Title

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Are the International Parkinson Disease and Movement Disorder Society Progressive Supranuclear Palsy (IPMDS-PSP) diagnostic criteria accurate enough to differentiate common PSP phenotypes?

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Abstract

The International Parkinson Disease and Movement Disorder Society PSP study group (IPMDS-PSP) recently published new clinical diagnostic criteria for progressive supranuclear palsy (PSP). Currently, there is no data regarding the accuracy of these sets of criteria for differentiating various PSP phenotypes. We discuss the accuracy of the IPMDS-PSP criteria for differentiation of patients with the PSP-Richardson phenotype (PSP-RS) from those with the PSP-Parkinsonism (PSP-P) using data from a sample of 274 clinically diagnosed PSP patients participating in the Environmental Genetic PSP (ENGENE-PSP) case control study. Using National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) criteria and the Williams criteria we categorized 259 of these patients as possible and probable PSP-RS and 15 as PSP-P. The IPD-MDS PSP-RS and PSP-P criteria were unable to distinguish the PSP-RS from the PSP-P phenotypes in this sample. Nearly all (92.6%; 240 out of 259) the PSP-RS patients and over half (60%; 9 out of 15) of the PSP-P patients fulfilled both the IPMDS criteria for PSP-RS and PSP-P. Applying the newly proposed multiple allocation extinction rules decreased the number of overlapping diagnoses among the NINDS-SPSP PSP-RS patients, however problems remained in the PSP-P group. Diagnostic accuracy might be improved by modification of timelines for development of falls and other parkinsonian features.

Keywords

Progressive supranuclear palsy; Criteria; Diagnosis

The International Parkinson Disease and Movement Disorder Society PSP study group (IPMDS-PSP) recently published new clinical diagnostic criteria for progressive supranuclear palsy (PSP) [1]. The goals of these criteria were to address the unsatisfactory sensitivity [2] of the prior criteria developed in 1996 by the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) [3] that identified the classical or Richardson PSP phenotype (PSP-RS) and to define and differentiate the various PSP phenotypes.

Parkinsonism-predominant PSP (PSP-P) is probably the second most common PSP phenotype after the PSP-RS. PSP-P was identified in 2005 by Williams et al [4] based on principal components analysis of the clinical features of 103 pathology-proven PSP cases. They identified a set of features indicative of a PSP-P phenotype including early occurrence of a parkinsonian feature such as bradykinesia, rigidity, positive levodopa response, or tremor at rest, and occurrence of PSP-specific features after the first two years, including postural instability/falls or vertical supranuclear gaze palsy or slow vertical saccades [4, 5]. Williams et al, as well as other researchers who used the “Williams criteria” for identification of PSP-P, reported better survival with longer disease duration and slower rate of disease progression in patients with this PSP phenotype compared to those presenting with the classical PSP-RS phenotype [4, 6–10]. Currently, there is an agreement that the various PSP phenotypes, especially the common PSP-RS phenotype must be differentiated from PSP-P not only because they have different clinical course but also for inclusion of a more homogenous group of PSP patients into therapeutic clinical trials.

The new IPMDS-PSP criteria includes sets of phenotype-specific features for identifying various PSP phenotypes that are both sensitive and specific for distinguishing PSP from related disorders [1, 11]. Currently, there is no data regarding the accuracy of these sets of criteria for differentiating various PSP phenotypes. Here we discuss the accuracy of the IPMDS-PSP criteria for differentiation of patients with the PSP-RS phenotype from those with the PSP-P using data from a large sample of PSP patients from the Environmental Genetic PSP (ENGENE-PSP) case-control study.

Criteria for IPMDS PSP-RS and PSP-P

The definition of the IPMDS-PSP phenotype-specific features was based on literature review and experts' panel consensus [1]. Probable PSP-RS is defined as the presence of supranuclear vertical gaze palsy (O1) or slow vertical saccades (O2) presenting at any time since symptom onset, plus non-accidental falls either spontaneously (P1) or on the pull-test (P2) during the first three years of symptom onset. Probable PSP-P is defined by the presence of vertical supranuclear gaze palsy or slow vertical saccades plus axial dominant/levodopa resistant (A2) or asymmetrical/levodopa responsive (A3) parkinsonism. These criteria do not define a timeline for the latency between symptom onset and presence of supranuclear vertical gaze palsy or parkinsonism [1]. The specificity of these features was examined in 206 pathologically confirmed PSP patients and 231 pathologically confirmed parkinsonian controls [11]. In that clinical-pathological study the specificity to differentiate PSP from disease controls was high for vertical supranuclear gaze palsy (91%), slow vertical saccades (85%), postural instability (81%), and akinetic-rigid, levodopa-resistant parkinsonism (92%), but was low for parkinsonism with tremor/asymmetry/levodopa response (47%) [11].

