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MOVEMENT DISORDERS - ORIGINAL ARTICLE

# In vivo comparison of Richardson's syndrome and progressive supranuclear palsy-parkinsonism

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**Abstract** Richardson's syndrome (RS) and progressive supranuclear palsy-parkinsonism (PSP-P) are the most common subtypes of PSP. Post-mortem data suggests that the clinical presentation of the two subtypes differs especially in the first 2 years of disease and then converges. This hypothesis has, to our knowledge, never been confirmed in a living cohort. Medical history was used to define subtypes retrospectively in 23 consecutive PSP patients from our outpatient clinic specialized in movement disorders. 14 patients suffered from RS, and 9 from PSP-P. Using a prospective cross-sectional approach, clinical, cognitive, behavioral, speech and biochemical (cerebrospinal fluid tau levels) features were compared. RS patients showed shorter time from disease onset to diagnosis and more neuropsychological and neurobehavioral deficits than PSP-P patients, but differed not significantly with regard to clinical and biochemical features. RS and PSP-P show considerable symptoms overlap during the disease course when using routine assessments, with persisting differences regarding non-motor symptoms. Shorter disease duration of the comparably affected RS patients indicates that this subtype has an accelerated disease progression at early disease stages.

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## Introduction

Progressive supranuclear palsy (PSP) is the most common atypical parkinsonian disorder (Schrag et al. 1999). Pathologic changes include neurofibrillary tangles (abnormal tau protein aggregates) and astrocytic tufts affecting most severely the subthalamic nucleus, the substantia nigra and the globus pallidus (Williams et al. 2007a). PSP therefore belongs to the tauopathies.

In vivo diagnosis remains a great challenge (Litvan et al. 2003), and gets more and more complicated: Once described by Richardson (1963) as a symptom constellation of supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia, research has widened the clinical spectrum of this disease. Features like executive and memory dysfunction (Grafman et al. 1995), behavioral symptoms like apathy and frontal disinhibition (Aarsland et al. 2001), profound speech impairment like speech spasticity as well as ataxia (Kluin et al. 2001, 1993) have been reported to occur in pathologically proven PSP.

Recent analysis of pathologically proven PSP cases revealed a phenotypic diversity of PSP, and distinct subtypes such as pure akinesia with gait freezing (PAGF), PSP-corticobasal degeneration (PSP-CBD) and progressive nonfluent aphasia (PNFA) have been defined (Birdi et al. 2002; Nath et al. 2003; Kaat et al. 2007; Williams et al. 2005; Williams and Lees 2009). These subtypes are mostly not covered by use of current diagnostic criteria (Litvan et al. 1996), and new models for the diagnosis of PSP subtypes must be considered. Based on Williams (2005)

the two most common PSP subtypes present regularly with the following symptoms at early disease stages: Richardson's syndrome (RS): falls, cognitive dysfunction, abnormality of gaze and postural stability; PSP-parkinsonism (PSP-P): asymmetric parkinsonian symptoms (including rigidity, bradykinesia and even tremor), non-axial dystonia and response to levodopa. Early occurrence of falls, cognitive decline and unintelligible speech (associated with the RS subtype) has been proven to predict shorter disease duration (Jellinger 2008; O'Sullivan et al. 2008), but, according to post-mortem confirmed data (Williams et al. 2005), the clinical pictures of these two subtypes may converge in the course of the disease. Pathologic studies revealed a more restricted and milder tau distribution, and a lower four-repeat/three-repeat tau ratio in PSP-P as compared to RS (Williams et al. 2007a), suggesting that the in vivo determination of tau proteins may have the potential to differentiate the subtypes.

This study aims, to our knowledge for the first time, to verify whether the differences between RS and PSP-P patients (which are based on retrospective and post-mortem studies) are also detectable in a living cohort by comparing medical history, clinical and biochemical parameters.

## Subjects, materials and methods

### Patients

Patients meeting criteria for possible or probable PSP (Litvan et al. 1996) were recruited by searching the database of the Department of Neurodegeneration, University hospital of Tuebingen, Germany. As PSP-P patients often present with symptoms according to Litvan (1996) at later disease stages, we did not apply the criterion 'in the first year of the disease' (Litvan et al. 1996). A similar inclusion procedure has recently been used by others (Agosta et al. 2010). All patients had to provide medical history for at least 2 years from first manifestation of symptoms. Patients who met clinical criteria for PAGF (Williams et al. 2007b) or other neurological disorders like PD (Gibb and Lees 1988), multiple system atrophy (Gilman et al. 1999) or corticobasal-degeneration (Boeve et al. 2003) were not included in the study as well as patients with previous or current history of other neurological diseases. 23 patients with PSP with a median age of 67 years (range, 57–81 years) were included. Every patient underwent all presented assessments within a day.

