Can a Screening Questionnaire Accurately Identify Mild Parkinsonian Signs?

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Key Words

Mild parkinsonian signs • Screening questionnaire • Validity • Sensitivity • Specificity

Abstract

Background: Mild parkinsonian signs (MPS) are early features that, when present, increase the risk of neurodegenerative disease and mortality. Current methods to identify MPS are limited to neurological examination. Our objective was to assess the ability of a 9-item Parkinson's Disease Screening Questionnaire (PDSQ), which has high sensitivity in the detection of overt Parkinson's disease (PD), to detect MPS. **Methods:** Measures including the PDSQ, Unified Parkinson's Disease Rating Scale and University of Pennsylvania Smell Identification Test were administered to 267 participants without neurodegenerative disease. Two published definitions of MPS were used to classify cases. **Results:** PDSQ scores were higher for cases compared to controls ($p < 0.001$ for the first case definition and 0.07 for the second). However, the questionnaire had low sensitivity (47 and 59%) and specificity (62 and 63%) in the detection of MPS. Adding factors such as age, gender and smell test score to the questionnaire in a predictive model only marginally improved the test characteristics. **Conclusion:** The results show the screen-

ing questionnaire does not accurately identify MPS. More accurate tests are needed to improve the detection of this early syndrome which can lead to motor disability, neurodegenerative disease and mortality.

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Introduction

Mild parkinsonian signs (MPS) such as tremor, rigidity, bradykinesia, and postural/gait changes affect up to 40% of older adults [1–4]. MPS has been variably defined, ranging from strict criteria [4] to a broader definition [2]. Recent studies have shown that MPS are progressive over time, are not features of normal aging, portend a greater risk of death, and may represent an early marker for neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease [2–8].

Studies that have screened for PD and parkinsonism in the community have largely utilized symptom questionnaires. One of these questionnaires [9] has been validated and used extensively in neuroepidemiological studies worldwide [10–18]. However, it is not known if this same questionnaire could accurately identify persons with MPS.

Table 1. Comparison of items from the PDSQ and the UPDRS used to define MPS

PDSQ	CD 1 → at least 2 of 4 cardinal signs as measured by items below	CD 2 → score greater than 1 on any of items below
Trouble rising from chair Change in facial expression Smaller handwriting Trouble buttoning Softer voice	Bradykinesia (at least score of 1 on UPDRS 19, 23, 24, 25 or 26) OR physician impression of bradykinesia; Rigidity (at least score of 1 on UPDRS 22) OR physician impression of rigidity	Body bradykinesia (UPDRS 31) Facial expression (UPDRS 19) Speech (UPDRS 18) Rigidity (neck, left arm and leg, right arm and leg; UPDRS 22)
Tremor	Tremor (rest/action/postural, at least score of 1 on UPDRS 20 or 21) OR physician impression of tremor	Rest tremor (UPDRS 20)
Imbalance Shuffling gait Freezing	Gait (at least score of 1 on UPDRS 29, 30 or 31) OR physician impression of gait abnormality	Posture (UPDRS 28)

The aim of the present study was to test the validity of this Parkinson's Disease Screening Questionnaire (PDSQ) to accurately identify subjects with MPS. We determined the sensitivity and specificity of the questionnaire in detecting MPS using two different case definitions (CD).

Materials and Methods

Study Population

Study participants were drawn from the ongoing Parkinson At-Risk Syndrome (PARS) study, a multicenter study conducted at 20 clinical centers throughout the United States. The details of the PARS study have been described previously [19]. First-degree relatives of patients with PD were invited to participate. Inclusion criteria were age greater than 50 years, or within 10 years of the age of onset of their affected relative, and not diagnosed with PD or other neurodegenerative disease. Institutional review boards approved this research study at each site and written informed consent was obtained from all participants.

Measures

Participants completed an evaluation that included a questionnaire with demographic items and a 9-item screening questionnaire for parkinsonian symptoms (PDSQ) [9] prior to examination. The PDSQ asks for a yes/no response from individuals regarding the presence of different parkinsonian symptoms. Sample items include: 'Is your balance, when walking or standing, poor?' and 'Do your arms or legs shake?' Each participant then had a blinded neurological examination performed by one of sixteen movement disorder specialists, including parts I–IV from the Unified Parkinson Disease Rating Scale (UPDRS) [20], with separate responses to whether cardinal signs of parkinsonism were present. The UPDRS demonstrates moderate-to-excellent inter- and intrarater reliability when administered by movement disorder specialists [20–23].

In addition, the University of Pennsylvania Smell Identification Test (UPSIT) was administered given the known association between hyposmia and MPS [24]. Lastly, the Center for Epidemiologic Studies Depression Scale was completed to assess if the presence of depression may confound the reporting of parkinsonian symptoms.

The PDSQ

We utilized a 9-item parkinsonism questionnaire [9] that has been found to be up to 100% sensitive and 100% specific in identifying PD [13].

