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ORIGINAL PAPER

Characterization of spontaneous Parkinsonism in drug-naive patients with nonaffective psychotic disorders

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Abstract Spontaneous Parkinsonism (SP) in schizophrenia-related disorders is poorly characterized. The objective of this study was to examine the concordance and clinical validity of alternative definitions of SP in patients with nonaffective psychotic disorders. Two-hundred drug-naive patients with nonaffective psychotic disorders were examined for core parkinsonian signs, including bradykinesia, rigidity, and tremor, and diagnosed of SP according to the Simpson-Angus Scale (SAS) cutoff criterion, the UK Parkinson's disease brain bank (UKPDBB) criteria, the National Institute of Neurological Disorders and Stroke (NINDS) criteria, and criteria requiring the presence of all three core features (full syndrome criteria). Parkinsonian signs and criteria were examined in relation to a number of relevant clinical variables. The most frequent sign was rigidity (33.5%) followed by bradykinesia (16%) and tremor (12%). The prevalence rate of SP according to the SAS cutoff criterion, the UKPDBB criteria, the NINDS criteria for possible and probable SP, and the full syndrome criteria were 20.5, 13, 25.5, 18.5, and 4%, respectively. Bradykinesia was specifically related to negative symptoms, rigidity to neurological soft signs, and tremor to dyskinetic movements. The set of criteria showing more associations with clinical variables were the NINDS criteria for probable SP. Patients fulfilling these criteria had higher ratings for poor premorbid adjustment, negative symptoms, dyskinesia, neurological soft signs, and poor global treatment response than those without that diagnosis. The NINDS criteria for probable SP, i.e., presence of any two of the three core parkinsonian signs, seem to be the most suitable for clinical and research purposes.

Keywords Spontaneous Parkinsonism · Diagnostic criteria · Schizophrenia · Validity

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Introduction

Whereas a broad number of neuromotor abnormalities were described in patients with schizophrenia during the preneuroleptic era [1], after the introduction of antipsychotic drugs, these abnormalities have been mainly viewed as side effects of antipsychotic medication. In the last few years, a new series of studies conducted in patients never exposed to antipsychotic drugs have challenged this view by demonstrating that neuromotor signs are both indigenous of the disorder and relatively prevalent [2–5]. These, so-called, spontaneous motor abnormalities are part of a more global psychomotor domain of the psychotic illness [6] and are thought to be the expression of a deviation of the brain structure and function [7] and more specifically of a dysfunction in the basal ganglia-cortical circuitry [4].

Spontaneous Parkinsonism (SP) is the most frequent movement disorder reported in drug-naive psychotic patients. Using conventional assessment means, the prevalence rate of SP ranges from 2.3 to 26.9% [3], although using instrumental measures of SP, the prevalence rate increases up to 52% [8]. The wide variability of clinical SP is mainly due to lack of standard definitions to diagnose it, since definitions have typically relied upon arbitrary guidelines [8–10], clinimetric-based definitions [5] or criteria developed for drug-induced Parkinsonism [11, 12]. More specifically, there is a lack of research diagnostic

criteria for SP that are comparable to those used for diagnosing Parkinson's disease (PD).

Accurate clinical diagnosis of SP is important for both research and practical purposes. The clinical phenotype of SP fits well to the notion of a modular dysfunction in brain distributed networks subserving a physiological function responsible for the regulation of motor behavior [13]. Parkinsonian signs typically arise from a dysfunction of the nigrostriatal dopamine pathway [14], thus the study of SP and its relationship with other clinical manifestations may shed light on the altered neurobiological mechanisms of psychiatric disorders [15, 16]. For example, it has been reported that schizophrenia patients show a reduced number of dopamine D_2 autoreceptors that regulate the nigrostriatal dopamine pathway [17], which could hypothetically explain SP in these patients. From a practical perspective, it is essential to differentiate spontaneous from drug-induced parkinsonian signs for a proper management of the motor disorders observed in patients with schizophrenia. With recent understanding of the complex relationships between primary and drug-induced movement disorders [18–20], this exercise is no longer merely academic. Primary and secondary parkinsonian symptoms may differ in their clinical expression, which may guide the clinician toward a better diagnosis of the condition.