### Medical history

Two movement disorders specialists independently reviewed all the medical history of each patient and grouped the patients into RS or PSP-P according to Williams et al. (2005). Early presence of the following symptoms were particularly considered: falls, cognitive decline, supranuclear gaze palsy, abnormal saccades, postural instability, dysphagia, speech disturbance, tremor, bradykinesia, asymmetric onset, extra-axial dystonia, and levodopa response (defined as documented response to levodopa in the medical record, and/or confirmation by patient and spouse that levodopa had some benefit). Additionally disease duration (time between disease onset and date of study visit), time to diagnosis and educational level were considered.

Fourteen patients were classified as RS (Williams et al. 2005) because falls, cognitive dysfunction, supranuclear gaze palsy, abnormalities of saccadic eye movements and postural instability were the predominant clinical features within the first 2 years of the disease. Nine patients were classified as PSP-P as they showed at least three of the following criteria in the first 2 years of the disease: predominant bradykinesia or tremor, positive response to levodopa, asymmetric onset and limb dystonia. The study was approved by the local ethics commission and performed according to the Declaration of Helsinki. Written informed consent was obtained from every patient.

### Clinical examination

All participants underwent a systematic neurological examination including the assessment of the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton 1987) and the PSP rating scale (Golbe and Ohman-Strickland 2007). Due to the fact that speech deficits have been shown to differ between Parkinson disease (PD) and PSP patients—PD patients often present with monotonous speech, reduced breathiness and loudness concomitant with articulatory inaccuracy in terms of mumbling utterances, whereas PSP patients rather have spastic, hypokinetic and some ataxic features (Sachin et al. 2008)—a speech therapist blinded to diagnosis (GM) assigned the patients either to RS or PSP-P, by use of a structured interview and by focusing on acoustic speech parameters.

### Cognitive and behavioral assessment

General cognitive function were assessed with the Mini-Mental Status Examination (MMSE) (Folstein et al. 1975), and frontal dysfunction with the Frontal Assessment Battery (FAB). The FAB screens for different executive functions like conceptualization, mental flexibility, motor programing, sensitivity to interference, inhibitory control and environmental autonomy (Dubois et al. 2000).

Psychopathology was examined with the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994). In addition, apathy was explored with the German version of the Apathy Evaluation Scale ($AES_D$) including $AES_D$-I (evaluation of patients apathy by the caregiver), $AES_D$-S (by the patient) and $AES_D$-C (by the clinician) (Marin et al. 1991).

Daily activity and caring necessity was assessed using the Nuernberger Alters Aktivitaetenskala (NAA, a daily activity scale) and Nuernberger Alters Beobachtungsskala (NAB, this scale evaluates caring necessity) (Oswald and Fleischmann 1997).

### Determination of cerebrospinal tau levels

Cerebrospinal fluid (CSF) collection and determination of routine diagnostic parameters were performed according to standardized protocols [for details see (Maetzler et al. 2009)]. All included subjects had normal routine CSF parameters. CSF total tau and tau phosphorylated at threonine 181 (p-tau) levels were measured with commercial ELISA kits (Innogenetics, Ghent, Belgium).

### Statistical analyses

Data were analyzed with JMP software (version 7, SAS). Due to the non-normal distribution of some parameters (e.g., MMSE, FAB) and the sample size non-parametric test procedures were applied. Medians and ranges are indicated. Levels of significance were calculated with the Fisher's Exact test, the Wilcoxon rank sum test and the Spearman correlation test. Differences were assumed to be significant at $p < 0.05$.

## Results

### Demographic data

Median age at disease onset was 63.7 years in RS patients, and 59.1 years in PSP-P patients ($p = 0.12$). Gender and education level did not differ significantly between the two subtypes. RS patients showed a trend towards shorter disease duration (until study inclusion) than PSP-P patients (median disease duration 3.4 vs. 6.1 years, $p = 0.08$). In addition, time from disease onset to diagnosis was shorter in RS patients as compared to PSP-P patients (1.9 vs. 4.3 years, $p = 0.04$).

### Medical history

Early falls occurred in all RS patients but one, a well-trained sailor. No PSP-P patients reported about early falls. Appearance of early cognitive impairment tended to be higher in RS patients. Supranuclear gaze palsy, abnormal saccades and postural instability were initially found in all RS patients, but only in a subset of PSP-P patients (supranuclear gaze palsy, 3 of 8; abnormal saccades, 5 of 8; postural instability, 3 of 9). Early occurrence of bradykinesia (8 of 9) and asymmetric limb signs (7 of 9) was observable in almost all PSP-P patients. 5 of 9 PSP-P patients, but also 4 out of 11 RS patients had initial responsiveness to levodopa (3 PSP-P patients provided insufficient data). Details about symptom presentation in the early course of the disease are presented in Table 1.