Lack of a timeline for development of supranuclear gaze palsy/slow vertical saccades, or more importantly postural instability in the IPMDS-PSP-P criteria raises a concern that, when using these criteria, PSP-RS patients who present with early parkinsonian features in addition to ocular motor features could be classified both as PSP-RS and PSP-P. This is a significant issue since multiple series of PSP-RS patients confirmed the high prevalence of parkinsonian features especially axial or limb bradykinesia and rigidity early in the disease [4, 6, 11–13]. In the IPMDS-PSP criteria PSP-RS patients are identified by early falls in the first three years of symptom onset. Hence, PSP patients who are recognized by the IPMDS-PSP-P criteria in the first three years of symptom onset would include a combination of: (1) those identified as PSP-P who develop supranuclear gaze palsy/slow vertical saccades early (under 3 years) in their course in addition to parkinsonism, and (2) those PSP-RS patients who develop parkinsonian features in addition to falls and supranuclear gaze palsy/slow vertical saccade, early in their disease period, which consist a large group of PSP-RS patients [4, 6, 11–13] (Figure 1). In our view this will limit the usefulness of these criteria to differentiate between the more benign and the more rapid progressive phenotypes.

Challenges in differentiating the IPMDS PSP-RS and PSP-P phenotypes

While the IPMDS-PSP criteria are quite useful in differentiating PSP from other disorders, as stated above, they may not be sufficiently specific to differentiate the two common

phenotypes: PSP-RS from PSP-P. To explore this further, we evaluated the new IPMDS PSP-RS and PSP-P criteria in a large sample of PSP patients participating in the ENGENE (Environmental Genetic-PSP case-control) study [14]. This study consisted of 350 PSP patients of which 259 met the probable and 76 the possible NINDS-SPSP criteria [3]. Fifteen cases were excluded: 13 due to missing data and two out of the 20 pathologically confirmed patients because they had corticobasal degeneration pathology presenting clinically with a PSP phenotype. We selected two pathologically confirmed diagnostic criteria as gold standards to identify probable PSP-RS (probable NINDS-SPSP) and probable PSP-P (Williams criteria for PSP-P) cases in this sample of 335 PSP patients. The NINDS-SPSP criteria were designed to identify patients with the classical PSP phenotype (PSP-RS) [2, 13]. The validation of this set of criteria in an independent pathologically confirmed sample showed that the NINDS-SPSP probable criteria was 100% specific and 50% sensitive and the NINDS-SPSP possible criteria was 93% specific and 83% sensitive for diagnosing classical PSP against various disorders [15]. High correlation of these criteria to a pathological PSP diagnosis was later confirmed in a large sample of pathologically proven PSP patients [2]. These criteria define probable PSP by the presence of prominent postural instability with falls in the first year of the symptom onset associated with supranuclear vertical gaze palsy independent of its time of onset. Possible PSP in these criteria is defined as either vertical supranuclear gaze palsy or prominent postural instability in the first year of symptom onset accompanied with the slowing of vertical saccades independent of its time of onset. The Williams definition of PSP-P requires presence of parkinsonism (bradykinesia plus rigidity or tremor) but lack of both postural instability/falls and vertical supranuclear gaze palsy in the first two years of symptom onset.