In the present study, we sought to characterize SP in regard to the cardinal signs of Parkinson's disease (PD), namely bradykinesia, rigidity, and tremor, and to examine the clinical validity of alternative sets of diagnostic criteria for SP. Specific aims of the study were: (a) to describe SP according to alternative diagnostic criteria including standard diagnostic guidelines for PD, (b) to examine the prevalence of and concordance among alternative definitions of SP, (c) to examine the clinical correlates of individual parkinsonian signs, and (d) to comparatively examine the validity of the alternative criteria for diagnosing SP according to relevant clinical variables.

Methods

Subjects

The study sample comprised 200 patients diagnosed of a nonaffective psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [21]. Patients had never been exposed to antipsychotic medication and were admitted to the Psychiatry Section B of the Complejo Hospitalario of Navarra in Pamplona, Spain, to receive their first treatment for the disorder. The study population and design has been described in detail elsewhere [5]. Exclusion criteria were: a history of drug abuse or dependence, a history of head trauma resulting in loss of consciousness, mental retardation, a history of any neurological disease in the patient or a hereditary neurological disease in their first-degree relatives, and meaningful somatic disease that could either interfere with the assessment of motor abnormalities or potentially cause CNS damage. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local institutional review board. All the patients or their legal representatives gave written informed consent to participate after the study had been explained.

All but three patients were of Caucasian origin, 133 (66.5%) were men, and 163 (81.5%) were single. The mean age of the patients was 29.8 (±4.1) years, and their mean age at first illness-related symptom was 26.6 (±9.7) years. Specific DSM-IV diagnoses were as follows: schizophrenia ($n = 94$, 47%), schizophreniform disorder ($n = 36$, 18%), schizoaffective disorder ($n = 13$, 6.5%), brief psychotic disorder ($n = 38$, 19%), delusional disorder (15, 7.5%), and atypical psychosis ($n = 4$, 2%).

Clinical assessment

Demographics, diagnosis, and most illness-related variables were assessed by means of the Comprehensive Assessment of Symptoms and History (CASH) [22]. To examine the relationship of parkinsonian signs and diagnostic criteria with clinical parameters, we selected those clinical variables that have been related to SP signs or criteria in one or more previous studies [9–12, 23]. These variables included premorbid functioning, duration of untreated illness (DUI), baseline positive and negative symptoms, other baseline neurological signs, and response to treatment. Premorbid functioning was rated according to the Phillips scale [24], and DUI (in months) was measured according to the Symptom Onset in Schizophrenia scale [25]. Positive and negative symptoms were rated by means of the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Positive Symptoms (SANS), which are included in the CASH [22] and typically cover the major symptoms of schizophrenia and related disorders.

Of the 200 patients assessed at baseline, 189 were reassessed for psychopathological ratings after a 4-week trial with antipsychotic medication (for details see reference [5]). Global response to treatment was rated according to the efficacy index included in the Clinical Global Impression (CGI) scales [26], which ranges from 1 (marked improvement) to 4 (no improvement). Specific response to treatment was also defined for positive and negative symptoms as the percent of improvement from baseline in SANS or SANS total score ratings as follows: 1 = full remission (>75% improvement), 2 = good remission (50–75% improvement), 3 = poor remission

(25–49% improvement), and no remission (<25% improvement).

Assessment of motor disorders

Motor disorders were rated on the basis of a structured neurological examination before starting antipsychotic medication by VP or MJC, who have extensive experience in assessing motor disorders in schizophrenia. The main outcome measure for the present study was the Simpson-Angus Scale (SAS) [27]. This scale was originally developed for the assessment of Parkinsonism and related extrapyramidal adverse events, and it has become the most used instrument to assess Parkinsonism in schizophrenia, both drug-induced and spontaneous. The SAS consists of 10 items measuring bradykinesia (1 item), rigidity (6 items), and tremor, glabella tap and salivation (1 item each). The items are scored on a 5-point scale (0–4), and a total score >3 is used to define the presence of Parkinsonism. The SAS scoring was conservative; hence, if a symptom was not clearly present, then it was scored absent. For the purposes of the present study, only the SAS items corresponding to bradykinesia, rigidity, and tremor were considered. The 6 rigidity items were collapsed into a single item, which was scored on the basis of the most severe rating of each individual item. We also defined a Parkinsonism total score by summing-up the ratings for bradykinesia, rigidity, and tremor.

