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A Modified Progressive Supranuclear Palsy Rating Scale for Virtual Assessments

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Abstract

Background: The reliability of the Progressive Supranuclear Palsy Rating Scale (PSPRS) using teleneurology has not been assessed.

Objectives: To test whether removing items inadequately assessed by video would impact measurement of PSP severity and progression.

Methods: We performed secondary analyses of two data sets: the phase 2/3 trial of Davunetide in PSP and a large single-center cohort. We examined two modifications of the PSPRS: (1) removing neck rigidity, limb rigidity, and postural stability (25 items; mPSPRS-25) and (2) also removing three ocular motor items and limb dystonia (21 items; mPSPRS-21). Proportional agreement relative to the possible total scores was measured using the intraclass correlation coefficient, compared to the original PSPRS baseline values and change over 6 and 12 months. We examined the ability of both scales to predict survival in the single-center cohort using proportional hazards models.

Results: The mPSPRS-25 showed excellent agreement (0.99; $P < 0.001$) with the original PSPRS at baseline, 0.98 ($P < 0.001$) agreement in measuring change over 6 months, and 0.98 ($P < 0.001$) over 12 months. The mPSPRS-21 showed agreement of 0.94 ($P < 0.001$) with the original PSPRS at baseline, 0.92 ($P < 0.001$) at 6 months, and 0.95 ($P < 0.001$) at 12 months. Baseline and 6-month change in both modified scales were highly predictive of survival in the single-center cohort.

Conclusions: Modified versions of the PSPRS which can be administered remotely show excellent agreement with the original scale and predict survival in PSP. The mPSPRS-21 should facilitate clinical care and research in PSP via teleneurology.

Keywords

PSP; PSPRS; teleneurology; telemedicine; virtual

The COVID-19 pandemic has dramatically accelerated the adoption of teleneurology through web-based virtual visits.[1,2] The use of virtual visits has gained growing popularity with both providers and patients as it can significantly reduce the burden of transportation for patients with disabilities and for those who live far from clinical centers.[3] The use of web-based virtual visits was also adopted on an emergency basis by many clinical trials, as per Food and Drug Administration (FDA) guidance[4]; however, many of the outcome measures which are used in clinical trials have not been validated for use virtually. A modified version of the motor (Part III) portion of the Unified Parkinson's Disease Rating Scale (UPDRS), minus rigidity and retropulsion (which requires an examiner to perform a pull test), was shown to have high reliability and agreement with the full UPDRS[5] in a secondary analysis of the Comparison of the Agonist pramipexole vs. Levodopa on Motor complications in Parkinson's Disease (CALM-PD[6]). Subsequently, a virtual version of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to confirm the diagnosis of Parkinson's disease (PD) in a study that enrolled participants entirely remotely.[7] Recently, in response to the COVID-19 pandemic, Goetz et al. emphasized that the MDS-UPDRS Part III can only accommodate the consistent loss of three values on any given visit and still allow the total calibrated score to be valid[8]; however, Dr. Goetz and colleagues were referring to imputation of missing data to compare it to the original MDS-UPDRS. Similar to PD, a modified video version of the Unified Huntington's Disease Rating Scale (UHDRS), again removing rigidity and balance assessments, showed high reliability compared to in-person assessments in Huntington's disease.[9]

The Progressive Supranuclear Palsy Rating Scale (PSPRS),[10] the most established outcome measure for PSP, has not been validated for remote capture of disease severity and progression. We wished to test whether a modified version of the PSPRS, compatible with teleneurology assessments, would still be valid in measuring PSP severity and disease progression. These modified scales were selected based on their feasibility for remote video assessments, while still retaining the majority of the original PSPRS questions, as opposed to the recently proposed simplified 14-item modified PSPRS of Grotsch et al.[11] or the 10-item FDA-proposed scale.

Similar to the UPDRS, the PSPRS also includes rigidity and postural stability assessed using a pull test that cannot be appropriately performed by web-based video conference. Unlike Part III of the UPDRS, the PSPRS contains seven historical items which can easily be assessed by video. We therefore created a modified PSPRS rating scale, removing the three items which are impossible to rate through video (neck and limb rigidity and postural stability) and leaving 25 items.