The 259 patients who fulfilled NINDS-SPSP probable criteria were included as probable PSP-RS patients in our analysis since the NINDS-SPSP probable criteria lack sensitivity for recognizing other PSP variants [2]. We retrospectively applied the Williams criteria for PSP-P to the 76 patients with possible PSP from the ENGENE database and diagnosed 15 of them as probable PSP-P. We did not apply the Williams et al. criteria to patients fulfilling NINDS-SPSP probable criteria because by definition these patients present with falls/postural instability or vertical supranuclear gaze palsy at the first year of symptom onset. Hence none of these patients would fulfill the Williams et al. criteria which by definition excludes patients who present typical PSP-RS features in the first two years of symptom onset. Of those 15 patients diagnosed as PSP-P, 12 patients had asymmetrical parkinsonism with or without tremor. We did not consider levodopa response because the data is unavailable in the ENGENE database. The remaining 61 cases (shown as “other possible PSP” in Figure 3) were not diagnosed using Williams criteria because those patients with parkinsonism at the first 2 years also had at least one PSP-RS feature (i.e. postural instability / vertical supranuclear gaze palsy) presented in the first 2 years of symptom onset. To determine the accuracy of the IPMDS-PSP criteria for PSP-P and PSP-RS, we first applied these criteria to the 274 cases (259 probable PSP-RS and 15 probable PSP-P cases) We found that at the time that the patients were recruited all 259 probable PSP-RS patients (77.3% of 335 patients) fulfilled the IPMDS-PSP-RS criteria and 240 of them (92.6%) also fulfilled the IPMDS-PSP-P criteria. There were 19 patients without parkinsonian features, except for postural instability, at the time of evaluation. The whole sample of the 15

probable PSP-P patients fulfilled the IPMDS-PSP-P criteria at the time of evaluation, however, 9 of these patients (60%) also fulfilled the IPMDS-PSP-RS criteria. A considerable overlap was also found when we applied these criteria at the first, second, and third year of symptom onset or thereafter (Figure 2). At the time of evaluation, 240 out of all 255 (94.1%) PSP-P patients meeting the IPMDS-PSP criteria also met the probable NINDS-SPSP criteria.

To reduce the problems of multiple allocations in our sample we applied the set of four multiple allocation extinction (MAX) rules recently proposed by the Movement Disorder Society-endorsed PSP Study Group [16]. These four rules were specifically put forward to address the problem of multiple phenotype allocation which occurred while applying the new IPMDS-PSP criteria to various samples of PSP patients [17, 18]. The first rule prioritizes diagnoses with higher levels of certainty over those of lower certainty (diagnostic certainty). The second rule indicates that the diagnosis appearing first in the course of disease should be accepted (temporal order). The third rule states that the phenotype with higher specificity to predict PSP pathology, higher impact on quality of life, or more severity should be preferred over other phenotypes. The forth rule indicates when there is multiple allocations based on the first three rules, MAX 1 is preferred over MAX 2 and MAX 2 is favored over MAX 3. The overall degree of overlap at the time of evaluation reduced slightly (from 92.6% to 78%) in the probable PSP-RS group and did not change in the probable PSP-P group after application of the first two rules (Supplementary Figure 1). Application of MAX 1 (diagnostic certainty) or MAX 2 (temporal order) did not change the diagnostic phenotype because these patients met both probable PSP-P (phenotypic hierarchy) and PSP-RS criteria simultaneously at the time they develop PSP-specific features due to the development of supranuclear vertical gaze palsy. We found that in this case the application of the third extinction rule (phenotypic hierarchy) was problematic since it is not clearly operationalized in terms of symptom severity and effects on quality of life. However, we interpreted it as prioritization of the PSP-RS phenotype over PSP-P phenotype when there is postural instability in the first 3 years of symptom onset. Applying this rule, all probable PSP-RS patients and 9 probable PSP-P patients (60%) were diagnosed as PSP-RS by the IPMDS-PSP criteria (Supplementary Figure 2). Of these 9 patients 7 had asymmetrical parkinsonism with or without tremor.

There are clear challenges in differentiating these phenotypes using the current definition of the IPMDS-PSP-P criteria. The average latency from symptom onset to development of parkinsonian features except for postural instability in the ENGENE sample was 13.34 months (95% CI: 11.25 – 15.44, n=240) for the probable PSP-RS patients and 5.33 months (95% CI: 0.91 – 9.75, n=15) for the probable PSP-P patients. These were shorter than the latency for supranuclear gaze palsy/slow vertical saccades which was 24.74 months (95% CI: 22.25 – 27.22, n=259) in the probable PSP-RS and 56.20 months (95% CI: 45.51 – 66.89, n=15) among the probable PSP-P patients. Latency to development of postural instability in the probable PSP-P patients was 33.36 months (95% CI: 28.89 – 37.83, n=15). All patients in the probable PSP-RS group had a latency of one year or less by definition (Figure 2). Thus, the most important reason for a delay in diagnosing probable PSP-P was the latency between the onset of the parkinsonism and the emergence of oculomotor features. A major factor as explained above is the simultaneous fulfillment of both MDS-

