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Can we accurately diagnose different clinical variants of Progressive Supranuclear Palsy using IPMDS-PSP criteria?

Progressive Supranuclear Palsy (PSP) is the second most common degenerative parkinsonian syndrome after idiopathic Parkinson's disease. PSP is a clinically heterogeneous disorder with several clinical variants. The two most common clinical variants are the Richardson (PSP-RS) and parkinsonian (PSP-P) variants. The original diagnostic criteria for PSP [the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP)] was introduced in 1996. These criteria are very specific for diagnosing Richardson variant of PSP but, because all other clinical variants were recognized after the introduction of these criteria, NINDS-SPSP is not sensitive enough for diagnosing variants other than PSP-RS. In 2017, the International Parkinson Disease and Movement Disorder Society PSP study group (IPMDS-PSP) criteria were published as a new diagnostic tool to allow diagnosis of all different PSP variants. These new criteria use four core clinical features including: Ocular motor dysfunction (O), Postural instability (P), Akinesia (A), and Cognitive dysfunction (C) for diagnosis of different variants of PSP. Each of these core features are defined at three levels of relevance for diagnosis (O1, O2, O3, P1, etc.). Various combinations of these twelve clinical definitions make a basis for the diagnosis of each clinical variant in two levels of certainty (Probable and Possible). For example, an individual who presents signs consistent with O1 or O2 plus P1 or P2 will be diagnosed as Probable PSP-RS.

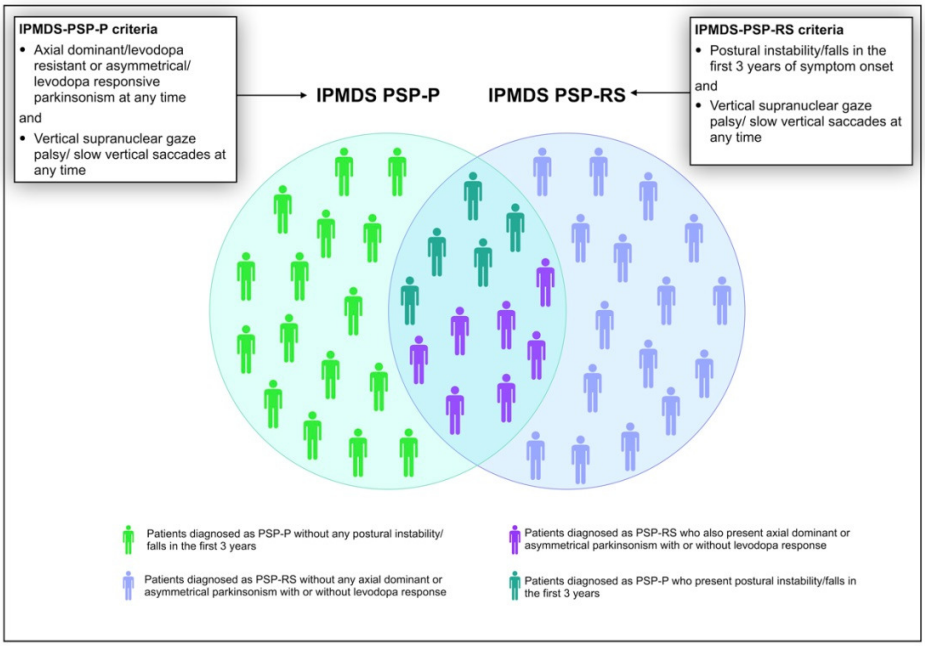

Fig. 1. Overlap of PSP-P and PSP-RS diagnoses using IPMDS-PSP criteria.

We applied IPMDS-PSP criteria to 259 patients who were diagnosed as probable PSP-RS based on NINDS-SPSP criteria and 15 patients who had PSP-P according to the Williams criteria. Williams criteria were the first diagnostic criteria of the PSP-P phenotype, proposed by Williams and colleagues who first described this

variant. The above patients were selected from 274 PSP patients previously enrolled in the Environmental Genetic PSP (ENGENE-PSP) case control study. Two hundred forty out of the 259 patients with PSP-RS also fulfilled the IPMDS-PSP criteria for PSP-P showing an overlap of 92.7% between these two phenotypes. Meanwhile, 9 out of 15 PSP-P patients fulfilled the IPMDS-PSP criteria for PSP-RS, again showing a high degree of overlap of 60%. After applying four multiple allocation extinction (MAX) rules which was introduced by the MDS task force to decrease the rate of double or multiple diagnosis, the overall overlap decreased only mildly from 92.6% to 78%. Still, most PSP-RS patients fulfilled criteria for both IPMDS-PSP-RS and IPMDS-PSP-P (Fig. 1).

In the IPMDS-PSP criteria, presence of atypical parkinsonian signs (predominantly neck and trunk parkinsonism not responsive to levodopa) at any time in the disease course can fulfill the "A" category of symptoms which are needed for diagnosis of IPMDS-PSP-P. This may lead to many PSP-RS patients simultaneously fulfilling the criteria for IPMDS-PSP-P since this is a common feature in both variants. On the other hand, in IPMDS-PSP criteria, there is no time limit for "O" group of symptoms and there is a limit of three years for presence of "P" symptoms. At the same time, based on Williams criteria, PSP-P patients do not have recurrent falls ("P" group of IPMDS-PSP criteria) or eye movements abnormalities ("O" group of IPMDS-PSP criteria) during the first two years of disease course. This mismatch can be a reason for a considerable percent of PSP-P cases fulfilling the IPMDS-PSP-RS criteria. As we show in Figure 2, the degree of overlap goes up as the time from first symptom increases.

Years from onset	Probable PSP-R (n=259)	Probable PSP-P (n=15)
1	PSP-R: 94 PSP-P: 65 — Total analyzed: 259, Not diagnosed: 165, Overlap: 69.15%	PSP-P: 0 PSP-R: 0 — Total analyzed: 15, Not diagnosed: 15, Overlap: 0%
2	PSP-R: 160 PSP-P: 138 — Total analyzed: 256, Not diagnosed: 96, Overlap: 86.25%	PSP-P: 0 PSP-R: 0 — Total analyzed: 15, Not diagnosed: 15, Overlap: 0%
3	PSP-R: 188 PSP-P: 177 — Total analyzed: 249, Not diagnosed: 61, Overlap: 94.15%	PSP-P: 4 PSP-R: 4 — Total analyzed: 15, Not diagnosed: 11, Overlap: 100%
4	PSP-R: 216 PSP-P: 207 — Total analyzed: 246, Not diagnosed: 30, Overlap: 95.83%	PSP-P: 6 PSP-R: 6 — Total analyzed: 15, Not diagnosed: 9, Overlap: 100%
3.58±1.77**	At the time of evaluation	
	PSP-R: 259 PSP-P: 240 — Total analyzed: 259, Not diagnosed: 0, Overlap: 92.7%	PSP-P: 15 PSP-R: 9 — Total analyzed: 15, Not diagnosed: 0, Overlap: 60%

Fig. 2. The percent of overlap at different time points after application of the IPMDS-PSP criteria to the patients who were diagnosed as probable PSP-RS [based on the NINDS-SPSP criteria (259 cases)] and as probable PSP-P [according to the Williams criteria (15 patients)].

In conclusion, it seems that the IPMDS-PSP criteria are not accurate enough in separating the parkinsonian variant from the Richardson variant. Defining new time limits for "A", "O", and "P" core features of the

criteria and removing atypical parkinsonian features from "A" core feature of the criteria may help increase power of the criteria in distinguishing these two main clinical variants of PSP.

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Publication

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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Parkinsonism Relat Disord. 2019 Dec