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A clinical rating scale for progressive supranuclear palsy

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We devised a Progressive Supranuclear Palsy (PSP) Rating Scale comprising 28 items in six categories: daily activities (by history), behaviour, bulbar, ocular motor, limb motor and gait/midline. Scores range from 0 to 100, each item graded 0–2 (six items) or 0–4 (22 items). Inter-rater reliability is good, with intra-class correlation coefficient for the overall scale of 0.86 (95% CI 0.65–0.98). A single examiner applied the PSPRS at every visit for 162 patients. Mean rate of progression was 11.3 (±11.0) points per year. Neither onset age nor gender correlated well with rate of progression. Median actuarially corrected survival was 7.3 years. The PSPRS score was a good independent predictor of subsequent survival ($P < 0.0001$). For example, for patients with scores from 40 to 49, 3-year survival was 41.9% (95% CI 31.0–56.6) but 4-year survival was only 17.9% (95% CI 10.2–31.5). For those patients, likelihood or retaining some gait function was 51.7% (40.0–66.9) at 1 year but only 6.5% (1.8–23.5) at 3 years. We conclude that the PSPRS is a practical measure that is sensitive to disease progression and could be useful as a dependent variable in observational or interventional trials and as an indicator of prognosis in clinical practice.

Keywords: progressive supranuclear palsy; validity; longitudinal; Steele–Richardson–Olszewski; rating scale

Abbreviations: ADL = activities of daily living; IRR = inter-rater reliability; LD/CD = levodopa/carbidopa; MMSE = Mini-Mental Status Examination; PSP = progressive supranuclear palsy; PSP-P = progressive supranuclear palsy-parkinsonism; PSPRS=Progressive Supranuclear Palsy Rating Scale; RS = Richardson's syndrome; UPDRS = Unified Parkinson's Disability Rating Scale

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Introduction

Despite the anatomic focality suggested by its name, progressive supranuclear palsy (PSP) affects many areas of the brain and spinal cord to produce a complex clinical syndrome (Golbe, 2005). The first manifestation in a majority of cases is postural instability with falls (Maher and Lees, 1986), but most patients eventually exhibit frontal behavioural dysfunction, predominantly axial rigidity, bradykinesia, a wide range of ocular motor defects, facial spasticity, insomnia, spastic/ataxic dysarthria, pharyngeal dysphagia, urinary incontinence and constipation (Steele *et al*., 1964). Less common features include psychosis, depression, apraxia, dystonia and tremor.

Although the progression of certain aspects of PSP has been studied before (Table 1), these studies were cross-sectional or retrospective, included small numbers of subjects, did not assess a wide range of the contributing deficits, or did not lend themselves to routine application in the clinic. The Unified Parkinson's Disease Rating Scale (UPDRS) is useful in assessing PSP (Cubo *et al*., 2000), but it does not consider (or emphasize) some features that are important in PSP and minor in Parkinson's disease. A scale assessing quality of life in PSP has recently been described (Schrag *et al*., 2006).

Median actuarially corrected survival in PSP is only 6 to 10 years (Maher and Lees, 1986; Golbe *et al*., 1988; Testa *et al*., 2001). Pharmacological treatment for PSP is highly unsatisfactory, providing only modest, transient, symptomatic benefit for the gait and speech disorder (Nieforth and Golbe, 1993). Therefore, clinical assessment of PSP over time could serve as an accurate measure of its natural history modified only by palliative care. Until disease-modifying therapy becomes available, such data would have important prognostic value for clinicians, patients and families. These data could also serve as a source of historical controls for use in futility studies (Schwid and Cutter, 2006) and as an aid in power calculations for other interventional studies.

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Table 1 Previous studies of the natural history of progressive supranuclear palsy

Authors	Year	*N* with PSP	% confirmed by investigator exam	% confirmed by autopsy	Patient source	Progression data source	Outcome measure
Maher *et al*.	1986	52	>27%	Not stated	Tertiary referral	Record review	Clinical events
Golbe *et al*.	1988	50	100%	8%	Tertiary referral and search of community health care facilities	Standardized patient/ family interview	Major disability milestones
Litvan *et al*.	1996*c*	24	0	100%	Collections of seven academic neuro-pathologists	Record review	Clinical events
Nath *et al*.	2003	187	33%	Not stated	Community	Record review	Clinical events
Goetz *et al*.	2003	55	100%	34%	Tertiary referral	Prospective exams	Major disability milestones
Macia *et al*.	2003	47	Not stated	6%	Tertiary referral	Prospective exams	Clinical events, MRI features
Diroma *et al*.	2003	25	100%	Not stated	Tertiary referral	Record review	Clinical events
Papapetropoulos *et al*.	2005	22	0	100%	Brain donors	Record review	Clinical events
Golbe (present report)		162	100%	4%	Tertiary referral	Prospective exams	Quantitative rating scale

This report describes a clinical rating scale for PSP that takes account of most of the features contributing to disability. Longitudinal data from its use from 1994 through 2005 are presented as a validation for the scale, as a measure of the progressivity of PSP, and as a clinical prognostic guide.

Material and methods

Scale development

In 1992, author LIG, with advice from many colleagues, constructed the initial version of the PSP Rating Scale (PSPRS) and began to use it routinely in evaluating patients referred to the tertiary Movement Disorders Center at Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA. The PSPRS underwent minor revisions over the following 4 years and reached its present form in November 1996 (Golbe *et al*., 1997). It was possible to map data from the versions used since 1994 into the current PSPRS form. The working database for this report therefore includes entries from as early as April 1994. Data were censored on December 31, 2005.

Goals and limitations of the PSPRS

The PSPRS is not designed as a diagnostic tool, but as a quantitative measure of disability. It therefore attempts to include all of the important areas of clinical impairment in PSP, including relatively minor items such as tremor and dystonia. However, at the potential risk of statistical redundancy, it emphasizes those areas that contribute most to overall disability such as balance loss, behavioural change and ocular motor deficits.

The PSPRS was designed for use by neurologists as a routine part of patient care. Its administration requires ~10 min and the only apparatus needed is a cup of water to test swallowing. Some of the examination items, especially those of eye movements, require training not usually available to non-neurologists. Furthermore, many of the scoring criteria that present a choice between 'mild' and 'severe' require a familiarity with the range of possible affection that can only be acquired through clinical experience.

