration and Alzheimer’s disease. Diagnoses were made by well-accepted criteria. We examined whether each patient showed any of the core clinical features of PSP at the first-ever clinic visit. We compared the patients with the two PSP groups (i.e. later fulfilled the NINDS-SPSP criteria for possible PSP, and had a clinical diagnosis of PSP but never fulfilled the NINDS-SPSP criteria for possible PSP) and the patients with other neurodegenerative disorders showing at least one core clinical feature of PSP, in an effort to determine whether a core clinical feature occurred more often in the two PSP groups and could potentially be used to differentiate these diagnoses early on. Differences between the two groups were evaluated using the χ²-test. A P-value <0.01 was considered significant.

Results
In part I, 40 patients with a clinical diagnosis of PSP (29 men and 11 women) were included. Clinical phenotypes at the last clinic visit were PSP-RS (n = 20), PSP-P (n = 14), PSP-CBS (n = 3), PSP-PNFA (n = 1), PSP-C (n = 1) and PSP-FTD (n = 1). No patients with PSP-PAGF were included. The age at onset ranged from 59 to 83 years (mean 71 years). The duration between the onset of subjective symptoms and the first clinic visit ranged from 1 to 72 months (mean 3 months). The follow-up period ranged from 12 to 173 months (mean 63 months).

As shown in Table 1, 16 patients fulfilled the NINDS-SPSP criteria for possible PSP at the first clinic visit. A total of 15 patients manifested “movement disorders,” “pseudobulbar palsy” and “dementia of frontal type” 2–105 months earlier than they fulfilled the NINDS-SPSP criteria for possible PSP. The presenting signs were postural instability with falls (n = 9), postural instability (n = 13), symmetric parkinsonism (n = 6), freezing of gait (n = 7), dysarthria and/or dysphagia (n = 7), and dementia of frontal type (n = 2). In the remaining nine patients, whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP, the presenting signs were postural instability with falls (n = 7), postural instability (n = 6),

| Sex (male/ female) | Age at onset (years) |
|-------------------|---------------------|
| Fulfilled the NINDS-SPSP criteria for possible PSP at the first clinic visit | 16 (13/3) | 72 ± 5 |
| Later fulfilled the NINDS-SPSP criteria for possible PSP | 15 (11/4) | 71 ± 7 |
| Never fulfilled the NINDS-SPSP criteria for possible PSP | 9 (4/5) | 73 ± 7 |

NINDS-SPSP, National Institute for Neurological Disorders and Stroke and Society for progressive supranuclear palsy criteria for possible progressive supranuclear palsy.
symmetric parkinsonism \((n = 6)\), freezing of gait \((n = 4)\), dysarthria and/or dysphagia \((n = 6)\), and dementia of frontal type \((n = 4)\). Overall, there were 24 patients (15 men and 9 women) that either later fulfilled the NINDS-SPSP criteria for possible PSP or whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP. The age at onset ranged from 59 to 83 years (mean 72 years).

Table 2 summarizes the manifestations observed at the first clinic visit and by the last clinic visit. The manifestations of each patient are shown in Table S1. One patient presented with cerebellar ataxia at the first clinic visit; this was coded as the “movement disorders” manifestation in Tables 2 and S1. This was the only patient that presented with a single manifestation that was not “movement disorders” \((n = 8)\). No patient displayed psychosis at the first clinic visit. All but two patients had the “movement disorders” manifestation, either alone or in combination with other manifestations. A total of 20 patients with “pseudobulbar palsy” and eight patients with “dementia of frontal type” also presented with other manifestations; no patients displayed “pseudobulbar palsy” or “dementia of frontal type” alone. No patients showed “vertical supranuclear gaze abnormality” as a single manifestation; however, this manifestation was observed in 17 patients at their first clinic visit. The frequency of the “vertical supranuclear gaze abnormality” manifestation increased over the disease course, and was observed in 32 patients by the last clinic visit. The manifestation “movement disorders” was observed in all patients. At the last clinic visit, all four manifestations occurred in 19 out of 40 patients. Three patients presented with supranuclear gaze slowness, two patients developed supranuclear gaze palsy within 2 months and one patient had experienced supranuclear gaze slowness for 3 months at the end of the follow-up period.

The present results showed that the vertical supranuclear gaze abnormality was not an early sign of PSP. There were patients showing postural instability with or without falls, and thus we merged these two signs and labeled them as postural instability. Other presenting signs in the present results included symmetric parkinsonism, freezing of gait, dysarthria and/or dysphagia, and dementia of frontal type. Therefore, we labeled these signs as the core clinical features of PSP.