PSP-R and MDS-PSP-P phenotypes criteria at the time patients develop supranuclear vertical gaze palsy. This occurs among those patients who develop postural instability/falls in the first 3 years of symptom onset. Although this issue could be addressed by addition of another MAX, in our opinion, it would be more appropriate if this is addressed in the definition of these phenotypes. Inclusion of a timeline for development of postural instability/falls to the definition of the MDS-PSP-P criteria could likely address this issue. Another possible explanation of the overlap between PSP-RS and PSP-P could be that in contrast to the PSP-P criteria originally defined by Williams, the IPMDS-PSP-P criteria lump atypical parkinsonism (including those with axial predominance and without levodopa response) along with more typical parkinsonism. However, we do not know this because we could not compute levodopa response. Future standardized prospective natural history studies are required to investigate the exact combination of features that could differentiate these two phenotypes. It is important to differentiate PSP-RS and PSP-P because they have different disease progression and possibly different pathogenesis [4, 19–21]. Our observations suggest that while the IPMDS-PSP-P diagnostic criteria are valuable for separating PSP from other disorders, and the proposed MAX rules might reduce multiple phenotype allocations due to phenotype conversion along the disease course, these criteria need to be revised in order to better distinguish between PSP-RS and PSP-P phenotypes. Moreover complexity of the criteria plus the newly added extinction rules makes their routine application difficult and subject to inter-rater bias. of evaluation Prospective criteria these will allow to determine the rate of progression of patients with PSP-RS and PSP-P and their relationship to underlying neuropathology, which in turn, would allow to determine if further refinement and simplification of its application is needed. The major limitation of our study is the lack of pathological confirmation. However, we used the NINDS-SPSP probable and Williams criteria which are both highly specific for a pathologically confirmed diagnosis of PSP-R and PSP-P, respectively. In addition, currently there is no pathologic criteria to differentiate between various PSP phenotypes and it is mainly based on clinical findings. Lack of information on levodopa-response in our database is another limitation of this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- It is critical to differentiate between PSP phenotypes for prognostication and patient inclusion in trials
- Using the IPMDS-PSP criteria a significant proportion of PSP patients could be classified both as PSP-RS and PSP-P
- This will limit the usefulness of these criteria to differentiate between the more benign and progressive phenotypes
- Use of multiple allocation extinction rules partially improves diagnostic accuracy of the IPMDS-PSP criteria
- Further refinement of the IPMDS-PSP criteria is needed