For research focusing on one area such as behaviour or eye movements, more detailed, time-consuming evaluative methods will be necessary. Nevertheless, the PSPRS is intended to serve as a convenient global measure of the course of PSP that could be used in the exploratory phases of interventional studies or as a measure of the disorder's progressivity in an individual or in groups.

Subjects and scale administration

Author L.I.G. personally administered the PSPRS to every patient referred to him at the Movement Disorders Center, Robert Wood Johnson Medical School, who satisfied a published, validated set of the diagnostic criteria (Golbe *et al*., 1988). This set of criteria has a positive predictive value of 92% and specificity of 98% (Litvan *et al*., 1996*a*, *b*). He also administered it to patients who did not quite satisfy the criteria, expecting that the syndrome in such patients may evolve in the future. Data from patients who did not subsequently evolve to satisfy PSP criteria are not analysed here.

Patients were evaluated at typical intervals of 3–4 months, but a few patients who returned to their referring neurologist revisited the authors' centre only some years later or not at all. There was no attempt to evaluate patients off medication. Interviews and examinations were performed without reference to previous evaluations. When patients disagreed with their accompanying family member or caregiver on a subjective rating, the examiner encouraged discussion among the parties and chose an

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answer based on his clinical judgement. Only integer values were assigned.

The month and year of symptom onset were determined from the history given at the initial visit by the patient and family. Early reported symptoms were not considered as the disease onset if they antedated all other symptoms by years and did not evolve into clear parts of the PSP clinical picture. In most cases, the first symptom was an unheralded fall, a clearly datable onset. When the onset was more subtle and could only be dated to a span of time, the middle month of that span was entered as the onset month. The date of each visit was entered only as a month and year. Year of birth and month/year of death were obtained from medical records and family reports.

Scale content

The PSPRS comprises 28 items in six areas. The available total score ranges from 0 (normal) to 100. Six items are rated on a 3-point scale (0–2) and 22 are rated on a 5-point scale (0–4). The History/Daily Activities area includes seven items with a total maximum of 24 points, the mentation area four items with 16 points, the bulbar area two items with 8 points, the ocular motor area four items with 16 points, the limb motor area six items with 16 points and the gait area five items with 20 points.

Table 2 shows the items and the definitions of each score level along with details regarding administration of the test.

Statistics gathered for the present report

In addition to tabulating demographic and descriptive data, we calculated survival, both raw and actuarially corrected. We calculated the risk of reaching certain PSPRS score milestones within given time intervals given a starting score. We calculated the rate of disease progression as PSPRS points per year, relating this to PSP onset age, gender and a variable we term 'gait ratio'.

We created the 'gait ratio' variable as an attempt to confirm in our subject group the recent observation (Williams *et al*., 2005) that patients with autopsy-confirmed PSP tend to fall into two clinical syndromes. One of these, termed 'Richardson's syndrome' (RS), conforms to the classic picture of PSP described by Steele, Richardson and Olszewski (Steele *et al*., 1964). The other, termed 'PSP-parkinsonism' (PSP-P), has clinical features suggestive of Parkinson's disease, at least early in its course. The PSPRS was designed long before the observations of Williams *et al*. and is not well-suited to sorting patients into the two syndromes. The lone feature separating RD from PSP-P that the PSPRS may identify is the disproportionate postural instability and gait difficulty in RD. Therefore, we created the 'gait ratio' variable as the ratio of the sum of the scores on the six PSPRS gait-related items to the sum of the other 22 items. We calculated the frequencies of the values of this variable, seeking a bimodal distribution that, if observed in our material, would tend to support the conclusions of Williams *et al*.

We measured inter-rater reliability (IRR) by videotaping author L.I.G. applying the PSPRS to five patients at various stages of PSP. Three movement disorders specialists who had not previously used the PSPRS received very brief orientation from author L.I.G. before viewing the tape alone and recording their scores without consultation with one another. We made no attempt to include rigidity in the IRR assessment, as it cannot be assessed visually. We calculated intra-class correlations according to the method of Shrout and Fleiss (1979).

Intervals were calculated as months but in many cases are presented here after conversion to years for convenient application to the clinical setting. Hence many of the median figures shown are not integers. Statistical analysis was performed using SAS software.

Results

Demographics and visit statistics

The subjects (Table 3) comprise 162 patients with PSP, 72 (44.4%) males and 90 (55.6%) females. Ninety-eight (60.5%) were known to have died as of the censoring date, December 31, 2005, and 40 (24.7%) were known to be alive at that date. Twenty-four (14.8%) were lost to follow-up. Subjects made an average of 4.1 (SD 3.6, median 3) visits spanning a mean of 1.2 (SD 1.4, median 0.8) years. This figure is low because 45 patients (28%) made only a single visit. Forty patients (25%) made more than five visits, all at 3–4 month intervals. Mean time from PSP onset to the first visit was 3.8 years (SD 2.8, median 3.4).

Inter-rater reliability

IRR results appear in Table 4. Reliability overall was excellent (IRR = 0.86, 95% CI 0.65–0.98) and ranged from 0.57 for the mentation subscore to 0.94 for the gait/midline subscore. The low IRR for the mentation items may be explained by the fact that the videotapes did not include a detailed health history interview or the informal interaction that would occur during actual clinical care. The sole opportunity for the IRR raters to judge the patients' mentation was during the questions relating to daily activities.

PSP onset and survival

Mean age at PSP symptom onset was 67.2 (SD 7.3, median 67.0, range 49–86). Mean survival for the 98 patients who died during the observation period was 6.8 years (SD 3.06, median 6.5, range 1.5–20.2) (Table 5).

The actuarially corrected median survival from onset was 7.3 years. This calculation included all 162 patients: those deceased, those known to be alive on December 31, 2005 and those lost to follow-up. For the last group, we censored the observation on the date of the last visit. The Kaplan–Meier curve showing actuarially corrected survival from onset appears as Fig. 1.

Five of the 98 patients who died underwent autopsy, all performed by Dennis W. Dickson, MD, director of the Eloise H. Troxel Memorial Brain Bank of the Society for PSP, at Mayo Clinic, Jacksonville, FL. All five were confirmed to have PSP.

