

Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study

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Received: 4 February 2009 / Revised: 12 June 2009 / Accepted: 8 July 2009 / Published online: 9 August 2009
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Abstract The PRIAMO study is a cross-sectional longitudinal observational study aimed at describing epidemiology and evolution of non-motor symptoms (NMS) in patients with different forms of parkinsonism recruited in 55 Italian centres and evaluated over 24 months. In this paper, we are reporting prevalence and clinical characteristics of NMS in patients with atypical and secondary parkinsonism. Out of 1307 consecutive patients with a

diagnosis of parkinsonism, 83 patients had vascular parkinsonism (VP), 34 had multiple system atrophy (MSA), 30 had progressive supranuclear palsy (PSP), 14 had dementia with Lewy bodies (DLB) and 11 had corticobasal degeneration (CBD). MSA and DLB had the highest number of NMS domains and symptoms, respectively. Gastrointestinal symptoms, pain, urinary problems and postural instability due to orthostatic hypotension were most frequent in MSA. Sleep disturbances were also common with a prevalence of approximately 70% in all

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diagnostic groups but CBD (36%). Psychiatric symptoms and attention and memory impairment were frequently observed in all diagnoses but were most prevalent among DLB patients, whereas the prevalence of skin and respiratory disorders was rather low in all forms, ranging between 10 and 30%. Atypical parkinsonism patients also reported a low QoL, with no significant differences among the different forms, whereas PD and VP patients had a better QoL.

Keywords Atypical parkinsonism · Secondary parkinsonism · Parkinson and cognitive impairment · Non-motor symptoms

Introduction

Atypical parkinsonism is a group of sporadic, neurodegenerative diseases of the central nervous system, less common and usually more severe than Parkinson's disease (PD). The most common forms are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB). They are characterised by rapid disease progression and the presence of features that are atypical for PD, such as early postural instability and dementia, severe autonomic failure, or pyramidal and cerebellar signs. Even though some of the therapeutic strategies reserved for PD patients may be adopted with variable success in atypical

parkinsonian syndromes, these patients often have a poor or transient response to dopaminergic treatment [5, 16]. Survival time is shorter and more complications occur in earlier stages and with higher degree of severity than in PD [17, 24, 27, 31]. The differential diagnosis of the various atypical parkinsonian syndromes can be challenging as they may have similar clinical presentations and misdiagnosis can be frequent, especially in the early phases [6]. However, the use of well-defined diagnostic criteria [12, 18, 23, 30], recently reviewed by the Task Force of the Movement Disorder Society [19], has improved the accuracy of diagnosis among these different conditions. A correct diagnosis is critical, as prognosis and symptomatic treatment of atypical parkinsonism are different from those of PD.

Secondary parkinsonism may be of various origins, the most common being drug-induced, or secondary to cerebrovascular diseases [36]. The so-called vascular parkinsonism (VP) is a heterogeneous clinical entity with a broad clinical spectrum and variable natural history.

Relatively little is known on the epidemiology and clinical characteristics of non-motor symptoms (NMS) in atypical and secondary parkinsonism. The PRIAMO study (PaRkinson dIsease non-MOtor symptoms) is an ongoing cross-sectional longitudinal prospective observational study, primarily designed to assess the prevalence and the evolution of NMS in a large cohort of patients affected by various parkinsonian syndromes, recruited in different Italian centres and followed up for 24 months [1]. In this

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paper we analysed the subgroup of patients with atypical and secondary parkinsonian disorders, focussing on the frequency of NMS, the level of cognitive dysfunction and their impact on the patients' quality of life, in comparison with PD.

Patients and methods

The methods of the PRIAMO study have been extensively reported in a previous paper [1]. Here we report details on the subpopulation of patients affected by atypical and secondary, namely vascular, parkinsonism.

Study design

PRIAMO is a 2-year ongoing longitudinal observational study that has consecutively enrolled 1,307 patients with a diagnosis of parkinsonism (prior or at baseline) during a 12-month period. The only exclusion criterion was essential tremor. A 24-month follow-up has been then performed. Consecutive subjects were enrolled between July 2005 and June 2006 at the 55 participating centres distributed throughout Italy. The Steering Committee for the project (see Appendix 1) designed the study and defined the instruments for data collection and disease evaluation. The study was approved by the Ethics Committees of the participating centres and all patients signed a written informed consent. Participating centres included academic and non-academic hospitals and were selected on the basis of their previous participation in clinical studies and their documented ability to administer the study tools (see Appendix 1).