While there has been no prior evaluation of the reliability of remote assessments of PSP, Hall et al. used a videotaped version of the motor items of the PSPRS (excluding rigidity which was not scored) to examine the reliability and construct validity of the PSPRS in 44 patients with PSP, rated by several independent reviewers.[12] They found good inter-rater reliability (intraclass correlation coefficient of 0.64) for the total PSPRS score using the videotaped version of the examination. The limb dystonia and dysphagia items were found to be less reliable; however, dysphagia was not formally assessed in many of the subjects.

In addition, the authors' personal experience with performing the 28-item PSRPS virtually during the pandemic also raised concerns about the reliability of the ocular motor examination. We therefore examined a 21-item version of the PSPRS which excluded four additional items (ocular motor and limb dystonia) that, for the above reasons, we felt would not perform well via teleneurology. We compared each of these modified versions of the PSPRS to the original 28-item scale.

Methods

All secondary analyses were performed in accordance with the ethical standards of Mass General Brigham Institutional Review Board in accordance with the Declaration of Helsinki. Written informed consent was obtained at the time of data collection and reconsent was not required for this secondary analysis. The Davunetide in Patients with PSP clinical trial (AL-108-231) was a multicenter, randomized, double-blind, placebo-controlled trial testing AL-108, an eight amino acid peptide to promote microtubule stability, in 313 participants with PSP-Richardson's syndrome.[13] Participants were randomized 1:1 to Davunetide or placebo and followed for 1 year. The co-primary end-points, the PSPRS, and the Schwab and England Activities of Daily Living Scale (SEADL), were performed every 3 months in the clinic. No differences were seen between the treatment arms and therefore all participants with complete data (n = 312) were included in this secondary analysis. Time since symptom onset was not collected; however, the study did identify participants with disease onset greater than 5 years prior to enrollment. The Davunetide dataset was available through a data use agreement with the University of California at San Francisco.

The single-center cohort was collected by one of the authors (L.I.G.) during routine clinical visits. The dataset can be made available by request to this author. Time since symptom onset was collected in all participants. A total of 489 patients with PSP were included, for whom survival data were available for 413 patients. As the visits were not uniformly spaced over time, the data were analyzed using a range of dates corresponding approximately with the Davunetide visits: month 3 included visits which occurred on days 70–112, month 6: days 152–212, and month 12: days 320–410.

We created two modified versions of the PSPRS. First, we created a 25-item PSPRS (mPSPRS-25) by removing limb rigidity, neck rigidity, and postural stability (questions 18, 24, and 27) as these are impossible to rate virtually, and in alignment with the prior published work on the UPDRS and UHDRS. Next, we abridged that version to create a 21-item PSPRS (mPSPRS-21), removing the additional questions 14–16 (ocular motor) and 19 (limb dystonia) due to the authors' concern that these may be less reliable when performed virtually.

Statistical Analysis

The maximum possible score for the original 28-item PSPRS is 100 points, correlating with more advanced disease. For the mPSPRS-25, the maximum is 88 points and for the mPSPRS-21, 72 points. For this analysis, we converted each participant's score to a proportion of the maximum possible score for each respective scale. Agreement was calculated using the intraclass correlation coefficient (ICC, two-way random effects) to

compare modified scales to the original PSPRS on bias, scale, and correlation. In all tables, test statistics are presented along with 95% confidence intervals. For ICC measures of agreement, 0.81 to 1.00 is considered to be “nearly perfect” agreement.[14] Criterion validity was assessed using survival in the single-center cohort. As there were very few deaths in the 1-year Davunetide study, an alternative survival endpoint was defined as a Schwab and England Activity of Daily Living (SEADL) score <20% (severe invalid). The SEADL was not available for the single-center cohort. Survival analysis was performed with Cox proportional hazards models with the PSPRS variable as the predictor of interest and adjusted for age, sex, and years since symptom onset. Hazard ratios with 95% confidence intervals are presented along with *P* values. Finally, power calculations were performed to calculate 80% power based on a two-sided significance level of 5% to detect a 20% to 50% slowing in disease progression over 6 months using the mean and standard deviations of the rates of change in the PSPRS over 6 months in 312 participants from the Davunetide trial.[15] All analyses used an alpha of 0.05 and were performed in R 4.1.[16] Sample size calculations were performed using the Massachusetts General Hospital Mallinckrodt General Clinical Research Center online calculator.[17]