In part II, we retrospectively reviewed and included 361 patients with other neurodegenerative disorders, such as Parkinson’s disease \((n = 258)\), multiple system atrophy \((n = 32)\), dementia with Lewy bodies \((n = 22)\), corticobasal degeneration \((n = 18)\), frontotemporal lobar degeneration \((n = 10)\) and Alzheimer’s disease \((n = 21)\). Among them, we observed one or more core clinical features at the first clinic visit in 49 patients \((27 \text{ with Parkinson’s disease or Parkinson’s disease with dementia, 10 with frontotemporal lobar degeneration, 6 with corticobasal degeneration, 4 with dementia with Lewy bodies and 2 with multiple system atrophy). The age at onset ranged from 47 to 83 years (mean 72 years; 27 men and 22 women). As shown in Table 3, among the core clinical features of PSP, freezing of gait seemed to be more common in PSP than in other neurodegenerative disorders \((P < 0.01)\). Freezing of gait was observed in 11 patients that either later fulfilled the NINDS-SPSP criteria for possible PSP or whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP: six patients that presented with freezing of gait before fulfilling the NINDS-SPSP criteria for possible PSP; one patient that presented with freezing of gait at the same clinic visit when the patient fulfilled the NINDS-SPSP criteria for possible PSP; and four patients whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP.

Freezing of gait was observed in four patients that showed one or more core clinical feature that had other neurodegenerative disorders. The latter included three with Parkinson’s disease or Parkinson’s disease with dementia and one with multiple system atrophy. Brain computed tomography or magnetic resonance imaging scans were available for all of the 24 patients that either later fulfilled the NINDS-SPSP criteria for possible PSP or whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP, and in 38 of the 49 patients with other neurodegenerative disorders. In 22 of the 24 patients and 20 of the 38 patients, midbrain and/or frontal lobe atrophy were observed.

### Discussion

Several phenotypes of PSP are currently accepted, and patients with PSP that do not fulfil the NINDS-SPSP criteria for possible PSP likely exist. To identify potential preceding signs or symptoms, we included all patients whose clinical diagnosis was PSP regardless of whether they fulfilled the NINDS-SPSP criteria for possible PSP.

In the first part of the present study, we reviewed the symptomatic evolution of the signs and symptoms observed...
in each patient. This resulted in the classification of four PSP manifestations: “vertical supranuclear gaze abnormality,” “movement disorders,” “pseudobulbar palsy” and “dementia of frontal type.” Among them, the “movement disorders” manifestation was the most common in patients with early PSP. Although the frequencies were low, some patients showed the “pseudobulbar palsy” and “dementia of frontal type” manifestations.

No patients presented with the “vertical supranuclear gaze abnormality” manifestation alone; 18 out of the 40 patients had the “vertical supranuclear gaze abnormality” manifestation at the first clinic visit. During the disease course, the frequency of each feature increased. We observed supranuclear gaze slowness that preceded supranuclear gaze palsy in only two patients. Compared with the “movement disorders” manifestation, “vertical supranuclear gaze abnormality” was rare and did not appear solely at the first clinic visit. We suppose that most patients with a vertical supranuclear gaze abnormality at the first clinic visit were labeled as having PSP-RS; this phenotype might include straightforward cases or cases that progress rapidly.

PSP-RS and PSP-P can be differentiated by their clinical pictures in the first 2 years.4 Patients with PSP-P show atypical features of PSP, including normal eye movement, resting tremor, no early falls or early postural instability or a good levodopa response.4 Pathologically, tau burden and distribution is restricted and milder in patients with PSP-P compared with those diagnosed with PSP-RS.2,15 We classified 14 patients as having PSP-P despite the lack of established specific criteria for PSP-P.

We further surveyed the signs and symptoms that appeared before the patients fulfilled the NINDS-SPSP criteria for possible PSP, as well as in patients whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP. These are the core clinical features of PSP. We enrolled patients with other neurodegenerative disorders where a differential diagnosis was problematic (Table 3). From the viewpoint of differential diagnoses, among the core clinical features, freezing of gait best improved the early clinical diagnosis of PSP. This was observed in a substantial number of patients with PSP over the disease course. The other core clinical features had a wide overlap with the features observed in other neurodegenerative disorders at the first clinic visit, as did midbrain and/or frontal lobe atrophy on the computed tomography or magnetic resonance imaging scans.