Defining MPS

We identified MPS cases in the following two ways:

CD 1 was based on one published MPS criteria [4]. The presence of cardinal motor signs of parkinsonism (bradykinesia, gait disturbance, rigidity and tremor) was identified from UPDRS III ratings and any notation of these signs by the examining neurologist. At least two of the cardinal features of PD had to be present to qualify as a case in this definition.

CD 2 was based on another published MPS criteria [2]. An abbreviated 10-item motor UPDRS, including speech, facial expression, rest tremor, rigidity, posture, and body bradykinesia, was scored from 0–4. The presence of MPS was defined as a rating of at least 1 on any of the 10 items. Table 1 compares the screening questionnaire items with the assessment of MPS by examination using the two CD.

Subjects diagnosed with PD by the examining physician were excluded from further analysis.

Statistical Analyses

To test for associations between the PDSQ score and the presence of MPS, we compared the median number of positive responses between the subjects with and without MPS using Wilcoxon rank sum tests. We also tested whether individuals with at least one positive response on the PDSQ had higher odds of having MPS, using logistic regression. We then adjusted for potential confounders in this relationship. Next, we calculated the sensitivity,

Table 2. Comparison of clinical factors and MPS

	(-) MPS	(+) MPS	p value
CD 1	n = 221	n = 46	
Age, years	54.1 ± 8.6	56.9 ± 9.5	0.05
Male, %	39.4	43.5	0.61
PDSQ score	0 (0–6)	1 (0–7)	<0.001
UPSIT score	28.4 ± 8.2	24.5 ± 8.5	<0.01
CES-D score	14.6 ± 4.6	14.9 ± 6.0	0.69
CD 2	n = 189	n = 78	
Age, years	53.8 ± 8.5	56.6 ± 9.3	0.02
Male, %	36.5	48.7	0.06
PDSQ score	0 (0–6)	0 (0–7)	0.07
UPSIT score	28.2 ± 8.1	26.7 ± 8.9	0.18
CES-D score	14.8 ± 4.8	14.3 ± 5.2	0.47

Results are presented as means ± SD or medians with ranges in parentheses. For CD 1 see Bennett et al. [4] and for CD 2 see Louis and Bennett [2]. UPSIT score is number correct. PDSQ range = 0–9; UPSIT range = 0–40; CES-D = Center for Epidemiologic Studies Depression Scale (range = 0–60).

specificity and area under the receiver-operating characteristic (ROC) curve for individual items and the total score on the PDSQ relative to the standard of being diagnosed with MPS by the two CD. To assess the accuracy of combining multiple variables (PDSQ, UPSIT and age) that may help predict MPS, a multivariable logistic regression model was created and an overall risk score was calculated from the model. The ability of this risk score to correctly identify cases of MPS was then tested using ROC analysis. We also compared the accuracy of the risk score to single variables using nonparametric tests for differences in the ROC area.

Results

A total of 267 (40% male, 98% white, mean age 54.6 years, SD 8.8) participants were included. The sample was highly educated overall with an average of 16 years of total education (SD 2.7). The PDSQ had high reliability (Cronbach's $\alpha = 0.71$) in this cohort. Of the total sample, 108 (40.5%) answered yes to one or more questions in the PDSQ, and 59 (22.1%) answered affirmatively to 2 or more questions. The mean UPDRS motor subscore was 1.8 (SD 2.8, range 0–19). Forty-six (17.2%) patients fulfilled the MPS CD 1 criteria while 78 (28.3%) fulfilled CD 2. Individuals with MPS by CD 1 were older (56.9 vs. 54.1 years; $p < 0.05$), had a higher median score on the PDSQ ($p < 0.001$) and a lower mean UPSIT score (24.5 vs. 28.4; $p < 0.01$) than those without MPS (table 2). The subset with MPS by CD 2 were also older (56.6 vs. 53.8 years;

$p = 0.02$), had higher, but not significantly, median scores on the PDSQ ($p = 0.07$) and a weaker association with the mean UPSIT score (26.7 vs. 28.2; $p = 0.18$). The odds ratio (OR) of fulfilling CD 1 in subjects with at least 1 positive response on the PDSQ was 2.46 (95% CI 1.29, 4.7; $p < 0.01$) versus an OR of 1.50 (95% CI 0.88, 2.56; $p = 0.14$) for CD 2. The OR did not change significantly after controlling for the potential confounders of age, years of education or depression scores.