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Table 2 The progressive supranuclear palsy rating scale with comments and instructions

Item name and score definitions	Comments, instructions
I. *History*	
1. Withdrawal 0 None 1 Follows conversation in a group, may respond spontaneously, but rarely if ever initiates exchanges 2 Rarely or never follows conversation in a group	• Relative to baseline personality • Consider lack of conversation due to dementia or bradyphrenia as 'withdrawal'
2. Irritability 0 No increase in irritability 1 Increased, but not interfering with family interactions 2 Interfering with family interactions	• Relative to baseline personality • Ask if patient shouts or loses temper easily
3. Dysphagia for solids 0 Normal; no difficulty with full range of food textures 1 Tough foods must be cut up into small pieces 2 Requires soft solid diet 3 Requires pureed or liquid diet 4 Tube feeding required for some or all feeding	• Ignore difficulty related to overloading mouth • If certain foods like bread crusts or leafy vegetables must be avoided, but meats OK, score '2'
4. Using knife and fork, buttoning clothes, washing hands and face 0 Normal 1 Somewhat slow but no help required 2 Extremely slow; or occasional help needed 3 Considerable help needed but can do some things alone 4 Requires total assistance	• Rate the worst of the 3 • If difficulty is related to downgaze, score as if it were purely motor
5. Falls 0 None in the past year 1 <1 per month; gait may otherwise be normal 2 1–4 per month 3 5–30 per month 4 >30 per month (or chairbound)	• Average frequency if patient attempted to walk unaided • Assume no access to walking aids • Ignore near-falls
6. Urinary incontinence 0 None or a few drops less than daily 1 A few drops staining clothes daily 2 Large amounts, but only when asleep; no pad required during day 3 Occasional large amounts in daytime; pad required 4 Consistent, requiring diaper or catheter awake and asleep	• If daytime pad used as precaution but no recent wetting, score '3'
7. Sleep difficulty 0 Neither 1° nor 2° insomnia 1 Either 1° or 2° insomnia; averages ⩾5 h sleep nightly 2 Both 1° and 2° insomnia; averages ⩾5 h sleep nightly 3 Either 1° or 2° insomnia; averages <5 h sleep nightly 4 Both 1° and 2° insomnia; averages <5 h sleep nightly	• 1° insomnia is difficulty falling asleep • 2° is difficulty remaining asleep • Ignore trips to bathroom after which pt. returns to sleep easily
II. *Mentation* Items 8–11 use this scale: 0 Clearly absent 1 Equivocal or minimal 2 Clearly present, but does not interfere with activities of daily living (ADL) 3 Interferes mildly with ADL 4 Interferes markedly with ADL	• Estimate the degree to which each deficit would interfere with performance of daily cognitive tasks
8. Disorientation	• Use MMSE items 1–10 or history to estimate interference in ADLs
9. Bradyphrenia	• If delayed responses prompt the caregiver to answer for the patient or limit your ability to interview patient, rate at least a '3'
10. Emotional incontinence	• If there is a history of inappropriate laughing or crying but none at the time of the examination, rate a '1' or '2', depending on its frequency

(*continued*)

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Table 2 Continued

Item name and score definitions	Comments, instructions
11. Grasping/imitatative/utilizing behaviour	• If none is displayed spontaneously (e.g. grabbing your coat or arm, or the wheelchair arm), ask patient to rest hands on thighs, palms up. Hold your hands 5–10 cm above his and say nothing. • If he grabs them, rate a 3 • If he only imitates your actions during the exam, rate a 2
III. *Bulbar*	
12. Dysarthria 0 None 1 Minimal; all or nearly all words easily comprehensible 2 Definite, moderate; most words comprehensible 3 Severe; may be fluent but most words incomprehensible 4 Mute; or a few poorly comprehensible words	• Ignore palilalia and dysphonia • 'Comprehensible' means to examiner, not caregiver • If generally silent but can be coaxed to speak a few words, rate a '4' no matter how clear those words may be
13. Dysphagia 0 None 1 Single sips, or fluid pools in mouth or pharynx, but no choking/coughing 2 Occasionally coughs to clear fluid; no frank aspiration 3 Frequently coughs to clear fluid; may aspirate slightly; may expectorate frequently rather than swallow secretions 4 Requires artificial measures (oral suctioning, tracheostomy or feeding gastrostomy) to avoid aspiration	• Give 30–50 cc of water in a cup, if safe • Do not give water if secretions are audible with breathing, if there is a history of frequent aspiration or if caregiver is apprehensive • 1 cough rates '2', multiple coughs '3'
IV. *Ocular motor* Items 14–16 use this scale: 0 Saccades not slow or hypometric; 86–100% of normal excursion 1 Saccades slow or hypometric; 86–100% of normal excursion 2 51–85% of normal excursion 3 16–50% of normal excursion 4 15% of normal excursion or worse	• Use a stationary target and a verbal command • If improves with repetition, use the initial (i.e. worst) result • May hold lids to observe downward saccades • Normal range of gaze is 50° in each direction • Ignore square-wave jerks
14. Voluntary upward command movement	
15. Voluntary downward command movement	
16. Voluntary left and right command movement	
17. Eyelid dysfunction 0 None 1 Blink rate decreased (<15/min) but no other abnormality 2 Mild inhibition of opening or closing or mild blepharospasm; no visual disability 3 Moderate lid-opening inhibition or blepharospasm causing partial visual disability 4 Functional blindness or near-blindness because of involuntary eyelid closure	• Recruitment of frontalis muscle rates at least '2'. • Isolated difficulty closing lids on command rates at least '2'
V. *Limb motor*	
18. Limb rigidity 0 Absent 1 Slight or detectable only on activation 2 Definitely abnormal, but full range of motion possible 3 Only partial range of motion possible 4 Little or no passive motion possible	• Rate the worst of the four limbs • Count flexion contracture in advanced pts as dystonia, not rigidity
19. Limb dystonia 0 Absent 1 Subtle or present only when activated by other movement 2 Obvious but not continuous 3 Continuous but not disabling 4 Continuous and disabling	• Rate the worst of the four limbs • When subtle, may be evident only with activating tasks such as sustention task or tapping by other limbs

(*continued*)