Diagnosis of parkinsonian syndromes

The centres adopted the same diagnostic criteria for the diagnosis of PD [11], MSA [12], PSP [18], DLB [23], CBD [30], and VP [36]. Even if no formal attempt was made to standardise the diagnosis of other secondary parkinsonism, the identification of these patients was suggested to be made according to the operational criteria proposed by Morgante et al. [26].

Data collection and methods

Patients underwent a clinical examination, including tests investigating for possible NMS. NMS were evaluated by clusters (gastrointestinal symptoms, pain, urinary symptoms, cardiovascular autonomic symptoms, sleep disorders, fatigue, apathy, attention, skin disorders, psychiatric symptoms, respiratory symptoms, other symptoms), each one including 2–10 specific symptoms (Table 1). Specific

symptoms and domains were evaluated as “present or absent”, as reported by the patient in the month prior to the visit. During their interview, patients were usually assisted by a caregiver, in order to maximise data collection in case of severe cognitive impairment.

The usual PD scales were administered to all enrolled patients, even though not specific for atypical and secondary forms of parkinsonism, namely the modified Hoehn & Yahr scale (H&Y) [15] to evaluate overall disease severity, and the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) to evaluate patients' motor disability [8]. Cognitive function was investigated by means of two screening tools: the Mini-Mental State Examination (MMSE) [9] and the Frontal Assessment Battery (FAB) [7]. Quality of life was assessed by means of the Parkinson's Disease Questionnaire (PDQ-39) [28]. Depression was assessed by means of the Hamilton Depression Scale (HAM-D) [14]. All the scales used in the study are available and validated in Italian.

Statistical analysis

The prevalence of the different forms of parkinsonism was calculated and the demographic characteristics per diagnostic group were described. The frequency distribution of the different forms of parkinsonism-specific NMS and domains was calculated as the ratio between the total number of patients complaining of a symptom/domain and the total number of patients with that form of parkinsonism.

Only the fully completed scales were considered evaluable for the statistical analysis, i.e. no re-coding or interpolation of missing items was performed, except for MMSE. Missing responses to MMSE items were considered equal to 0, according to McDowell [22]; MMSE scales with ≥ 1 completed item were considered evaluable for statistical analysis. PDQ-39 and UPDRS-III total scores were calculated by summing single items. As for MMSE and FAB, we calculated age- and education-adjusted scores and used a cut-off of 23.8 and 13.48, respectively [2, 25].

We used mean and standard deviation (SD) when statistical distribution of quantitative variables was not skewed. In all other cases we applied non-parametric statistics, i.e. median and interquartile range (IQR). Comparisons were performed by means of analysis of variance for mean values and of Chi-square test or Fisher exact test for frequency distribution. The significance threshold was set to 0.05 with Bonferroni's correction in case of multiple comparisons. Data were analysed using SAS for Windows, release 8.2. Project management including data banking, quality control and statistical analysis, was performed by MEDIDATA (Modena, Italy). All data are shown as mean \pm SD.

Table 1 Non-motor symptoms (NMS): domains and single symptoms

Domain (number of symptoms per domain)	Symptoms
Gastrointestinal (7)	Drooling of saliva Dysphagia Nausea/vomiting Constipation Lowered number of evacuations (<3 times/week) Incomplete bowel emptying Incontinence
Pain (5)	Undefined pain Leg pain Abdominal pain Pain related to intake of drugs (e.g. levodopa) Shoulder pain
Urinary (3)	Urgency Frequency (voiding every 2 h) Nocturia
Postural symptoms due to orthostatic hypotension (2)	Lightheadedness/dizziness during the postural changes Falls because of syncope
Sleep (4)	Behavioural sleep disturbances (REM) Insomnia Excessive day time sleepiness Restless legs
Fatigue (1)	Fatigue limiting the patient's day activities
Apathy (3)	Loss of interest in surrounding matters Loss of interest in activities of daily living Awareness deficit
Attention/memory (3)	Difficulties to maintain concentration Short-term memory problems Forget to do daily things
Skin (2)	Seborrhoea Hyperhidrosis
Psychiatric symptoms (10)	Anhedonia Anxiety Panic attacks Aggressive behaviour Suicidal ideas Nervousness Frightened without reason Sadness/depression Delirium Hallucinations
Respiratory (3)	Dyspnea Cough Stridor

Table 1 continued

Domain (number of symptoms per domain)	Symptoms
Other symptoms (5)	Olfactory dysfunction Dysgeusia Diplopia Weight change Sexual dysfunction