All the patients were also assessed at the drug-naive state for dyskinesia, akathisia, and catatonia signs, which were, respectively, rated according to the Abnormal Involuntary Movements Scale [26], the Barnes Akathisia Rating Scale [28], and the catatonia subscale from the Modified Rogers Scale [29]. Furthermore, 131 patients were also assessed for neurological soft signs (NSS) using the Neurological Evaluation Scale [30]. Inter-rater reliability for psychopathological and neurological ratings has been reported elsewhere [23] and found to be good or excellent.

Diagnostic criteria for SP

We examined 5 definitions of SP: the SAS total score cutoff >3 criterion [26], the UK Parkinson's disease brain bank (UKPDBB) criteria [31], the National Institute of Neurological Disorders and Stroke (NINDS) criteria for possible and probable PD [32], and criteria requiring the presence of all three core features (full syndrome criteria). To diagnose SP according to the UKPDBB criteria, we used the step 1 criteria excepting postural instability, which was not assessed. Thus, SP according to the UKPDBB criteria was defined as the presence of bradykinesia plus rigidity or tremor. To diagnose SP according to the NINDS criteria, the Group A features excepting asymmetric onset, which was not assessed, were considered. Diagnosis of possible SP according to NINDS criteria was based on the presence of tremor or bradykinesia. Diagnosis of probable SP according to NINDS criteria was based on the presence of at least 2 of the three core signs.

Statistical analysis

Internal consistency of parkinsonian signs was examined by Cronbach's α and the concordance among the sets of criteria by the κ statistic. Parkinsonian signs had a highly skewed distribution that did not normalize after logarithmic and squared roots transformations, thus nonparametric statistics were used. Categorical variables were compared by means of χ^2 tests. The association among continuous variables was examined by means of Spearman rank-order correlation coefficients. The association between continuous and categorical variables was examined by using Mann–Whitney U or Kruskal–Wallis tests as appropriate. All test of hypothesis were done at a 2-sided 0.05 level of significance. Bonferroni corrections for multiple testing were performed when examining associations of a given variable with the different parkinsonian sign ratings ($n = 4$) and sets of diagnostic criteria ($n = 5$), where sign ratings and diagnostic criteria were treated as separate family of hypotheses [33].

Results

Prevalence and severity of parkinsonian signs

The most frequent symptom was rigidity (33.5%) followed by bradykinesia (16%) and tremor (12%) (Fig. 1). Bradykinesia and tremor were mostly present at the mild level, while almost half of the patients with rigidity had moderate or higher levels for that symptom (Table 1). The level of overlap among signs was moderate as reflected by a Cronbach's α of .58. The percent of patients with bradykinesia, rigidity, or tremor presenting with any other symptom was 81.3, 52.3, and 87.5%, respectively (Fig. 1).

Agreement and concordance among alternative definitions of SP

The prevalence rate of SP highly varied as a function of set of diagnostic criteria, with the most restrictive and inclusive criteria being, respectively, the full syndrome criteria (4%) and the NINDS criteria for possible SP (25.5%) (Table 2). In total, 64 of the 200 investigated cases (32%) met at least one of SP definitions. The NINDS criteria for probable SP showed the highest concordance with the other