### Clinical examination

At the time of study inclusion patients with PSP-P, initially fulfilling the criteria proposed by Williams and colleagues, presented a similar phenotype like the RS patients with severe postural instability (9 of 9 patients), frequent falls (6 of 9 patients), supranuclear gaze palsy (9 of 9 patients), abnormal saccades (9 of 9 patients) and cognitive decline (6 of 9 patients). A distinct distribution of clinical features as reported for the first 2 years of disease (Table 1) was basically not detectable. Both subtypes scored similarly in the PSP rating scale at study inclusion. There was a trend towards a higher UPDRS motor score in PSP-P patients. By use of a structured interview, the assignment of the speech therapist in differentiating the subtypes RS and PSP-P reached a sensitivity of 90%, and a specificity of 60%.

### Cognitive and behavioral assessment

General aspects of cognition assessed with the MMSE, and frontal dysfunction assessed with the FAB were similarly impaired in both subtypes (Table 2). RS patients scored worse in the subitem "conceptualization" of the FAB, compared to PSP-P patients ($p = 0.03$).

RS patients had a higher frequency of neuropsychiatric symptoms compared to the PSP-P patients ($p = 0.01$). Detailed data are supplied in Table 2.

Apathy tested with the $AES_D$ affected both RS and PSP-P subtypes comparably. Comparing $AES_D$ subtests from caregivers ($AES_D$-I) with those of patients ($AES_D$-S) the caregivers of RS patients evaluated the degree of apathy higher than the patients themselves. This phenomenon could not be seen in the PSP-P cohort (ratio $AES_D$-I/$AES_D$-S in RS: 1.64, in PSP-P: 0.94; $p = 0.057$).

Daily activity as assessed with the NAI was markedly impaired in all PSP patients and did not differ significantly between the subtypes.

### Total tau and phospho-tau in the CSF

CSF total tau and phospho-tau levels were in the normal range in the RS ($n = 10$) and in the PSP-P patients

**Table 1** Demographic and clinical features of RS and PSP-P

| | RS | | | PSP-P | | | | *p* value |
|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | |
| Subjects (f/m) | 14 (8/6) | | | 9 (6/3) | | | | 0.64 |
| Age (years) | 67 (57–81) | | | 65 (59–75) | | | | 0.43 |
| Age of disease onset (years) | 63.7 (55.2–75.7) | | | 59.1 (55.4–68.9) | | | | 0.12 |
| Disease duration (years) | 3.4 (2.0–6.3) | | | 6.1 (2.0–9.8) | | | | 0.06 |
| Time to diagnosis (years) | 2.0 (0.2–4.8) | | | 4.3 (1.1–5.7) | | | | 0.02 |
| Education level (years) | 9 (8–16) | | | 9 (9–14) | | | | 0.18 |
| PSPRS total score | 35 (16–58) | | | 34 (18–63) | | | | 0.51 |
| UPDRS motor subscore | 31 (13–60) | | | 46 (28–63) | | | | 0.08 |
| Clinical features | Early | Late | *p* value | Early | Late | *p* value | *p* value early, respectively | *p* value late, respectively |
| Falls | 92.9 (13/14) | 100.0 (14/14) | 0.31 | 0.0 (0/9) | 66.7 (6/9) | <0.001 | <0.0001 | 0.02 |
| Cognitive decline | 64.3 (9/14) | 78.6 (11/14) | 0.40 | 22.2 (2/9) | 66.7 (6/9) | 0.06 | <0.05 | 0.53 |
| Supranuclear gaze palsy | 100.0 (14/14) | 100.0 (14/14) | 1.00 | 33.3 (3/9) | 100.0 (9/9) | 0.01 | 0.0008 | 1.00 |
| Abnormal saccades | 100.0 (14/14) | 100.0 (14/14) | 1.00 | 55.6 (5/9) | 100.0 (9/9) | 0.08 | 0.01 | 1.00 |
| Postural instability | 100.0 (14/14) | 100.0 (14/14) | 1.00 | 33.3 (3/9) | 100.0 (9/9) | <0.01 | <0.001 | 1.00 |
| Tremor | 7.1 (1/14) | 7.1 (1/14) | 1.00 | 11.1 (1/9) | 11.1 (1/9) | 1.00 | 0.75 | 0.74 |
| Bradykinesia | 42.9 (6/14) | 100.0 (14/14) | <0.001 | 88.9 (8/9) | 100.0 (9/9) | 0.37 | 0.03 | 1.00 |
| Asymmetric onset | 21.4 (3/14) | 50.0 (7/14) | 0.11 | 77.8 (7/9) | 66.7 (6/9) | 0.70 | 0.01 | 0.43 |
| Extra axial dystonia | 14.3 (2/14) | 7.1 (1/14) | 0.54 | 33.3 (3/9) | 33.3 (3/9) | 1.00 | 0.34 | 0.13 |
| Response to Levodopa | 33.3 (4/12)[a] | n.a. | – | 55.6 (5/9) | n.a. | – | 0.30 | – |
| Speech disturbance | 64.3 (9/14) | 92.9 (13/14) | 0.06 | 55.6 (5/9) | 100.0 (9/9) | <0.05 | 0.15 | 0.41 |
| Dysphagia | 57.1 (8/14) | 64.3 (9/14) | 0.69 | 22.2 (2/9) | 66.7 (6/9) | 0.06 | 0.19 | 0.91 |