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Table 2 Continued

Item name and score definitions	Comments, instructions
20. Finger tapping 0 Normal (>14 taps/5 s with maximal amplitude) 1 Impaired (6–14 taps/5 s or moderate loss of amplitude 2 Barely able to perform (0–5 taps/5 s or severe loss of amplitude)	• If asymmetric, rate worse side
21. Toe tapping 0 Normal (>14 taps/5 s with maximal amplitude) 1 Impaired (6–14 taps/5 s or moderate loss of amplitude 2 Barely able to perform (0–5 taps/5 s or severe loss of amplitude)	• If asymmetric, rate worse side
22. Apraxia of hand movement 0 Absent 1 Present, not impairing most functions 2 Impairing most functions	• Test for ideomotor apraxia • Two tasks with each hand (e.g. salute, throw ball, hitchhike, V-for-victory)
23. Tremor in any part 0 Absent 1 Present, not impairing most functions 2 Impairing most functions	• Upper extremities extended • Finger-to-nose with each hand
VI. *Gait and midline*	
24. Neck rigidity or dystonia 0 Absent 1 Slight or detectable only when activated by other movement 2 Definitely abnormal, but full range of motion possible 3 Only partial range of motion possible 4 Little or no passive motion possible	• Rate the resistance to passive antero-posterior rotation • Ignore spontaneous posture (kyphosis, dystonic rotation, retrocollis)
25. Arising from chair 0 Normal 1 Slow but arises on first attempt 2 Requires more than one attempt, but arises without using hands 3 Requires use of hands 4 Unable to arise without assistance	• If patient must use hands, do not allow hands to contact arms of the chair • If cane needed, to arise, rate '4' • If patient can arise unassisted but falls forward ('rocket sign'), rate '4'
26. Gait 0 Normal 1 Slightly wide-based or irregular or slight pulsion on turns 2 Must walk slowly or occasionally use walls or helper to avoid falling, especially on turns 3 Must use assistance all or almost all the time 4 Unable to walk, even with walker; may be able to transfer	• If patient staggers across room, using wall or furniture when possible, rate '3'
27. Postural stability 0 Normal (shifts neither foot or one foot) 1 Must shift each foot at least once but recovers unaided 2 Shifts feet and must be caught by examiner 3 Unable to shift feet; must be caught, but does not require assistance to stand still 4 Tends to fall without a pull; requires assistance to stand still	• If pt. can remain standing unassisted, pull backward by shoulders and be ready to catch him/her • Pull should be hard enough to make normal adult take one step back to retain balance
28. Sitting down 0 Normal 1 Slightly stiff or awkward 2 Easily positions self before chair, but descent into chair is uncontrolled 3 Has difficulty finding chair behind him/her and descent is uncontrolled 4 Unable to test because of severe postural instability	• May use hands to touch seat of chair, but not arms or back of chair

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Table 3 Subject numbers

	N (%)
Total number	162
Gender	
Male	72 (44.4%)
Female	90 (55.6%)
Status as of December 31, 2005	
Deceased	98 (60.5%)
Living	40 (24.7%)
Lost to follow-up	24 (14.8%)

Table 4 Inter-rater reliability data

Measure	ICC	95% CI
History	0.91	0.73, 0.99
Mentation	0.57	0.15, 0.93
Bulbar	0.79	0.52, 0.97
Ocular motor	0.80	0.52, 0.97
Limb motor	0.61	0.29, 0.94
Midline	0.94	0.83, 0.99
Total	0.86	0.65, 0.98

Intra-class correlations and corresponding 95% confidence intervals for each subscale and for the total PSPRS score.

Table 5 Description of subjects and visits

	Mean (SD)	Median	Range
Age at PSP onset	67.2 (7.3)	67	49–68
Age at first visit	71.2 (7.40)	72	50–91
Number of visits	4.1 (3.61)	3	1–23
Years from first to last visit	1.2 (1.40)	0.8	0–8.0
Total PSPRS score at first visit	42.0 (15.63)	40	8–88
Years from PSP onset to first visit	3.8 (2.43)	3.4	0.3–14.9
Years from PSP onset to death	6.81 (3.06)	6.5	1.5–20.2

Time spans are shown to a decimal place because they were calculated as integer numbers of months and converted to years.

Rate of progression

Rate of progression of the PSPRS was calculated using a mixed linear model applied to longitudinal data from the 65 subjects who made at least three visits that spanned at least 12 months. The mean rate of progression was 9.7 points per year (SD 5.4, median 9.0). Between the first visit and the next visit that occurred at least 6 months later, the progression was 8.7 points per year (SD 10.9, median 7.5). Patients who made only one visit or who made two or more over a period of fewer than 6 months were not considered in that calculation.

For the 74 patients who made at least three visits in which there were at least 6 months between the second visit and any subsequent visit, the mean rate from the second to the last visit was 12.4 points per year (SD 11.6, median 12.0). Thus, patients' rate of progression in PSPRS score tended to be slower during the earliest portion of their period of attendance at our clinic.

We considered the possibility that the 45 (28%) patients who made only a single visit may have been undergoing more rapid progression than the others. In fact the disease progression for the one-visit group, as measured by PSPRS/years since onset, was 17.8 points/year (SD 11.0) and for the other patients was 13.7 points/year (SD 8.9), $P = 0.0166$. This effect did not influence our progressivity data, which was generated only from patients with more than one visit, using the difference between PSPRS scores.

Males and females did not differ with respect to their rates of disease progression ($F = 0.55$, df = 1,99, $P = 0.4585$, ANOVA), but in our multivariate analysis described later, gender did have a modestly significant effect on survival in one of our eight models (Table 6). Our overall observation is that any relationship of gender to PSP progressivity is too weak to influence clinical care or trial design.

Survival was shorter for older-onset patients, as expected. Table 7 presents the actuarially corrected median, 25th and 75th percentile survival durations in years for each onset-age group.

Rate of PSPRS progression did not significantly correlate with age at PSP onset (Pearson $r = 0.71$, $P = 0.087$). However, when we categorized the patients into three groups according to age of onset (<65, 65–74 and >74), there was a highly significant difference among them with respect to PSPRS score 2 years after PSP onset, with the older-onset patients progressing more rapidly during that interval (Fig. 2). However, the groups converged to the same point over the following 6 years (likelihood ratio statistic: $\chi^2 = 49.6$, df = 6, $P < 0.0001$).

PSP subtypes

We found no evidence for a bimodal distribution of either PSPRS progression rates or gait ratio (data not shown).