Results

The baseline demographics of all participants in the two datasets are shown in Table 1. Data from 312 participants from the Davunetide trial and 489 participants in the single-center cohort were included as having complete PSPRS data. The mean age of the Davunetide participants was lower and fewer participants had symptom onset more than 5 years prior to their visit, as would be expected for participants in a clinical trial, compared to a real-world clinic. The mean PSPRS scores of the two groups were similar despite the differences in participant selection.

The baseline comparisons of the proportional modified scales compared to the total PSPRS are shown as scatter plots in Figure 1. The overall agreement of the mPSPRS-25 was 0.99 (95% CI 0.96–0.99, $P < 0.001$) and agreement using the shorter mPSPRS-21 was 0.94 (95% CI 0.77–0.98, $P < 0.001$). Change over the first 6 months also had a high level of agreement: for the mPSPRS-25, agreement was 0.98 (95% CI 0.97–0.98, $P < 0.001$), compared to 0.92 (95% CI 0.90–0.93, <0.001) for the mPSPRS-21 (also shown graphically in Fig. 1).

Next, we examined whether the baseline values and change over 6 months of both modified virtual PSPRS scales could predict survival. We used the single-center cohort for this analysis due to the very low number of deaths in the Davunetide study. Table 2 shows Cox proportional hazard ratios for survival using the baseline total PSPRS and both modified PSPRS variables. A total of 483 people with PSP were included in this analysis. Both the mPSPRS-25 and mPSPRS-21 were highly predictive of survival. The greater hazard ratios in the modified scales were due to the compressed nature of those scales. Male sex was associated with decreased survival in all three models. The reduced hazard ratios for participants who had a longer time since symptom onset was likely due to slower disease progression leading to a delay in diagnosis. Table 3 shows the Cox proportional hazards models including both the baseline and the 6-month change from baseline, adjusted for age, sex, and time since symptom onset (in years). Only 70 PSP patients had visits at 6 months

and could be included in this analysis; however, change at 6 months was still a significant predictor of survival even adjusting for baseline PSPRS score. Notably, sex and time since symptom onset were no longer significant after including the rate of change, suggesting that this variable captured the variance of these other predictors.

The hazard ratio for each higher score on the baseline Progressive Supranuclear Palsy Rating Scale (PSPRS) was 1.037 (95% CI 1.028–1.045, $P < 0.001$) for the original PSPRS, 1.042 (95% CI 1.033–1.052, $P < 0.001$) for the mPSPRS-25, and 1.047 (95% CI 1.035–1.059, $P < 0.001$) for the mPSPRS-21. In other words, participants with higher scores at baseline experienced a shorter disease survival. The increased hazard ratios observed with the modified scales were due to the compressed nature of these scales.

The hazard ratio for change over time (over 6 months) was 1.270 (95% CI 1.011–1.596, $P = 0.04$) in the original PSPRS, 1.286 (95% CI 1.006–1.645, $P = 0.045$) in the mPSPRS-25, and 1.418 (95% CI 1.064–1.891, $P = 0.017$) in the mPSPRS-21. In other words, participants whose PSPRS scores changed by 1 point faster than the average change over 6 months were 30% to 40% more likely to die than the average participant, after adjusting for their baseline scores.

We performed a similar time-to-event analysis in the Davunetide trial data using a SEADL score of 20% or below (time to being a severe invalid). Some 171 participants in the trial began the study with a score >20% and were included in this analysis. Table S1 shows the Cox proportional hazards models including both the baseline and the 6-month change from baseline, adjusted for age, sex, and duration of disease (greater than 5 years). Both the baseline and 6-month change in the 25-item and 21-item PSPRS scores predicted time to severe disability.