Results

Demographic characteristics of the patients, age at disease onset and duration of disease, divided by diagnosis, are summarised in Table 2. Five patients were diagnosed with drug-induced parkinsonism; since they represent a very small set of patients, they were not analysed in this paper. A total of 172 patients had a diagnosis of atypical or secondary parkinsonism: 83 had VP, 34 MSA, 30 PSP, 14 DLB and 11 CBD. The remaining 1130 patients of the PRIAMO study had PD. For all forms of parkinsonism, except for CBD, prevalence of males was higher than females, but the difference was not statistically significant ($p > 0.05$). Mean age was higher in VP and DLB patients and lower in PD and MSA patients (significant Tukey's t values were for VP vs. PD and vs. MSA, DLB vs. MSA). VP and DLB patients were also significantly older at disease onset than PD and MSA patients (significant Tukey's t test at 0.05 threshold), while disease duration was significantly shorter for VP and MSA as compared to PD patients (significant Tukey's t test at 0.05 threshold). Severity of disease, as assessed by the H&Y scale (Table 3), was significantly higher in atypical parkinsonisms than in PD and VP patients ($p \leq 0.001$). Motor disability, measured by UPDRS, was significantly worse in MSA and CBD than in PD (significant Tukey's t test at 0.05 threshold for PD vs. MSA and CBD). 93% ($N = 13$) of DLB, 82% ($N = 926$) of PD, 74% ($N = 25$) of MSA, 67% of PSP ($N = 20$) and VP ($N = 56$) and 45% of CBD patients ($N = 5$) were under pharmacological treatment.

Concerning the prevalence of non-motor symptoms (NMS) in the different diagnostic groups, the mean values of domains and specific symptoms are summarised in Fig. 1. Table 4 summarises the frequency of the NMS domains in the different forms of parkinsonism. Gastrointestinal (GI) symptoms were most frequent in DLB, MSA and PSP; pain and urinary symptoms as well as postural symptoms due to orthostatic hypotension were most frequent in MSA. On the other hand, sleep disturbances in CBD and fatigue and apathy in PD were much less frequent than in all the other diagnostic groups. Attention and

memory impairment were most frequent among DLB patients and again least frequent in PD. Frequency of psychiatric symptoms was highest in DLB, lowest in CBD and similar in all other forms.

The frequency of patients with a low score at MMSE (cut-off value ≤ 23.8) is reported in Fig. 2. The most compromised are DLB and CBD patients, the less compromised are MSA and PD patients, while the intermediate group consists of PSP and VP patients, ($p < 0.001$ among diagnoses). Also considering the FAB (cut-off value < 13.48), the frequency of patients with a low score had a similar ranking among diagnoses (data not shown). Depression, as assessed by the Hamilton depression scale, was mild in all diagnostic groups, with mean scores ranging from 7.91 (SD 5.65) in PD to 11.34 (SD 6.97) in MSA patients (significant Tukey's t test at 0.05 threshold).

Quality of life was evaluated by the specific Parkinson's Disease Questionnaire (PDQ-39): the lower the score, the higher the patients' quality of life. The mean scores in the different forms of parkinsonism are depicted in Fig. 3: MSA and PSP patients reported a significantly worse quality of life compared to PD patients (significant Tukey's t test at 0.05 threshold).

Discussion

NMS in parkinsonism as a whole and, in particular, in atypical and secondary forms (particularly VP), have been relatively neglected in the neurological literature until recent years. This paper was aimed at assessing the prevalence and characteristics of NMS in those patients with atypical and vascular parkinsonism enrolled in the large observational PRIAMO study [1]. In these disorders, we found a higher prevalence of NMS as compared to the more common PD. This result is not unexpected given that atypical parkinsonian syndromes are characterised by an earlier and more severe involvement of areas outside the basal ganglia [4, 35], such as the cerebellar cortex and fibres, the oculomotor nuclei in the brainstem, the spinal cord, the limbic lobe and the neocortex [16]. MSA and DLB had the highest number of NMS domains and symptoms, respectively. Considering the type of NMS per diagnostic group (Table 4), gastrointestinal (GI) symptoms were most frequent in DLB, MSA and PSP. It has been previously reported that MSA patients often show GI problems, initially mainly dysphagia, which is a prominent characteristic also of PSP [20, 34]. Half of DLB