PSPRS as a prognostic tool

We assessed the ability of the PSPRS to predict subsequent survival by creating several multivariate models using Cox proportional hazards models with survival duration as the dependent variable. These results are shown in Table 6. The tests use either the total group ($n = 162$) or the subset with at least two visits spanning at least 6 months ($n = 101$). We examined nine independent variables. The first six are not time-varying: gender, onset age, PSPRS score at Visit 1, gait ratio (see above for definition) at Visit 1 and initial progressivity (over the first set of two visits that were at least 6 months apart). The other three are time-varying: PSPRS score, progression rate of PSPRS score over the previous 6 months and progression rate of PSPRS score since Visit 1.

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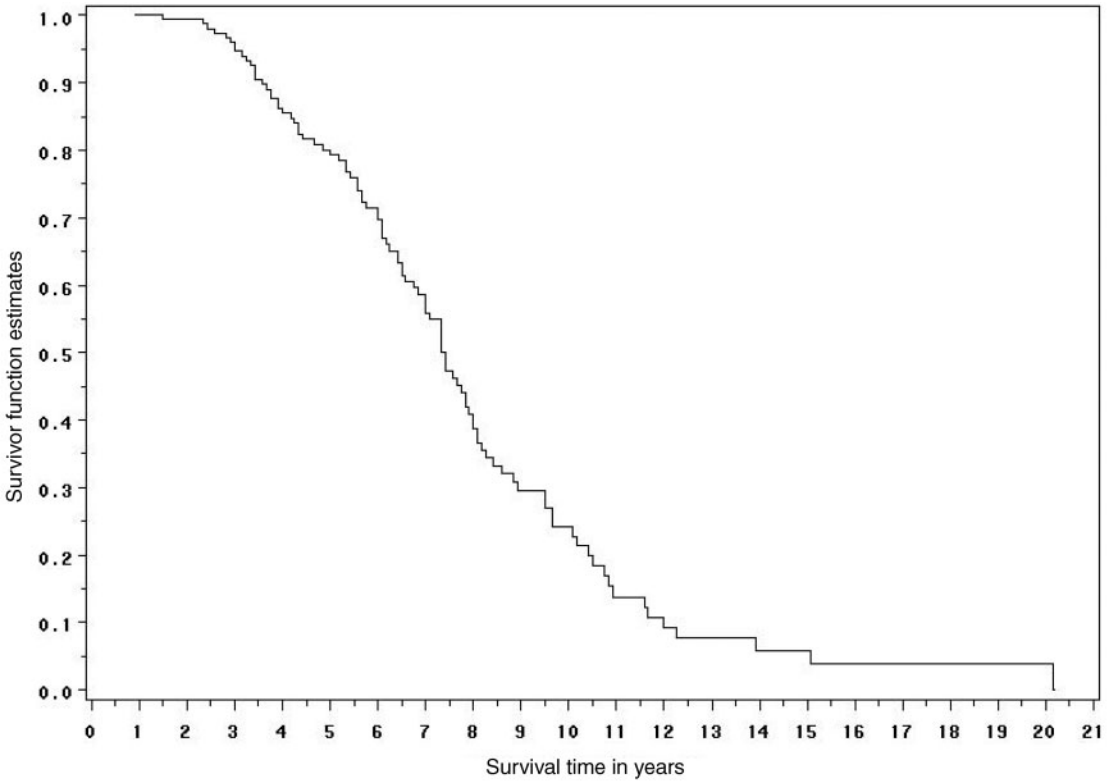

Fig. 1 Survivor function estimates by year since symptom onset in patients with PSP.

Table 6 Multivariate analysis of predictors of survival

Variable	Entered as single variables in separate models		Multivariate models					
N	101	162	162	162	101	162	101	101
Gender	1.174 (0.2785)	1.502 (0.2204)	1.665 (0.1970)	1.683 (0.1946)	1.041 (0.3076)	4.804 (**0.0284**)	1.409 (0.2352)	1.506 (0.2197)
Onset age	2.099 (0.1474)	7.113 (**0.0077**)	7.393 (**0.0065**)	7.469 (**0.0063**)	1.329 (0.2490)	3.422 (0.0643)	0.0927 (0.7608)	0.0108 (0.9172)
PSP score at Visit 1	1.484 (0.2232)	0.006 (0.9383)	0.018 (0.8931)					
Gait ratio at Visit 1	0.018 (0.894)	0.091 (0.7636)		0.017 (0.8949)				
PSP score at Visit 2	0.805 (0.3695)							
Initial progressivity	1.724 (0.1892)				0.953 (0.3290)			
PSP score (time-varying)						17.051 (**<0.0001**)		
Progression of PSP score over the previous 6 months (time-varying)							3.904 (**0.0482**)	
Progression of PSP score over total time in care (time-varying)								3.235 (0.0721)

The dependent variable throughout is time from PSP onset to death, last observation or December 31, 2005 using a proportional hazards model. Shown are Wald chi-square statistics and *P*-values for testing effects of baseline variables on survival time. Tests use either the total group ($n = 162$) or the subset with at least two visits spanning at least 6 months ($n = 101$). Significant *P*-values are in bold. See text for detailed explanation.

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Entered singly as univariates, onset age predicted survival, but only in the total group ($P = 0.0077$) and not in the subset of 101 subjects with multiple visits. None of the other univariables gave a significant result. However, some of our multivariate models gave significant results. The time-varying PSPRS score was the most robust ($P < 0.0001$). This is, of course, the result expected and helps validate the PSPRS as a measure of disease burden. Gender, onset age and PSPRS progression over the previous 6 months each gave lesser but still statistically significant results.

Table 7 Percentiles of survival distribution (actuarially corrected) for subjects with onset of disease at <65 years of age, between 65 and 75 and >75 years of age

Onset age (years)	25%	50% (median)	75%
<65	9.78[a]	7.69	6.26
65–75	10.11	7.40	5.31
>75	7.01	5.62	3.65

Shown are years from onset to death. [a]Only 25% of the subjects in the <65 age group survived 9.78 years after onset.