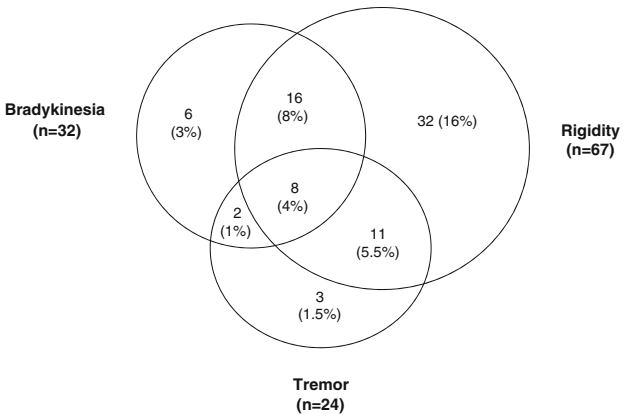

Fig. 1 Prevalence and overlap of core parkinsonian signs in 200 drug-naive patients with nonaffective psychotic disorders

criteria (κ between .62 and .81), with the NINDS criteria for probable SP and the UKPDBB criteria showing the highest level of agreement (94.5%) and concordance ($\kappa = .81$).

Association of parkinsonian signs with demographic variables

There were no differences in symptom ratings across gender (Mann–Whitney Z between -0.67, $p = .946$ for bradykinesia and -1.45, $p = .172$, for tremor) nor diagnosis (Kruskal–Wallis $\chi^2_{(df=5)}$ between 4.46 ($p = .485$) for bradykinesia and 9.31 ($p = .097$) for the Parkinsonism total score).

Years of education was unrelated to any symptom rating: r_s between $-.011$ ($p = .875$) for the Parkinsonism total score and .093 ($p = .192$) for tremor. Age showed a week, but nonsignificant association after Bonferroni correction, with rigidity ($r_s = .15$, $p = .029$) and tremor ($r_s = .14$, $p = .042$).

Association of parkinsonian signs and SP criteria with clinical features

The association pattern between parkinsonian signs and clinical features slightly differed across individual symptoms (Table 3). Specific significant associations between clinical features and parkinsonian ratings were found for bradykinesia with negative symptoms, rigidity with NSS, and tremor with dyskinetic movements. Overall, the Parkinsonism total score captured well the associations of individual signs.

The alternative diagnostic criteria for SP showed a rather different association pattern with clinical variables (Table 4). DUI, baseline positive symptoms, akathisia, and remission scores for positive and negative symptoms were all unrelated to any diagnostic criteria for SP. The clinical feature most consistently related to diagnostic criteria for SP was dyskinesia. The NINDS criteria for probable SP showed more associations with clinical variables than any other criteria, and the criteria for a full syndrome did not revealed any significant association with clinical variables.

Given the age range of the study sample along with the weak correlation of age with rigidity and tremor, the question arises as to whether the presence of early stage PD in some patients. We examined this possibility by repeating the analyses in those patients under age 50 ($n = 189$). The prevalence of SP according to the SAS cutoff score,

Table 1 Prevalence and severity of core parkinsonian signs in 200 drug-naive patients with nonaffective psychotic disorders

	Absent *n* (%)	Mild *n* (%)	Moderate *n* (%)	Marked *n* (%)	Severe *n* (%)
Bradykinesia	168 (84.0)	27 (13.5)	5 (2.5)	0	0
Rigidity	133 (66.5)	37 (18.5)	20 (10.0)	6 (3.0)	4 (2.0)
Tremor	176 (88.0)	22 (11.0)	2 (1.0)	0	0

Table 2 Agreement (%) and concordance (κ) among alternative definitions of spontaneous Parkinsonism

	n (%)	1	2	3	4	5
1. SAS cutoff score	41 (20.5)	*	85.5	85.5	88	81.5
2. UKPDBB	26 (13)	0.48	*	88.0	94.5	91.0
3. NINDS possible	50 (25.5)	0.47	0.62	*	93.5	79.0
4. NINDS probable	37 (18.5)	0.62	0.79	0.81	*	85.5
5. Full syndrome criteria	8 (4)	0.19	0.44	0.22	0.31	*

Agreement values are above the diagonal and concordance values under the diagonal

SAS Simpson-Angus Scale, *UKPDBB* UK Parkinson's Disease Brain Bank criteria, *NINDS* National Institute of Neurological Disorders and Stroke criteria

Table 3 Spearman rank correlation coefficients between parkinsonian signs and clinical variables in 200 drug-naive patients with nonaffective psychotic disorders