While the PDSQ was associated with MPS by CD 1 and 2, its usefulness to detect MPS was not as strong. Using a PDSQ cutoff of ≥ 1 , the sensitivity to detect MPS as defined by CD 1 was 58.7% and specificity was 63.4%. Similarly, the sensitivity to detect MPS by CD 2 was 47.4% and specificity was 62.4%. No single item had sensitivity greater than 35% to detect MPS by either CD. At higher cutoff points, sensitivity decreased along with a mild increase in specificity. For CD 1, a cutoff of 2 led to a sensitivity of 43.5% and specificity of 82.4%, while a cutoff of 3 led to a sensitivity of 21.7% and a specificity of 90.1%. For CD 2, a cutoff of 2 led to a sensitivity of 28.2% and a specificity of 80.4% and a cutoff of 3 led to a sensitivity of 19.2% and a specificity of 91.0%. Due to the low sensitivity and moderate specificity of using the PDSQ alone in detecting MPS, we sought to develop a predictive model utilizing other clinical features to enhance detection. When age and UPSIT are added to the PDSQ, sensitivity and specificity are only slightly improved (fig. 1). The optimal performance of the PDSQ was among individuals under 50 with MPS by CD 1, where a cutoff of ≥ 1 resulted in a sensitivity rate of 80% and specificity of 60% (ROC area 0.75). Table 3 depicts the performance of the PDSQ stratified by age.

Discussion

Subjects with MPS had higher median scores on the PDSQ than subjects without MPS, and those who gave at least one positive response had nearly twice the odds of having MPS. However, these associations were not strong enough to make the PDSQ useful as a diagnostic test for MPS. We found that this screening tool has low sensitivity and specificity when applied to the two CD for MPS. Even after the addition of statistically significant clinical predictors of MPS such as age and olfactory function to the PDSQ, the combined screening score still had modest clinical utility in detecting MPS.

This study has several limitations. First, subjects were recruited from a convenience sample of first-degree rela-

Fig. 1. ROC curves for CD 1 (a) and CD 2 (b). ROC curves are shown for the PDSQ alone (open arrow) and for output from a logistic regression model that includes the PDSQ, UPSIT, age and gender (closed arrow). There were no significant differences between the PDSQ and the model ($p > 0.05$ for both CD). The diagonal line below the ROC curves identifies the ROC area that would be achieved by chance alone.

tives of PD patients. This selection bias might lead to a greater awareness and self-report of symptoms which would falsely elevate sensitivity. Alternatively, participants may deny symptom onset because of known implications. Second, the study population was homogeneous which limits the generalizability of the findings. Furthermore, additional clinical information and a larger sample would have allowed for additional analyses of factors related to MPS. Finally, we used a modified version of CD 1 by correlating each parkinsonian sign with an item on the UPDRS motor subscore. However, the

Table 3. ROC areas of PDSQ when stratified by age

Age	MPS by CD 1 ROC area	MPS by CD 2 ROC area
<50 years	0.75	0.52
50–60 years	0.59	0.61
>60 years	0.62	0.54

combination of UPDRS data and clinical impression provided a very close approximation of the original published criteria, and it is unlikely that our modifications substantially affected the overall sensitivity and specificity rates found.

Other studies have tested the performance of the PDSQ in the detection of mild parkinsonism. However results have varied, largely because of different samples and parkinsonism CD. In one German study, a PDSQ cutoff of 3 or more positive responses resulted in a sensitivity of 91.7% and specificity of 83.7% to detect bradykinesia and at least one additional parkinsonian feature, a slightly stricter definition of parkinsonism than we used [10]. On the other hand, a similar study performed in the United Kingdom using the same cutoff (3) led to a lower sensitivity (77%) and specificity (49%) which also defined parkinsonism as at least 2 out of 4 cardinal signs [25]. Yet another study [14] that tested the PDSQ among an at-risk population found that a cutoff of 1 resulted in a sensitivity to detect clinically probable (2 out of 4 cardinal signs) to clinically possible PD (1 out of 4 cardinal signs) of 48% which was similar to our findings.

The present study found that the PDSQ had a lower sensitivity and specificity in identifying MPS compared to most prior studies. However, it is important to note that many previous studies sought to utilize the PDSQ to determine the prevalence of early symptomatic or asymptomatic PD, rather than the detection of MPS. Potential explanations for the low sensitivity may include the following: (1) MPS is a different disease process from idiopathic PD and, therefore, needs a different questionnaire, (2) symptoms may be so mild that they do not lead to any functional deficit that could be detected through a screen and (3) family members of PD patients may underreport parkinsonian symptoms. Low specificity could in part be explained by the lack of discrimination between MPS and other common conditions (arthritis, stroke, etc.) that can lead to symptoms such as poor balance, reduced dexterity and difficulty arising out of a chair.

Conclusions

The accurate detection of MPS and its relationship to early neurodegenerative diseases are areas that warrant further exploration. A more sensitive screening questionnaire to detect MPS may need additional items and the incorporation of observations by family or friends to identify subtle parkinsonian signs. Quantitative measurements of parkinsonian signs such as rigidity and bradykinesia may also help in the detection of these subtle signs [26–28]. Lastly, a longitudinal follow-up of individuals with MPS to understand who develops neurodegenerative disease will ultimately help in the development of more specific screening instruments.

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