Finally, we examined whether use of the modified scales would alter the sample size required to detect a 20% to 50% reduction in the rate of disease progression over 6 months. As shown in Table 4, the original PSPRS would require 135 participants per group to detect a 30% difference between intervention and placebo arms at 6 months, compared to 142 participants using the mPSPRS-25, and 158 participants using the mPSPRS-21. This number is without adjusting for study dropouts. To detect a 50% difference, the original PSPRS would require 50 participants per group, compared to 52 participants using the mPSPRS-25, and 58 participants using the mPSPRS-21.

Discussion

Our analysis suggests that modified 25- and 21-item versions of the PSPRS that can be performed remotely, even without the ocular motor items, are reliable in predicting survival and disease progression in PSP and strongly agree with the full PSPRS. While Goetz et al. cautioned against removing items from the MDS-UPDRS, our modified versions do not require imputation of missing data because these items have been consistently removed from the mPSPRS-21 and mPSPRS-25. Using the modified scales does not appear to significantly increase the number of participants required to enroll in clinical trials. Indeed the total number of participants required using these modified scales was almost identical

to the original PSPRS and similar to prior power calculations for PSP.[15] These data support the use of the mPSPRS-25 or m-PSPRS-21 as modified scales that can be performed remotely through video visits without compromising the integrity of clinical trial data. Given the reliability, simplicity and ease of administering the shorter mPSPRS-21, we favor the adoption of this 21-item scale.

The primary caveat to our conclusion is that we did not perform a validation study comparing ratings performed in person to ratings performed virtually. While Hall et al.'s article examined videotaped versions of the motor items of the PSPRS,[12] virtual video-based assessments are subject to variability in internet quality, devices used, and technological knowledge of patients, caregivers, and their providers. These concerns prompted the removal of all ocular motor questions from the mPSPRS-21 because, in our clinical experience, these items are more sensitive to video and internet connection quality. As anecdotal evidence, the authors of this study have performed the PSPRS virtually as part of their clinical care and feel confident in the feasibility of these modified rating scales for teleneurology. One important difference from the in-person PSPRS is the enhanced role of the caregiver (beyond the usual Part I History questions). When performing the virtual mPSRPS-21, a caregiver may be required to adjust the camera, provide water to assess swallowing, and ensure patient safety during assessment of gait items.

Use of virtual modified PSPRS will facilitate in-home assessments for both clinical care and clinical trials research, may reduce travel burden, increase access to specialty care, and reduce exposure risks during a pandemic. This may also reduce the cost of clinical trials and improve trial retention, particularly in the case of PSP which rapidly progresses to severe disability. Additionally, it may allow more advanced PSP patients with poor mobility to better access clinical care and potentially clinical studies. Virtual assessments have been used successfully in Parkinson's clinical trials and we believe that they may have useful applications in PSP. The next step in validating their use would be to compare virtual to in-person administration of these modified PSP rating scales.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the University of California at San Francisco and from co-author LIG. Restrictions apply to the availability of these data, which were used under a data sharing agreement for this study.