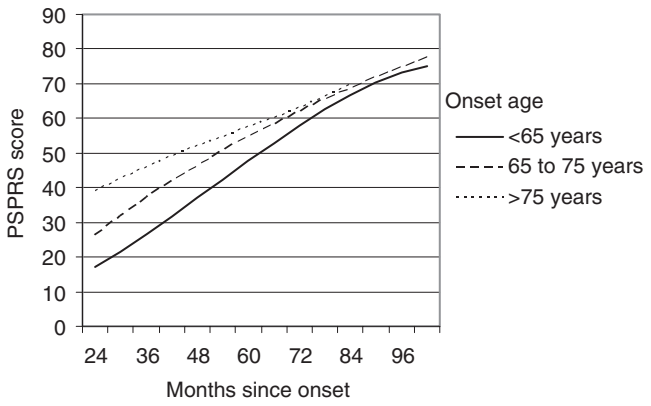

Fig. 2 Progression of PSPRS score in subjects of 3 onset-age groups. The scores diverged by the 2-year point and reconverged at the end stage of illness.

Table 8 shows the likelihood of reaching certain PSPRS score milestones over certain time periods given a starting score. Table 9 shows the percentages of patients who retain at least some gait ability (i.e. item 26 < 4) given a starting score. Table 10 shows the likelihood of death after reaching certain PSPRS score milestones. Particularly notable is the sharp drop in survival during the second year after reaching a PSPRS score in the 60s. These data provide clinicians with quantitative answers to patients' and families' questions regarding prognosis. They also serve as historical control data that may be useful in the design of interventional studies, including futility studies.

Discussion

This is the first attempt to devise a comprehensive clinical disability rating scale for PSP. The scale was applied prospectively over a period of a decade to obtain natural history data on a large cohort. Eight previous studies (Maher and Lees, 1986; Golbe *et al.*, 1988; Litvan *et al.*, 1996*c*; Diroma *et al.*, 2003; Goetz *et al.*, 2003; Macia *et al.*, 2003; Nath *et al.*, 2003; Papapetropoulos *et al.*, 2005) have assessed aspects of the natural history of PSP (Table 1). None has used a quantitative scale as the dependent variable. All of the studies are useful guides to the order and timing of occurrence of discrete disability milestones, but only one (Nath *et al.*, 2003) was as large as the present study and in only two (Goetz *et al.*, 2003; Macia *et al.*, 2003) were the evaluations prospective.

Our experience with the PSPRS suggests that it can be useful as a convenient global measure of clinical disability and its progression in patients with PSP. These observations can assist in formulating a prognosis for individual patients in terms of time to subsequent score milestones and death. They can also serve as a guide to design of interventional studies (Siderowf and Quinn, 2003).

We have found that the PSPRS score increases at a mean rate of approximately 1 point per month. This figure was slightly slower in the first 6 months of attendance at our centre (0.73 points per month) than subsequently (1.03 points per month). Patients with older onset had a higher mean PSPRS score at a point 2 years after onset,

Table 8 Percentage of patients starting with total PSPRS scores in the ranges specified (left column) who reached any of five subsequent PSPRS score milestones within 1 year, with 95% confidence intervals

PSPRS score	Percent reaching these scores within 1 year (95% CI)				
	30	40	50	60	70
20–29	73.0 (52.1–84.8)	24.5 (3.8–40.8)	[a]	[a]	[a]
30–39	–	65.9 (50.4–76.6)	17.1 (5.4–27.4)	2.7 (0.0–7.7)	[a]
40–49	–	–	69.4 (54.7–79.3)	24.7 (10.6–36.5)	2.6 (0.0–7.5)
50–59	–	–	–	68.0 (50.3–79.4)	22.2 (6.4–35.3)
60–69	–	–	–	–	39.1 (15.3–56.2)

[a]Not estimable, as no patients reached this target within 1 year.

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Table 9 Percentages (95% CI) of patients who retain at least some gait ability (i.e. PSPRS Item 26 < 4) at the given intervals

PSPRS score	Percentage still walking independently (95% CI)					
	6 months	12 months	24 months	36 months	48 months	60 months
20–29	93.1 (88.0–98.5)	76.4 (67.5–86.5)	48.8 (37.2–64.1)	22.7 (12.3–41.9)	13.6 (5.7–32.7)	9.1 (3.0–27.1)
30–39	92.3 (86.7–98.4)	72.4 (62.7–83.7)	41.8 (30.1–58.1)	15.9 (7.9–32.0)	[a]	[a]
40–49	90.2 (83.1–97.9)	51.7 (40.0–66.9)	21.7 (11.8–40.0)	6.5 (1.8–23.5)	[a]	[a]
50–59	64.7 (51.5–81.4)	39.1 (26.2–58.5)	11.1 (4.0–30.4)	[a]	[a]	[a]
>60	42.9 (25.4–72.2)	21.4 (9.9–46.3)	[a]	[a]	[a]	[a]

[a]No patients reached these timepoints with gait score <4.

Table 10 Survival estimates and 95% CI for patients with total PSPRS scores in the specified ranges

PSPRS Score	Subsequent survival percentage and 95% CI						
	6 months	12 months	24 months	36 months	48 months	60 months	72 months
20–29	97.1	94.2	83.8	64.1	40.1	18.0	9.0
	91.9–100	86.8–100	71.8–97.7	48.7–84.5	25.4–63.1	8.1–40.2	2.5–32.0
30–39	96.4	92.6	76.4	57.7	25.3	12.6	6.3
	91.7–100	86.0–99.7	65.7–88.8	45.3–73.6	15.1–42.3	5.6–28.5	1.8–22.6
40–49	91.5	86.9	58.9	41.9	17.9	13.0	5.2
	85.2–98.1	79.4–95.2	47.9–72.5	31.0–56.6	10.2–31.5	6.5–26.2	1.5–18.5
50–59	88.0	76.9	54.9	26.0	16.2	[a]	[a]
	80.6–96.0	67.4–87.6	44.0–68.6	16.8–40.2	8.7–30.2		
60–69	83.7	70.2	28.5	11.4	7.6[b]	7.6[b]	3.8
	74.1–94.4	58.5–84.3	17.8–45.4	4.7–27.6	2.5–22.8	2.5–22.8	0.9–16.6
>70	69.2	47.4	16.4[c]	16.4[c]	[a]	[a]	[a]
	54.9–87.2	33.0–68.0	7.5–30.4	7.5–30.4			

Survival times are calculated as the interval between initial entry into the specified score interval and death. [a]Not estimable because there were no survivors. [b,c]These are the same because there were no observed deaths between the two successive timepoints.

but tended to progress more slowly subsequently, with all three onset-age groups converging to the same average PSPRS score by the sixth year after onset. We infer that this non-linear behaviour reflects a complex interaction of the ageing process with the disease process. In addition, older patients may perform less well on many of the exam items for other reasons such as joint disease or cerebrovascular disease that exist at the onset of PSP. Later in the course of PSP, these effects may be swamped by the effect of PSP, causing the various onset-age groups' scores to converge. Regardless of the validity of this explanatory hypothesis, designers of clinical trials may wish to stratify their analysis by onset age.