*p* values were determined using Wilcoxon signed rank test or the Fisher's exact test

*RS* Richardson's syndrome, *PSP-P* PSP parkinsonism, early <2 years disease duration, late >2 years disease duration, *n.a.* not assessed. *PSPRS* PSP Rating Scale, *UPDRS* Unified Parkinson's Disease Rating Scale

[a] 2 RS patients had not received medication until study inclusion

**Table 2** Cognition, behavior, and biochemical features

| | RS | PSP-P | *p* value |
|---|---|---|---|
| Mini-Mental State Examination | 24 (17–30) | 26 (18–30) | 0.69 |
| Frontal Assessment Battery | 11 (5–15) | 12 (4–18) | 0.40 |
| Neuropsychiatric Inventory | | | |
| At least one test higher zero (Fisher's exact test) | 12/12 | 6/12 | 0.01 |
| Apathy Evaluation Scale | | | |
| $AES_D$-S | 21.0 (1–42) | 17.5 (6–33) | 1.0 |
| $AES_D$-C | 26.0 (0–45) | 16.0 (0–48) | 0.27 |
| $AES_D$-I | 31.5 (12–48) | 22.0 (0–42) | 0.09 |
| $AES_D$-I/$AES_D$-S | 1.64 (0.66–12.0) | 0.94 (0–1.17) | 0.06 |
| Cerebrospinal tau levels | | | |
| Total tau | 149 (86–256) | 180 (147–218) | 0.20 |
| Phospho-tau | 29 (21–53) | 36 (27–41) | 0.21 |

Data are presented with median (range)

$AES_D$ Apathy Evaluation Scale (German version), $AES_D$-*C* expert evaluation, $AES_D$-*I* caregiver evaluation, $AES_D$-*S* self-evaluation, *PSP-P* progressive supranuclear palsy-parkinsonism, *RS* Richardson's syndrome

*p* values were determined using the Wilcoxon rank sum test if not otherwise indicated

($n = 6$), and did not differ significantly between the subtypes (Table 2).

### Comparison of symptoms occurrence

In PSP-P patients, three of five RS-associated features (falls, supranuclear gaze palsy, postural instability) occurred significantly more often at study inclusion than during the early course of disease. The same tendency was observable for cognitive decline and the occurrence of abnormal saccades. In RS patients, one PSP-P-associated feature (bradykinesia) was significantly more abundant at study inclusion than in the first 2 years of disease. In the PSP-P group, in addition, speech disturbance appeared significantly more often throughout disease than in the early disease course. For details we refer to Table 1.

## Discussion

In this study we show that, in the course of the disease, PSP subtypes RS and PSP-P, which are distinguishable at early disease stages by definition (Williams et al. 2005), converge and are no longer sufficiently distinguishable using routine diagnostic methods (Fig. 1). This supports the idea that PSP is a multi-faced disease in particular at early stages but then assimilates to a common final path (Williams et al. 2005, 2007a). According to our data, PSP-P patients become more "RS-like" in the course of disease than the other way around. In this PSP subtype, three RS-associated features occurred significantly more often in the later course of the disease than in the first 2 years of disease. In RS patients, only one PSP-P-associated feature occurred significantly more often at later disease stage than during the first 2 years. This argumentation may be interpreted as circular reasoning because the included PSP-P patients had to fulfil PSP consensus criteria during disease course. However, our approach demonstrates that RS patients generally do NOT develop a PSP-P-like phenotype during disease course which, to our knowledge, has not yet been tested.