	Bradykinesia		Rigidity		Tremor		Parkinsonism total score	
	r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
Premorbid adjustment	.18	.010*	.19	.007*	.11	.134	.21	.005*
Duration of untreated illness	.06	.307	.11	.114	.00	.922	.12	.087
SAPS, total score	−.01	.882	.06	.200	−.06	.357	.05	.479
SANS, total score	.24	.001**	.12	.086	.11	.134	.16	.021
AIMS, total score	.05	.515	.16	.020	.27	.000**	.21	.002**
BARS, global rating	.02	.830	.03	.715	.12	.084	.05	.477
MRS, catatonia score	.18	.010*	.19	.007*	.10	.162	.20	.004*
NES, total score†	.17	.049	.23	.008*	.13	.153	.21	.017
CGI, efficacy index‡	.13	.066	.17	.022	.14	.049	.21	.005*
SAPS, remission score‡	−.07	.357	.13	.071	.09	.210	.05	.497
SANS, remission score‡	−.10	.192	.05	.481	−.08	.257	.04	.564

* $p < 0.05$ after Bonferroni correction, ** $p < 0.01$ after Bonferroni correction

† $n = 131$, ‡ $n = 189$

SAPS Scale for the Assessment of Positive Symptoms, *SANS* Scale for the Assessment of Negative Symptoms, *AIMS* Abnormal Involuntary Movements Scale, *BARS* Barnes Akathisia Rating Scale, *MRS* Modified Rogers Scale, *NES* Neurological Examination Scale, and *CGI* Clinical Global Impression

UKPDBB, NINDS possible, NIDSS probable, and the full syndrome criteria was virtually the same as in the whole sample: 20.1, 13.2, 24.3, 17.5, and 4.2%, respectively. Likewise, the association pattern between the sets of criteria and clinical variables remained basically unchanged (data not shown).

Discussion

The strengths of this study include the large number of drug-naive patients examined, the application of standard diagnostic criteria for Parkinson's disease to characterize SP, and the examination of the comparative validity of parkinsonian signs and criteria across a number of clinical variables. However, some caveats should be considered when interpreting our data. First, we relied on the SAS to assess the core parkinsonian signs, which is subject to a number of limitations including unbalanced symptom coverage and lack of representation of some relevant parkinsonian signs. Second, postural instability and asymmetric onset were not assessed, and the duration criterion was not considered when applying the UKPDBB and NINDS criteria; thus, our procedure needs to be considered as a proxy approach to these set of criteria. Postural instability, however, may not be relevant for diagnosing SP in schizophrenia; since in PD, this symptom does not manifest itself before the patient has reached an advanced stage [34] and its diagnostic utility has been questioned when the diagnosis still has to be established [35]. Notwithstanding, future studies of SP should use more standard instruments to rate parkinsonian signs such as the Unified Parkinson's Disease Rating Scale [34] and strictly adhere to the diagnostic criteria for PD. Lastly, diagnostic criteria for PD and SP may not be comparable, since PD is a neurodegenerative disease with Lewy body on autopsy as the criterion standard for diagnosis and SP has no definite test for diagnosis. Notwithstanding, assuming that the underlying pathology for SP in psychotic disorders and that for PD are different, the use of standardized clinical criteria for PD in patients with psychotic illness may guide the diagnosis of SP in order to better delineate their clinical correlates and underlying neurobiological mechanisms.

To the best of our knowledge, this is the first study examining SP according to standard definitions of PD such as their comparative validity. We found a moderate internal consistency for the core parkinsonian signs, and in line with some previous studies [8, 9], the most frequent parkinsonian symptom was rigidity followed by bradykinesia and tremor in that order. Diagnostic criteria for SP varied 6-fold in their rates for diagnosing the disorder, and as expected, the NINDS criteria for possible SP were the most inclusive and the full syndrome criteria the most restrictive. The UKPDBB criteria and the NINDS criteria for probable SP, with a respective prevalence rate of 13 and 18.5%, were the most parsimonious diagnostic schemes. These rates closely approach to the median prevalence rate of 17% reported in a recent systematic review of SP [3].