Table 2 Demographic features, divided according to diagnosis

Diagnosis	Patients N (%)	Male N (%)	Age ^a	Age at disease onset ^b	Disease duration ^c
VP	83 (6.4)	52 (62.7)	74.2 \pm 7.1	69.4 \pm 7.7	4.4 \pm 3.4
MSA	34 (2.6)	21 (61.8)	63.5 \pm 8.7	59.8 \pm 8.4	3.5 \pm 1.8
PSP	30 (2.3)	16 (53.3)	69.7 \pm 6.3	66.6 \pm 6.4	3.5 \pm 3.1
DLB	14 (1.1)	12 (85.7)	74.1 \pm 6.5	69.6 \pm 6.2	4.2 \pm 3.1
CBD	11 (0.8)	5 (45.5)	70.1 \pm 10.2	66.2 \pm 10.5	2.5 \pm 1.1
PD	1130 (86.8)	678 (60.0)	67.3 \pm 9.4	60.7 \pm 10.6	6.6 \pm 5.1

PD Parkinson's disease, VP vascular parkinsonism, MSA multiple system atrophy, PSP progressive supranuclear palsy, DLB dementia with Lewy bodies, CBD corticobasal degeneration. Age and disease duration are shown as mean number of years \pm SD

^a ANOVA's $p < 0.0001$

^b ANOVA's $p < 0.0001$

^c ANOVA's $p < 0.0001$

Table 3 H&Y scale and UPDRS III scores, split by diagnosis

Diagnosis	H&Y score median (IQR)	Pearson's correlation between H&Y score and PDQ-39 total score	UPDRS-III score Mean (SD) ^a	Pearson's correlation between UPDRS-III and PDQ-39 total score
PD	2.0 (1.5–2.5)	0.449 ($p < 0.0001$)	24.89 (13.49)	0.497 ($p < 0.0001$)
VP	2.0 (1.5–3.0)	0.396 ($p = 0.0009$)	29.41 (14.47)	0.452 ($p = 0.0003$)
MSA	3.0 (2.5–3.0)	0.457 ($p = 0.0164$)	36.23 (14.33)	0.605 ($p = 0.0008$)
PSP	3.0 (2.5–3.0)	0.032 ($p > 0.05$)	30.54 (9.36)	-0.004 ($p > 0.05$)
DLB	2.75 (2.0–3.0)	0.324 ($p > 0.05$)	35.54 (15.16)	0.399 ($p > 0.05$)
CBD	3.0 (2.5–3.0)	0.799 ($p = 0.0173$)	42.22 (23.47)	0.969 ($p = 0.0003$)

^a ANOVA's $p < 0.0001$

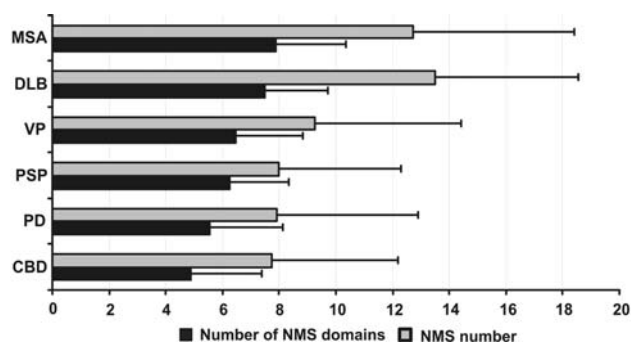


Fig. 1 Non-motor symptoms (NMS): mean number of domains and symptoms, divided according to diagnosis

patients were on anti-psychotics (vs. <6% of the other diagnoses), which might contribute to the high prevalence of GI symptoms. Pain was reported mainly by MSA patients, followed by PD and VP patients. Recently, pain, including musculoskeletal and visceral pain, has been described as fairly common in MSA and PD, even at disease onset [4, 10, 29, 32], and in VP, where it reflects the location of the cerebrovascular lesion. Interestingly, pain and other sensory disturbances are not included in the current diagnostic criteria of MSA, which conversely include, among NMS, urinary symptoms and orthostatic hypotension, which were actually present in 91 and 53% of our MSA patients, respectively [13]. Sleep disturbances were present in approximately 70% of patients in all diagnostic groups but CBD (only 36%). A recent review on the clinical differential diagnosis of parkinsonism [6] recognises sleep abnormalities, especially REM sleep behaviour disorders, as a common symptom in parkinsonism, especially PD and MSA. The generally higher prevalence of fatigue in atypical forms as compared to PD is probably related to motor disability, which is more severe in atypical

parkinsonism, making patients slower and more easily tired. The prevalence of skin and respiratory disorders was rather low in all forms, ranging between 10 and 30%, while attention and memory impairment were largely most prevalent among DLB patients, consistently with the diagnostic feature of dementia. Psychiatric manifestations are also extremely common in DLB—predominantly visual hallucinations, delusions, apathy and anxiety, usually present early in the course of the disease and tending to persist—as well as cognitive impairment. This is a core feature of DLB—typically manifesting with confusion episodes, substantial attention deficit and fronto-subcortical dysfunction [23]. In our population, CBD patients also showed selective cognitive dysfunction, as assessed by the MMSE and the FAB, which are prevalently focussed on memory and frontal function, respectively.