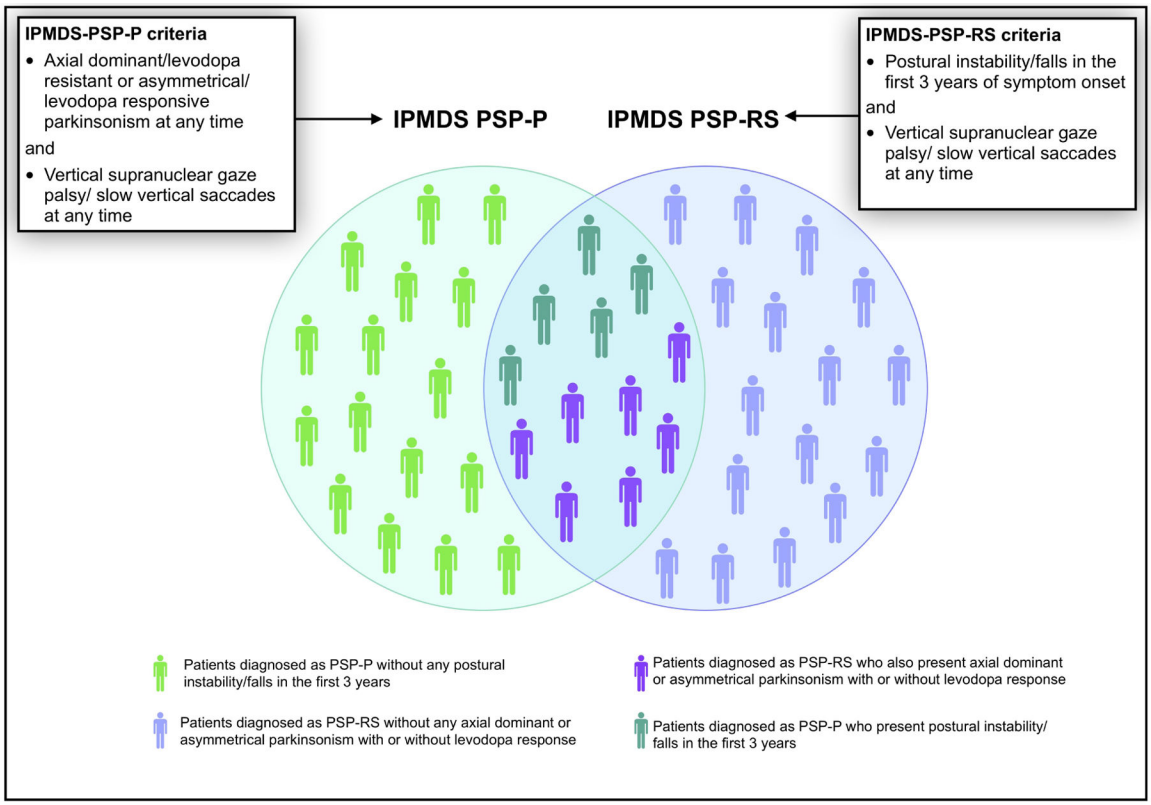

Figure 1:
Classification of patients using IPMDS PSP-RS and PSP-P criteria.

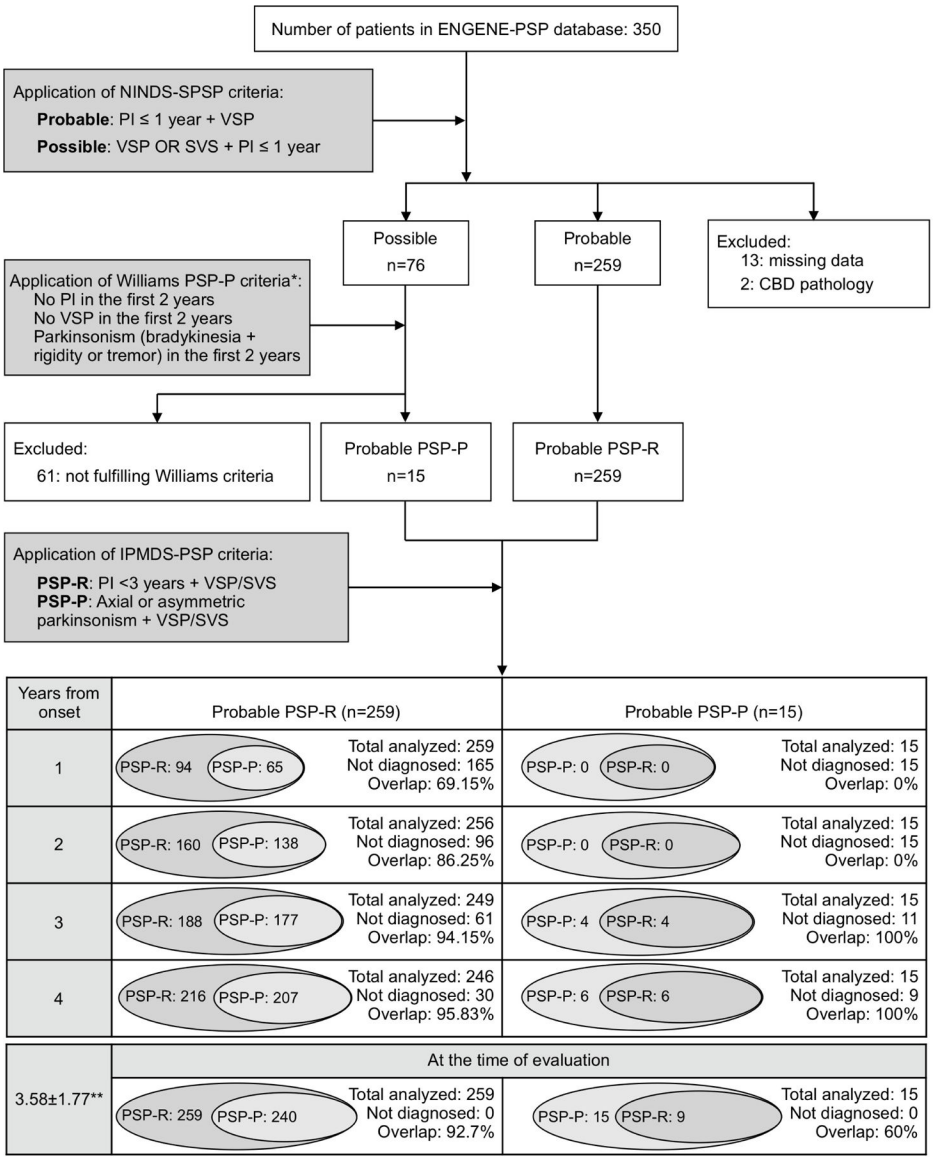

Figure 2:

Application of IPMDS-PSP-RS and -PSP-P criteria to the ENGENE-PSP sample at various times from symptom onset.