Perhaps of greatest utility for clinicians is Table 10, which fills the need for subsequent survival information based not just on data for PSP in general, but customized to the individual patient's status as measured by the PSPRS.

Validity measures

The various types of validity are discussed in turn.

Internal validity

Observer skill. It is possible that author L.I.G. became more consistent in the assignment of PSPRS scores over the 12 years of the study. The likelihood of this causing heterogeneity in the validity of the present data is minimized by the fact that he used earlier versions of the scale for 2 years before starting to gather the presently reported data using the latest version of the Scale. However, the validity of observations by novice examiners may be less than that attained by author L.I.G. over most of the course of this study.

Test experience. After the first one or two administrations of the PSPRS, patients, assisted by caregivers, may have practised their performances on some of the tests in advance of subsequent visits. Items such as those for orientation, speech, swallowing and attaining the standing or sitting positions may improve with practice or with specific attention. This could, in theory, reduce the apparent rate of disability progression.

Selection bias. Although the patients in this study were consecutively ascertained, they were highly referred. As such they may be unrepresentative of the community with respect to health care insurance coverage, educational attainment and availability of family support for care and transportation. A majority of patients in this study were referred by neurologists familiar with the first author's interest in PSP or because they or their family found him in an Internet search on PSP.

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Perhaps more important, most patients in the final, most immobile, stages of PSP were unable to travel to our tertiary centre for care. For those patients, PSPRS results for those stages were not obtained. Although 152 (23%) of the 671 patient visits in this study reached a PSPRS score in the highly disabled range over 60, this severe-disability subset is smaller than that of patients with mild or moderate levels of disability. The observations of the PSPRS as assessed here, therefore, may not apply as robustly to patients in the far-advanced stages.

Selection bias may also weight the present database against the early stages of PSP, before the signs or symptoms reached a stage that prompted medical attention or that caused the primary care physician or community neurologist to suspect PSP. Only 22 (13.6%) of the 162 patients in this study produced a PSPRS score in the very early, mild range of <30 at the initial visit.

Hawthorne effect. There is the possibility that patients' subjective responses and even their results on physical examination were favourably influenced by the fact that the physician administering the PSPRS was responsible for their neurological care. Patients may consciously or unconsciously wish to convey the impression that the physician's treatment or advice is effective, an effect that would depress PSPRS scores, at least in the short term. In fact this may be responsible for the relatively slow mean rate of progression from the first to second visits.

Regression toward the mean. For some patients, the decision to seek evaluation at our centre may have been precipitated by a transient worsening of their symptoms. Others, who were being followed by the author for some months, received their first PSPRS administration only after their parkinsonian illness, not previously suspected of being PSP, evolved in that direction. For either scenario, the initial PSPRS may have been administered at a period of relative exacerbation. In such instances, the second evaluation would tend to produce a lower score, a phenomenon known as regression toward the mean. This is another possible explanation for the relatively slow observed progression between the first and second visits.

Statistical validity

Reliability. IRR of the PSPRS is very good, with intra-class correlation coefficient for the overall scale of 0.86. The subscores for mentation and limb movement did least well and the scores for gait/midline best. Although the IRR was performed by movement disorders specialists, they received only a few minutes' orientation to the PSPRS in order to mimic the conditions likely to prevail in the field, where most neurologists have few patients with PSP. Even better reliability may occur after more formal instruction and practice, which should be part of multi-investigator studies.

Type II error. Although this database comprises 162 patients, there remains the possibility that some of the hypotheses posed by the present analysis cannot be adequately answered for lack of statistical power. This may apply particularly to the mortality probability calculations, where small numbers of patients in each prognostic category reduce the statistical validity of the comparison among categories. We provide 95% confidence intervals and *P*-values for these statistics to permit evaluation of that validity.

Construct validity

Convergent validity. While each of the five PSPRS physical examination item groups (behaviour, bulbar, eyes, limbs and gait) measures a different aspect of PSP, they all should reflect the extent to which the disease as a whole has progressed in the individual. They therefore should correlate among themselves to some extent, a property called construct validity. Cronbach's alpha, a measure of this property, appears in Table 11 and demonstrates the necessary moderate level of cross-correlation.

Discriminant validity. Balancing convergent validity is the notion that the test items must not be so closely correlated as to be redundant. Factor analysis using oblique varimax rotation is used to measure discriminant validity. As shown in Table 12, items tended to sort into five factors that were similar to the five physical examination groups identified *a priori*.

Content validity

Even the few test items with possible redundancy (i.e. relatively low discriminant validity) may improve the content validity of the PSPRS by increasing the total score to reflect the disability conferred by an important symptom area. The PSPRS was designed, in fact, to include contributions from as many phenomenological areas of PSP as possible, even if some of those areas contribute relatively little to disability. The items on limb rigidity, dystonia and tremor are examples. The purpose of this strategy is to permit identification of specific areas that may respond to treatment or that may permit subclassification of PSP into aetiologically or therapeutically relevant sub-types.

Criterion validity

A gold standard. The lack of a quantitative biomarker for PSP means that there is no 'gold standard' against which the PSPRS, a quantitative tool, can be compared as a

Table 11 Cronbach's alpha for the five PSPRS physical examination item groups

Area	Number of items	Cronbach's alpha
Behaviour	4	52.8
Bulbar	2	76.1
Eyes	4	78.5
Limbs	6	59.1
Gait	5	91.2