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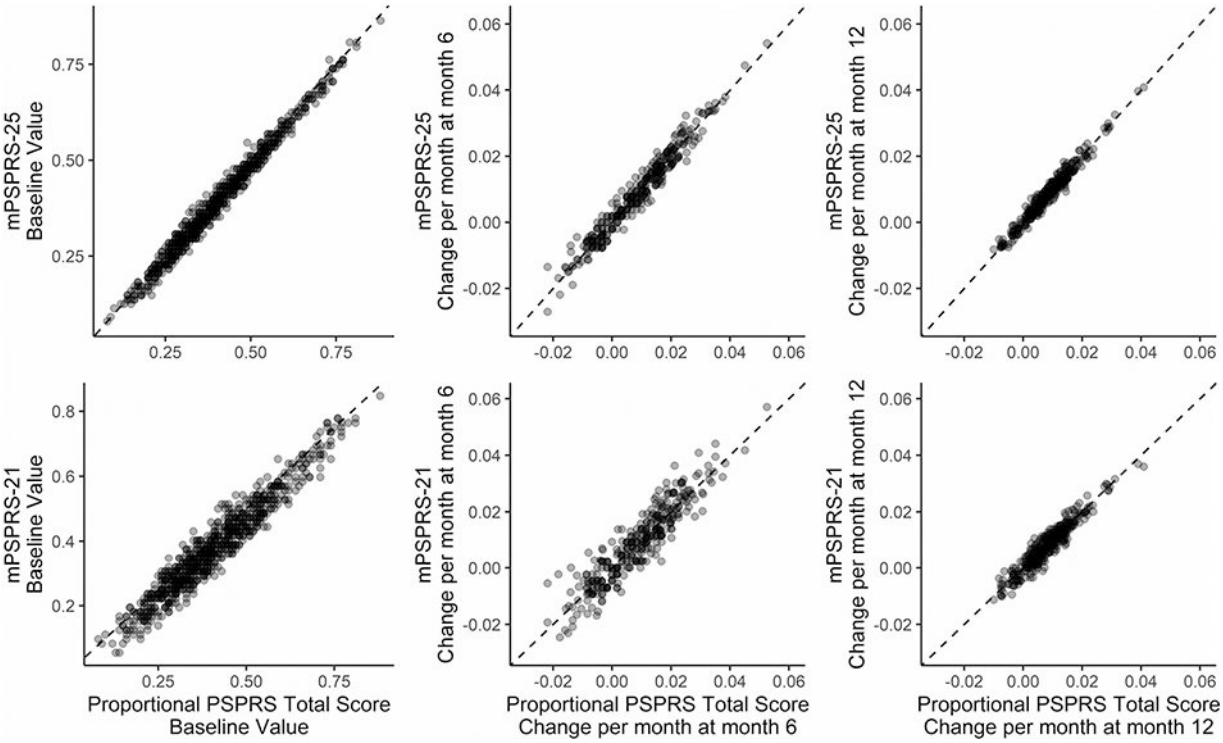

FIG. 1.

Comparison between the modified and shortened version of the Progressive Supranuclear Palsy Rating Scale (PSPRS) and the total PSPRS at baseline and over time. Scatter plots comparing the 25-item and 21-item versions of the PSPRS to the total PSPRS score at baseline, change over 6 months, and 12 months. All scores are shown as proportions (0–1) of the total possible score (100 points for the 28-item PSPRS, 88 points for the mPSPRS-25, and 72 points for the mPSPRS-21). The black line demonstrates the line of agreement.

TABLE 1

Baseline demographics of all participants

Demographic	Davunetide trial		Single-center cohort		
	N	Percent (n) or mean (SD)	N	Percent (n) or mean (SD)	*P* value
Age, years	312	67.7 (6.6)	489	71.5 (7.4)	<0.001
Male	312	52.9% (165)	489	50.7% (248)	0.563
Disease onset >5 years prior to enrollment	296	9.5% (28)	489	24.3% (119)	<0.001
Race					
Asian	312	2.6% (8)	NA		
Black	312	1.6% (5)	NA		
Not reported	312	6.7% (21)	NA		
Other	312	1.3% (4)	NA		
White	312	87.8% (274)	NA		
Baseline scores		Mean (SD)		Mean (SD)	
PSPRS total score (28 questions)	312	39.9 (11.1)	489	41.0 (15.2)	0.215
mPSPRS-25	312	34.2 (9.7)	489	34.9 (13.3)	0.414
mPSPRS-21	312	25.8 (8.1)	489	27.9 (11.1)	0.002

Abbreviations: SD, standard deviation; NA, not available; PSPRS, Progressive Supranuclear Palsy Rating Scale; mPSPRS-25, 25-item modified PSPRS; mPSPRS-21, 21-item modified PSPRS.

TABLE 2

Cox proportional hazard models for survival, adjusted for time since symptom onset, sex, and age at baseline (single-center cohort).