Both parkinsonian signs and diagnostic criteria showed a rather different association pattern with clinical variables. Bradykinesia was specifically related to negative symptoms, which appears to be due to overlapping definitions

Table 4 Relationship between alternative diagnostic criteria for spontaneous Parkinsonism and clinical variables

	Criteria	SAS cutoff score > 3			UKPDBB criteria			NINDS, possible criteria			NINDS, probable criteria			Full syndrome criteria		
		Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*	Mean ± SD	*z*	*p*
Premorbid adjustment	+	2.61 ± 1.41	−2.54	.011	3.04 ± 1.45	−3.47	.001**	2.50 ± 1.45	−2.12	.034	2.73 ± 1.42	−2.98	.003*	2.75 ± 1.28	−1.53	.125
	−	2.06 ± 1.41			2.05 ± 1.38			2.07 ± 1.41			2.05 ± 1.40			2.15 ± 1.43		
Duration of untreated illness	+	61.9 ± 99.8	−1.48	.138	59.4 ± 82.6	−1.27	.204	49.8 ± 86.4	−0.21	.830	61.0 ± 97.2	−1.01	.310	39.3 ± 99.6	−0.94	.343
	−	33.5 ± 52.9			36.3 ± 65.9			35.8 ± 61.3			34.4 ± 59.5			39.3 ± 67.2		
SAPS total score	+	10.6 ± 3.81	−0.68	.495	10.0 ± 2.99	−0.44	.660	9.96 ± 3.45	−0.85	.393	9.81 ± 3.29	−.886	.375	9.62 ± 2.87	−0.68	.497
	−	10.1 ± 3.33			10.3 ± 3.50			10.3 ± 3.43			10.3 ± 3.47			10.3 ± 3.46		
SANS total score	+	7.70 ± 6.05	−2.25	.024	9.42 ± 5.36	−3.55	.000**	7.27 ± 5.08	−2.33	.020	8.43 ± 5.67	−3.11	.002*	9.00 ± 5.01	−1.80	.072
	−	5.31 ± 4.98			5.26 ± 5.07			5.21 ± 5.15			5.20 ± 5.03			5.67 ± 5.26		
AIMS total score	+	2.78 ± 3.99	−3.31	.001**	1.62 ± 2.98	−.279	.780	2.04 ± 2.92	−3.57	.000**	2.11 ± 3.19	−2.54	.010*	1.75 ± 2.43	−0.94	.348
	−	0.97 ± 2.21			1.30 ± 2.73			1.11 ± 2.67			1.17 ± 2.63			1.32 ± 2.78		
BARS global rating	+	0.29 ± 0.75	−0.21	.830	0.15 ± 0.37	−.214	.830	0.26 ± 0.60	−1.51	.130	0.19 ± 0.46	−0.488	.626	0.38 ± 0.52	−1.91	.056
	−	0.16 ± 0.47			0.19 ± 0.56			0.16 ± 0.52			0.18 ± 0.57			0.18 ± 0.54		
MRS catatonia score	+	2.22 ± 3.36	−2.27	.023	2.46 ± 3.60	−2.27	.023	2.02 ± 3.61	−2.08	.038	2.00 ± 3.13	−2.24	.025	1.00 ± 1.01	−0.51	.613
	−	1.23 ± 2.57			1.28 ± 2.60			1.24 ± 2.41			1.31 ± 2.68			1.45 ± 2.82		
NES total score[†]	+	20.1 ± 10.9	−2.10	.036	19.9 ± 9.21	−1.74	.082	20.9 ± 11.8	−2.68	.007*	22.3 ± 10.7	−3.11	.002*	19.3 ± 8.02	−1.14	.254
	−	15.1 ± 0.94			15.6 ± 10.3			14.4 ± 9.15			14.8 ± 9.74			15.9 ± 10.4		
CGI efficacy index[‡]	+	2.23 ± 0.87	−2.67	.008*	2.29 ± 0.91	−2.25	.025	2.17 ± 0.89	−2.40	.016	2.33 ± 0.88	−2.55	.010*	2.00 ± 0.93	−0.28	.776
	−	1.82 ± 0.26			1.85 ± 0.96			1.82 ± 0.86			1.83 ± 0.86			1.90 ± 0.88		
SAPS remission score[‡]	+	1.95 ± 0.86	−2.20	.028	1.67 ± 0.92	−0.44	.663	1.71 ± 0.91	−0.63	.523	1.80 ± 0.87	−0.89	.425	1.50 ± 1.07	−1.08	.279
	−	1.67 ± 0.91			1.73 ± 0.90			1.63 ± 0.84			1.71 ± 0.91			1.73 ± 0.90		
SANS remission score[‡]	+	2.97 ± 1.13	−0.43	.670	2.67 ± 1.13	−1.93	.053	2.95 ± 1.10	−0.75	.453	2.99 ± 1.29	−0.43	.153	2.96 ± 1.16	−1.94	.068
	−	2.97 ± 1.23			3.01 ± 1.27			2.97 ± 1.30			2.85 ± 1.06			2.90 ± 1.23		