Concerning motor disability, the UPDRS-III score not unexpectedly mirrors the H&Y stage, with atypical parkinsonism patients obtaining a higher score when compared to VP and PD patients. It is also worth remarking that, from a clinical point of view, the difference between the median H&Y stage around 3, registered in atypical parkinsonism, and the median stage of 2 assessed in PD and VP patients, is critical, as this 1-point difference is associated with a balance impairment and an increase in falls, with subsequent increased risk of fractures and poorer prognoses [15]. Actually, patients with PSP, CBD and MSA have prominent balance difficulties [33]; in particular, early falls in the first year of the disease are a cardinal feature of PSP [20], while in PD postural instability and consequent falls usually occur later in the course of the disease [15].

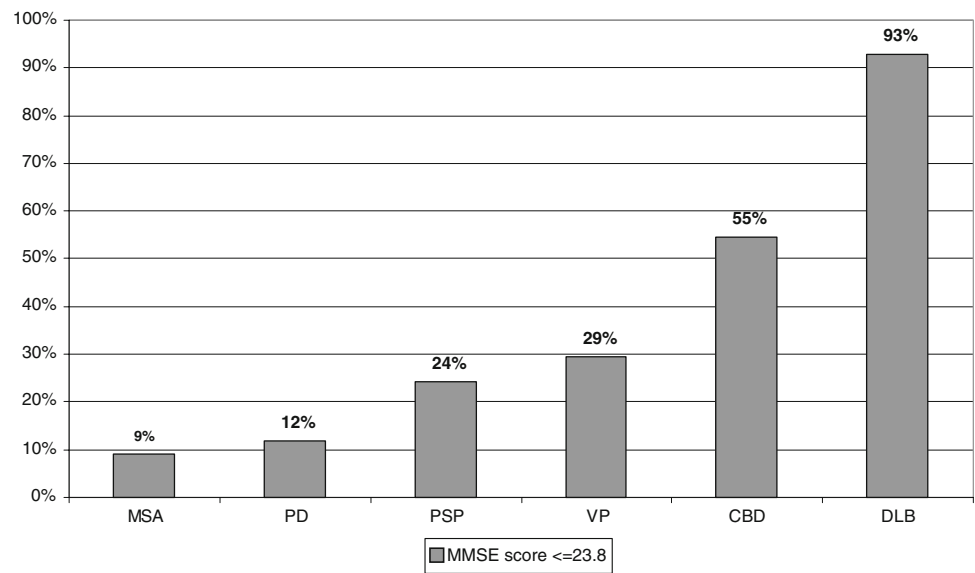
In our series, we also evaluated QoL by means of the specific PDQ-39 questionnaire (Fig. 3). Patients with atypical parkinsonism report the worst QoL, with no

Table 4 Frequency of the different NMS domains, divided according to diagnosis

Diagnosis	PD N (%)	VP N (%)	MSA N (%)	PSP N (%)	CBD N (%)	DLB N (%)
GI symptoms	695 (61.7)	54 (65.1)	28 (82.4)	24 (80.0)	7 (63.6)	12 (85.7)
Pain	690 (61.1)	50 (61.0)	24 (70.6)	12 (40.0)	4 (36.4)	7 (50.0)
Urinary symptoms	654 (58.0)	54 (65.1)	30 (90.9)	16 (53.3)	6 (54.6)	11 (78.6)
Postural symptoms ^a	165 (14.7)	15 (18.3)	18 (54.6)	4 (13.3)	0 (0.0)	3 (21.4)
Sleep disturbances	732 (65.0)	58 (70.7)	23 (67.7)	23 (76.7)	4 (36.4)	11 (78.6)
Fatigue	669 (59.4)	65 (79.3)	28 (82.4)	24 (80.0)	6 (54.6)	10 (71.4)
Apathy	363 (32.2)	35 (42.2)	22 (64.7)	20 (66.7)	7 (63.6)	12 (85.7)
Attention/memory impairment	515 (45.6)	61 (73.5)	23 (67.7)	19 (63.3)	7 (70.0)	13 (92.9)
Skin disorders	283 (25.1)	27 (32.5)	8 (23.5)	5 (16.7)	3 (27.3)	4 (28.6)
Psychiatric disorders	764 (67.8)	64 (77.1)	27 (79.4)	22 (73.3)	6 (54.6)	13 (92.9)
Respiratory disorders	202 (17.9)	21 (25.3)	12 (35.3)	6 (20.7)	1 (9.1)	4 (28.6)
Others	547 (48.6)	32 (39.0)	25 (75.8)	13 (43.3)	3 (27.3)	5 (35.7)