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Table 12 Factor analysis

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Disorientation	0.17825	0.16419	**0.27570**	0.23251	−0.02480
Bradyphrenia	−0.01323	0.15306	**0.45340**	0.19056	−0.07244
Emotion	−0.00643	0.00146	−0.01677	**0.33158**	−0.07911
Grasping	0.04401	0.05787	−0.01511	**0.36642**	0.15507
Dysarthria	0.26285	0.11565	0.19784	**0.39616**	−0.23587
Dysphagia	0.31694	0.07704	0.07049	**0.31720**	−0.24059
Upgaze	0.00975	**0.70954**	0.00551	0.00296	−0.05284
Downgaze	0.08108	**0.75639**	−0.02775	−0.01728	0.01054
Left/right gaze	0.05952	**0.63176**	0.00606	0.06970	0.06733
Eyelid	−0.01121	**0.36674**	0.10114	0.26167	0.02320
Rigidity	0.01167	0.18611	**0.55202**	−0.09985	−0.02519
Dystonia	0.08199	0.01444	**0.34272**	0.14583	0.27951
Finger tap	0.07294	−0.02613	**0.59587**	0.06958	0.05863
Toe tap	0.17322	−0.11009	**0.51971**	0.03404	0.10103
Apraxia	−0.03554	0.09645	0.17007	0.15909	**0.33802**
tremor	0.04486	−0.01589	−0.03165	−0.06374	**0.26027**
Neck rigidity	0.31042	0.25366	**0.38186**	−0.09956	−0.12070
Arising	**0.74760**	0.02219	0.08273	0.02155	0.05808
Gait	**0.78420**	0.09899	0.01082	0.11233	0.08702
Stability	**0.82948**	0.12911	0.02156	−0.02143	0.01387
Sitting	**0.78559**	0.02924	0.09297	0.06332	0.10093

To sort the items, we used oblique varimax rotation, allowing for correlation between factors. The factor loadings for five factors are given below, with items belonging to each factor bolded.

measure of criterion validity. Instead, we used the inexorable progressivity of PSP as a comparator. Indeed, the independent variable that gave the most robust association with survival was the PSPRS score at the time of survival estimation. Other variables with independent effects on survival were onset age, and progression of PSPRS score over the 6 months preceding the visit at which survival was assessed (Table 8).

Possible treatment efficacy. While the natural history of PSP may be smoothly inexorable, some medications or physical therapy (Sosner *et al.*, 1993) given in an attempt to influence the symptoms or the disease course may actually be modestly and briefly efficacious in some patients and may slightly affect the PSPRS results. Levodopa/carbidopa (LD/CD), amantadine and amitriptyline were the most frequently prescribed such drugs in the current patient group. LD/CD has been reported to lessen limb bradykinesia and rigidity in early stages of PSP (Klawans and Ringel, 1971), but neither of these is a major contributor to the PSPRS score or to the subjective reports of disability in PSPRS Section I.

Every patient who had not received amantadine prior to referral to the author was given that medication during the course of the present observation period. There has been no controlled study of amantadine in PSP, but retrospective and anecdotal observations (Nieforth and Golbe, 1993; Kompoliti *et al.*, 1998) suggest that it may have a mild, transient, symptomatic effect on the motor parkinsonism and may have prompted its widespread use. Amitriptyline has provided benefit in PSP in one small, blinded study, but again, its benefit is short-lived. Most of the current patients received at least a brief trial of amitriptyline, which gave only occasional benefit.

Other drugs that were tried in some patients in the present report are baclofen, creatine, coenzyme-Q10, donepezil, gabapentin, galantamine, nicotine (patch), pramipexole, valproic acid, yohimbine and zolpidem. None of these gave improvement greater or longer-lived than that expected from placebo. Botulinum toxin injection for blepharospasm was given to a few patients with clear efficacy that affected the score on the PSPRS item for eyelid function. Multiple medications were given with variable success for insomnia and for urinary incontinence, potentially affecting those PSPRS items. A variety of measures were used successfully for constipation, a symptom that, while not assessed by any specific PSPRS items, may impair the general sense of well-being that could affect many areas of the scale.

Possible medication adverse effects. Many of the drugs tried for PSP in the present patients did produce adverse effects that could have influenced the PSPRS. A phone report of some benefit with adverse effects often prompted a decision to continue the drug at least until the next visit, at which time the PSPRS could have been influenced by those adverse effects. The central and peripheral anticholinergic side effects of amantadine and amitriptyline are the most important examples. The PSPRS item most likely to be exacerbated by drug side effects was probably orientation.

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Drawbacks

Perhaps the principal drawback of the PSPRS is that it was not designed to reveal the level of detail in such areas as daily activities, cognition or dysphagia that would be necessary to an interventional study aimed specifically at those disabilities. Rather, the PSPRS is designed as a rapid, convenient, global scale that would be useful in a busy referral practice and as part of a battery of tests in a clinical trial.

Another drawback is the necessarily subjective nature of the scoring rubrics. To minimize this, we used a scoring model for many of the items that relies on the examiner's judgement as to the degree to which that aspect of disability interferes with normal activities. Future revisions of the PSPRS could attempt to introduce more objective measures such as the ocular excursion range in those items and the timing used in the tapping items.

As is the case for many neurological rating scales, many of the exam items are obscured by disabilities in other areas. For example, bradyphrenia and dysarthria may impede the efficient evaluation of orientation or frontal cognitive function. Balance difficulty and limb bradykinesia affect the evaluation of gait. To minimize this uncertainty, the 'score what you see' approach was used throughout.

Finally, effective use of this scale requires practice. The subjective nature of many of the exam items in the PSPRS demands a level of familiarity with PSP that most clinicians and even many neurologists do not have. Therefore, any attempt to use the PSPRS, particularly in a multicentre trial, should be preceded by training, practice and assessment using patient videos.

The relatively advanced onset age of our patients, 67.4 years, is greater than the 62 or 63 typically reported. This may be a result of the large concentration of retirement communities in central New Jersey. A more important potential source of bias in our patient ascertainment is the tertiary nature of our cohort. It is possible that patients with less access to sophisticated medical care may have an even less favourable prognosis than did our patients. Future studies using the PSPRS should examine this issue in a community-based cohort.

Conclusions

The validity of the PSPRS score is demonstrated by its increase over time in parallel with the subjective disability of the disorder and by its ability to generate a likelihood of survival based on progression to date. IRR here is excellent, but should be re-tested by any multi-investigator group contemplating use of the PSPRS in a research study. Ratios of its subscores and its overall rate of progression over time could be used to categorize patients into disease subtypes of potential epidemiological or genetic significance. The convenience of the PSPRS and its reproducibility, at least with practice by the clinician, make it potentially useful as a means of tracking an individual patient's progression and response to treatment. Its prognostic utility allows caregivers to plan for the onset of successive levels of disability and to estimate survival duration.

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