In 1974, pure akinesia was first described in two patients who developed freezing of gait, writing and speech, with paradoxical kinesia.16 For the purpose of improving the clinical diagnosis of PSP, Litvan et al. assessed the validity and interrater reliability of neurologists that assigned a clinical diagnosis of PSP with 105 autopsy-proven cases of PSP, Lewy body disease, corticobasal ganglionic degeneration, post-encephalitic parkinsonism, multiple system atrophy, Pick’s disease and other parkinsonian or dementia disorders.17 Osaki et al.3 assessed the accuracy of the clinical diagnosis using 60 cases clinically diagnosed with PSP when last assessed during life. However, freezing of gait was not specifically assessed in either of these two studies. Williams et al.7 defined specific diagnostic criteria, and introduced the nosology of PSP-PAGF. In that study, only seven (including 6 with PSP and 1 with Parkinson’s disease) out of 749 patients with movement disorders that satisfied the specific criteria for PSP-PAGF had a pathological diagnosis of PSP. The pathological distribution of PSP-PAGF was reported as atypical for classic PSP, with relative sparing of the pontine base and dentate nucleus. However, in the present clinical study, we never experienced patients that fulfilled the specific criteria for PSP-PAGF, which stipulate early freezing of gait or speech only appearing in the first 5 years. Hence, they were labeled as PSP-P or PSP-RS. Respondek et al. reported a retrospective analysis of 100 definite PSP cases. Interestingly, freezing of gait was observed in only 4% of the cases.18

The present results showed that there were three characteristics of freezing of gait in PSP. First, there were patients with PSP that showed freezing of gait both with and without symmetric parkinsonism. Second, all patients with PSP showing freezing of gait at the first clinic visit also had at least one of the other core clinical features. Third, freezing of gait is not exclusive to PSP, which is in accordance with earlier reports.7,19-21 Different pathological changes (i.e. tau, Lewy body-related or α-synuclein) might not point to a specific diagnosis; differences in their burden and distribution could exist, in terms of freezing of gait.7,19-21

The present study solely examined early clinical diagnoses, and signs and symptoms in an attempt to improve the early clinical diagnosis of PSP. One strength of the present study was that we observed the symptomatic evolution from an early stage of PSP through the standardized assessment. The mean latency between when the patient suffered any sign

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### Table 3 Comparison between patients with one or more core clinical features at the first clinic visit

| either later or never fulfilled the NINDS-SPSP criteria for possible PSP | Sex (male/female) | Age at onset (years) | PI | sym P | FoG* | Dysarthria and/or dysphagia | DF |
|---|---|---|---|---|---|---|---|
| Other neurodegenerative disorders with any of the core clinical features | 27/22 | 72 ± 9 | 25 | 32 | 4 | 15 | 15 |

*P < 0.01. Patients that fulfilled the National Institute for Neurological Disorders and Stroke and Society for progressive supranuclear palsy (NINDS-SPSP) criteria for possible progressive supranuclear palsy (PSP) later or whose clinical diagnosis was PSP but never fulfilled the NINDS-SPSP criteria for possible PSP versus patients with other neurodegenerative disorders. DF, dementia of frontal type; FoG, freezing of gait; PI, postural instability; sym P, symmetric parkinsonism.
and when they visited the clinic was 3 months. Conversely, a limitation of the present study was the absence of neuropathological confirmation of PSP, and this study could be biased by the relatively small number of patients with PSP.

We did not use the terms “sensitivity” or “positive predictive value” to avoid confusion. However, we showed that freezing of gait was a presenting sign or symptom in a substantial number of patients with PSP before the NINDS-SPSP criteria for possible PSP were fulfilled. If neuropathology confirms these cases as true positive PSP, this feature yields a higher sensitivity. As in the present study, if patients with other neurodegenerative disorders infrequently show freezing of gait during the early disease course, it results in a higher positive predictive value. Consequently, we propose that freezing of gait merits inclusion into the diagnostic criteria to improve earlier clinical diagnosis of PSP.

In conclusion, freezing of gait is an early feature, and its presence might improve clinical diagnosis of PSP, whereas vertical supranuclear gaze abnormality is not an early feature.

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Supporting Information
Additional Supporting Information may be found online in the supporting information tab for this article:
Table S1 Manifestations of each patient at the first and last clinic visits