PI: postural instability; VSP: vertical supranuclear gaze palsy; SVS: slow vertical saccades.

* The ENGENE database lacks data about levodopa response.

** Mean disease duration ± SD

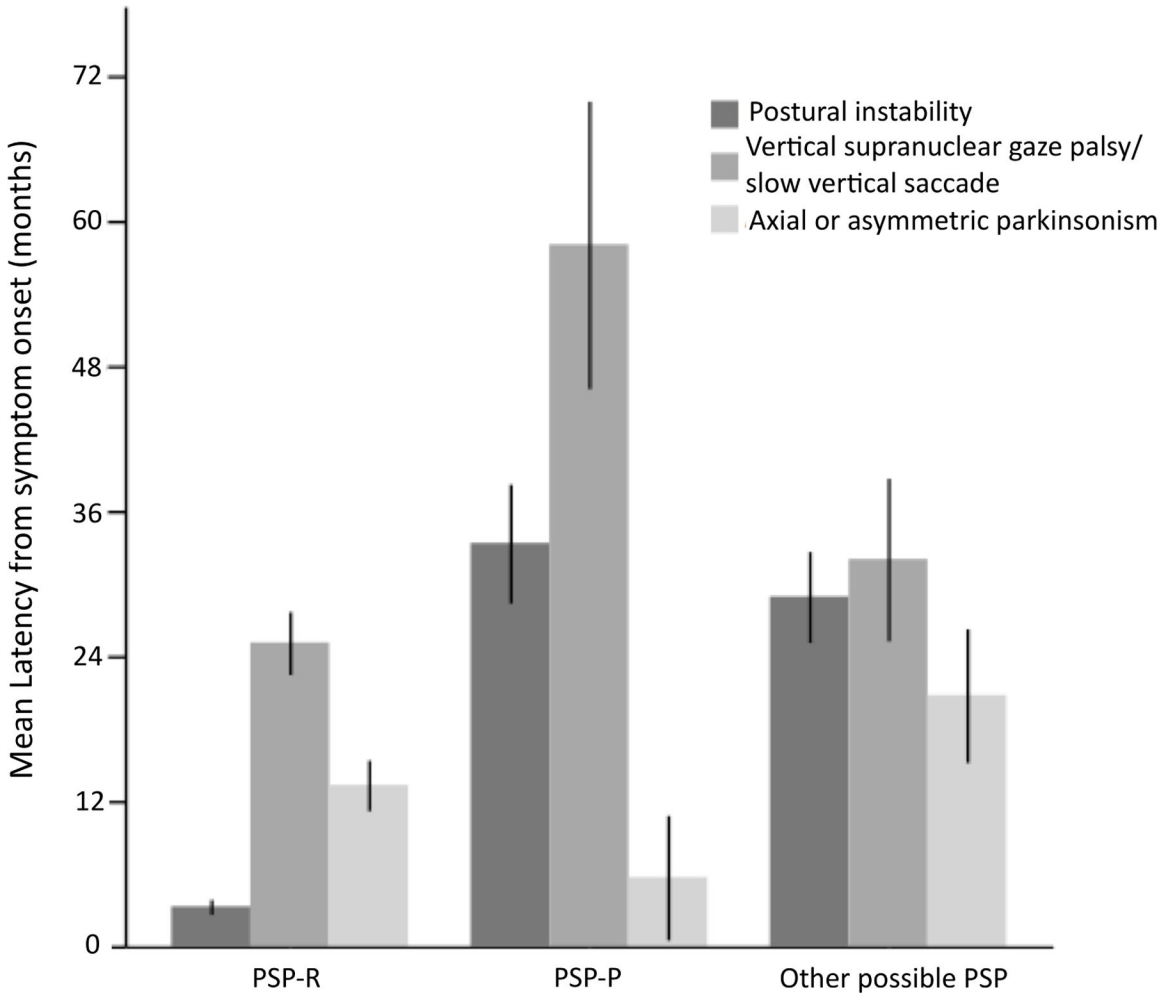

Figure 3:
Latency to development of PSP related clinical features in the ENGENE-PSP sample. Error bars: 95% confidence interval