* $p < 0.05$ after Bonferroni correction, ** $p < 0.01$ after Bonferroni correction

\+ and − indicate presence and absence of spontaneous Parkinsonism, respectively

[†] $n = 131$, [‡] $n = 189$

SAS Simpson-Angus Scale, *UKPDBB* UK Parkinson's Disease Brain Bank criteria, *NINDS* National Institute of Neurological Disorders and Stroke criteria, *SAPS* Scale for the Assessment of Positive Symptoms, *SANS* Scale for the Assessment of Negative Symptoms, *AIMS* Abnormal Involuntary Movements Scale, *BARS* Barnes Akathisia Rating Scale, *MRS* Modified Rogers Scale, *NES* Neurological Examination Scale, and *CGI* Clinical Global Impression

[36], and it explains the association between SP and negative symptoms in that and other studies of drug-naive patients [8, 9, 37]. The set of diagnostic criteria showing more associations with clinical variables were the NINDS criteria for probable SP. Patients fulfilling these criteria had higher ratings for poor premorbid adjustment, negative symptoms, dyskinesia, NSS, and poor global response to treatment than those without that diagnosis. Furthermore, these criteria captured well, and better than any other set of criteria, the relationships between individual parkinsonian signs and clinical variables. Thus, the NINDS criteria for probable SP appear to be the most valid ones in terms of the clinical variables examined in our study.

The few previous studies examining the relationship between SP and treatment response have reported conflicting results [9, 11, 23], probably because differences in definitions of both SP and treatment response. We found that poor global response to treatment was weakly related to individual parkinsonian signs and significantly related to the Parkinsonism total score such as to the SAS cutoff score criterion and the NINDS criteria for probable SP. A well-established fact is that schizophrenia patients with high rates of negative symptoms respond poorly to antipsychotic medication and develop more neurological side effects [38]. On the basis of our data, it could be hypothesized that the link among all these variables may be in part mediated by primary parkinsonian signs. Taking into account, the existence of SP in patients with schizophrenia may also help to explain because a substantial proportion of patients diagnosed of drug-induced Parkinsonism, parkinsonian signs do not remit after discontinuation of antipsychotic medication [39]. These cases have been often interpreted as having preclinical Parkinsonism, but an alternative explanation is that antipsychotic medication unmasks the disease-based Parkinsonism [23]. If not explored before starting antipsychotic medication, spontaneous (often subclinical) Parkinsonism may get undetected, and only when exacerbated by antipsychotic drugs, the clinician becomes aware of parkinsonian signs, which are usually diagnosed as drug-induced.

In conclusion, our results show that primary parkinsonian signs are relative prevalent in schizophrenia-spectrum disorders and that classification of SP according to different diagnostic clinical guidelines yields rather distinct groups of patients. Although the selection of a given set of criteria will depend on the purpose of their use, diagnostic criteria consisting of any two of the three core parkinsonian signs (i.e., the NINDS criteria for probable SP) seem suitable for most applications given both their parsimonious character and the higher clinical validity regarding the other criteria. Future studies should focus on examining these SP criteria regarding instrumental measures of parkinsonian signs [6, 40] such as their functional and structural neuroanatomical correlates.

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