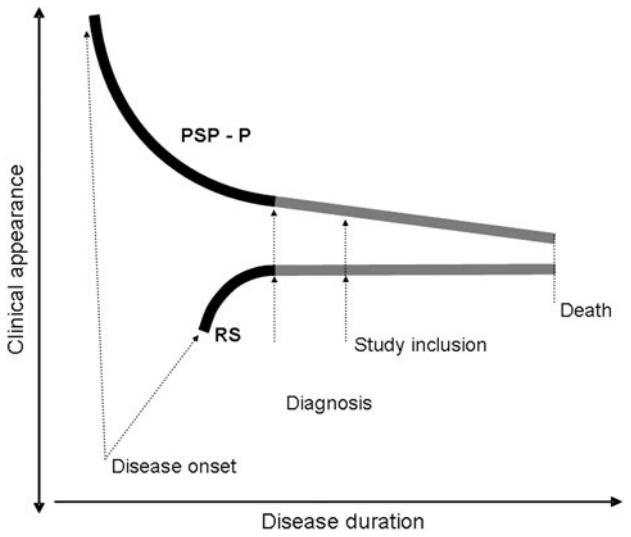


**Fig. 1** Hypothetical disease course of Richardson syndrome (*RS*) and progressive supranuclear palsy-parkinsonism (*PSP-P*). The PSP-P subtype progresses slower than the RS subtype, in particular in early disease stages, i.e., from disease onset to diagnosis (*black lines*), and the PSP-P phenotype may change more to a RS phenotype than vice versa. According to published survival times of PSP-P (9.1 years) and RS (5.9 years) (Williams et al. 2005), progression of clinical symptoms and time from diagnosis to death may be comparable

PSP-P patients were diagnosed at a later disease stage than RS patients. This is in accordance with our clinical experience. PSP-P patients are "PD-like" in particular at the beginning of the disease. This makes it often difficult, sometimes even impossible, to diagnose them as PSP patients according to given criteria (Litvan et al. 1996). The question remains whether, from the time point when RS and PSP-P assimilate, disease progression is comparable between these subtypes, or whether PSP-P patients continue with slower progression (Williams and Lees 2009).

With our test battery, we were almost unable to distinguish RS from PSP-P. For example, disease severity as assessed with the PSP rating scale was similar between the subgroups, as were tau CSF levels. These findings underscore the above-mentioned assimilation of the subtypes RS and PSP-P throughout disease. The observed trend towards a higher UPDRS motor score in the PSP-P subtype might indicate a persistent difference of severity of Parkinson-associated symptoms between the subtypes.

Although the expert opinion on speech impairment showed a sensitivity of 90% only a specificity of 60% was reached in differentiating the subtypes. This limited diagnostic accuracy is basically in line with a recent report which detected no significant differences of acoustical speech variables (Skodda et al. 2010).

Cognitive and behavioral changes are seen in about 50% of PSP patients, often within the first year of disease (Cambier et al. 1985; Brusa et al. 1980). These findings are confirmed by our results. However, neither the degree of general cognitive nor of frontal dysfunction differed significantly between RS and PSP-P at study inclusion. This may at least partly be explained by floor or ceiling effects of the tests used in this study. Nevertheless, RS patients scored worse in the FAB subitem "conceptualization" which argues for distinct degrees of frontal degeneration. In addition, RS patients had a significantly higher frequency of neuropsychiatric symptoms as compared to PSP-P patients, and RS patients showed a trend towards a higher $AES_D$-I/$AES_D$-S ratio compared to PSP-P patients,

possibly indicating a difference in self-perception (Table 2). This raises the question whether detailed neuropsychological testing, functional imaging such as PET and/or MRI-based morphometry may be more promising tools to sufficiently differentiate PSP subtypes, than clinical examination.

Limitations of this study are the relatively small sample size, lack of pathological confirmation, and retrospective evaluation of the first 2 years of disease using interview technique and clinical records. We tried to overcome these issues by as precise as possible evaluation of the medical history and clinical examination by a team of experienced neurologists. Further it has to be mentioned that patients never developing gaze palsy (e.g., 6 of 21 PSP-P patients in the study by Williams) were not included in this study. The observed convergence of the clinical phenotypes may in part be explained by the study design.

In conclusion, RS and PSP-P have comparable clinical and biochemical outcomes in the course of the disease. This corroborates the hypothesis proposed by Williams and Lees (2009) that the process of tau accumulation leads to different clinical phenomena at early PSP stages, is a dynamic process occurring at different rates but then may converge to similar clinical pictures. However, subtle non-motor differences may persist throughout disease.

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**Conflict of interest** All authors report no conflict of interest.

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