	HR (95% CI)	*P* values
Parameter Total PSPRS (*n* = 483)		
Baseline PSPRS	1.037 (1.028, 1.045)	<0.001
Years since symptom onset	0.937 (0.895, 0.981)	0.006
Male gender	1.420 (1.143, 1.765)	0.002
Age at baseline	1.013 (0.998, 1.028)	0.101
mPSPRS-25 (*n* = 483)		
Baseline mPSPRS-25	1.042 (1.033, 1.052)	<0.001
Years since symptom onset	0.938 (0.897, 0.982)	0.006
Male gender	1.422 (1.145, 1.767)	0.001
Age at baseline	1.014 (0.999, 1.029)	0.074
mPSPRS-21 (n = 483)		
Baseline mPSPRS-21	1.047 (1.035, 1.059)	<0.001
Years since symptom onset	0.945 (0.903, 0.989)	0.015
Male gender	1.400 (1.128, 1.737)	0.002
Age at baseline	1.014 (0.999, 1.030)	0.95

Abbreviations: HR, hazard ratio; CI, confidence interval; PSPRS, Progressive Supranuclear Palsy Rating Scale; mPSPRS-25, 25-item modified PSPRS; mPSPRS-21, 21-item modified PSPRS.

TABLE 3

Cox proportional hazard models for survival using change in the Progressive Supranuclear Palsy Rating Scale (PSPRS) over 6 months, adjusted for baseline score, time since symptom onset, sex, and age at baseline (single-center cohort).

	HR (95% CI)	*P* values
Parameter Total PSPRS (*n* = 70)		
Change in PSPRS over 6 months	1.270 (1.011, 1.596)	0.04
Baseline PSPRS	1.064 (1.031, 1.099)	<0.001
Years since symptom onset	0.913 (0.798, 1.044)	0.18
Male gender	1.340 (0.740, 2.426)	0.33
Age at baseline	0.989 (0.946, 1.034)	0.62
mPSPRS-25 (*n* = 70)		
Change in mPSPRS-25 over 6 months	1.286 (1.006, 1.645)	0.045
Baseline mPSPRS-25	1.072 (1.035, 1.111)	<0.001
Years since symptom onset	0.921 (0.807, 1.050)	0.22
Male gender	1.298 (0.719, 2.341)	0.39
Age at baseline	0.990 (0.947, 1.035)	0.66
mPSPRS-21 (*n* = 70)		
Change in mPSPRS-21 over 6 months	1.418 (1.064, 1.891)	0.017
Baseline mPSPRS-21	1.087 (1.042, 1.134)	<0.001
Years since symptom onset	0.935 (0.822, 1.063)	0.30
Male gender	1.314 (0.729, 2.367)	0.36
Age at baseline	0.999 (0.955, 1.045)	0.95

Abbreviations: HR, hazard ratio; CI, confidence interval; PSPRS, Progressive Supranuclear Palsy Rating Scale; mPSPRS-25, 25-item modified PSPRS; mPSPRS-21, 21-item modified PSPRS.

TABLE 4

Sample size calculations from estimated 6-month changes for a 20% to 50% difference between control and intervention groups using the Progressive Supranuclear Palsy Rating Scale (PSPRS) modified for virtual assessments

	Control arm mean (SD)	Intervention arm mean (SD)	Sample size per arm (n)
Parameter Total PSPRS			
20%	5.20 (0.16)	4.16 (0.16)	302
30%	5.20 (0.16)	3.64 (0.16)	135
40%	5.20 (0.16)	3.12 (0.16)	77
50%	5.20 (0.16)	2.60 (0.16)	50
mPSPRS-25			
20%	4.50 (0.14)	3.60 (0.14)	318
30%	4.50 (0.14)	3.15 (0.14)	142
40%	4.50 (0.14)	2.70 (0.14)	80
50%	4.50 (0.14)	2.25 (0.14)	52
mPSPRS-21			
20%	3.54 (0.12)	2.84 (0.12)	353
30%	3.54 (0.12)	2.48 (0.12)	158
40%	3.54 (0.12)	2.13 (0.12)	89
50%	3.54 (0.12)	1.77 (0.12)	58

Abbreviations: PSPRS, Progressive Supranuclear Palsy Rating Scale; SD, standard deviation; mPSPRS-25, 25-item modified PSPRS; mPSPRS-21, 21-item modified PSPRS.