^a Due to orthostatic hypotension

Fig. 2 Percentage of patients with MMSE score under the cut-off value (≤ 23.8), divided according to diagnosis



PDQ-39 (Mean score)

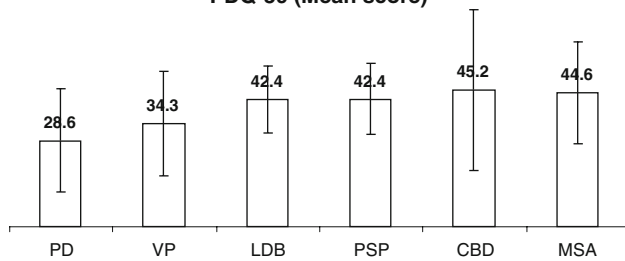


Fig. 3 Mean \pm SD PDQ-39 Summary Index score per diagnosis

significant differences among the different forms, whereas PD and VP patients have a better QoL. QoL ranking seems to mirror the severity of the disease—the higher the H&Y score, the lower the QoL—but not strictly the prevalence of NMS, which was lowest in CBD. In addition, UPDRS-III score was also positively correlated with PDQ-39 scores for CBD, MSA, PD and VP. These results might be affected by the fact that H&Y staging and UPDRS, which are specifically designed for PD patients, were used to assess disease severity in atypical and secondary parkinsonism. The choice of using such instruments was due to the unavailability of reliable similar tools for the other diagnostic groups.

Unfortunately, due to the small sample size in this group of subjects, a specific analysis on the type of NMS with the greatest impact on the QoL for each diagnostic group would not have had been powerful enough to draw any conclusions.

The PRIAMO study found a high prevalence of NMS in all patient groups. Based on these findings, it might be concluded that the presence of specific NMS does not help in differentiating parkinsonian syndromes, the exception being autonomic features which are strongly associated

with MSA. The clinical features of patients affected by MSA and PSP who were included in the PRIAMO study may now be compared to the larger cohort of patients affected by the same conditions recently reported by the NNIPPS study [3]. They have remarkably similar demographic features, such as a mean disease duration, which in the NNIPPS study was around 4 years for both MSA and PSP. However, in contrast with our study, in the NNIPPS study no robust measurement of motor impairment (such as the motor part of the UPDRS) or QoL measures were used. This does not allow us to draw any conclusion on the relationship between motor impairment, NMS and QoL measures.

A confounding factor for the prevalence of NMS is dopaminergic therapy, which may aggravate some symptoms (e.g. psychiatric, gastrointestinal or autonomic symptoms) but may alleviate others, such as apathy or pain. However, since the efficacy of dopaminergic drugs is often poor in atypical and secondary parkinsonian disorders, a smaller number of patients—as compared to PD—is chronically treated with these compounds and usually with a lower mean daily dose. As a consequence, the risk of confounding the prevalence of NMS through the use of dopaminergic drugs is actually lower in these conditions than in PD. However, since specific and novel therapeutic approaches for atypical forms have been recently reported and are currently under evaluation [3, 31, 34], a change in this trend can be expected in the next future for these patients.

This study has some limitations. Despite the rather large population of patients with parkinsonism included in the survey, the few subjects with drug-induced parkinsonism were not analysed (also because of the inherent difficulties in defining this diagnostic category) and for some atypical

forms (DLB, CBD) the sample size is too small to make reliable associations and draw definite conclusions. Another limitation may be the lack of control on the reliability of the different diagnoses. However, it has to be pointed out that diagnostic criteria were well defined and that the PRIAMO study group included only centres that are specialised in movement disorders and have experience in the use of specific diagnostic and evaluation tools for these disorders. A further methodological weakness is that the use of evaluation tools which are specific for PD but not for atypical parkinsonism may have led to an underestimation of NMS and disease severity in the latter group of diseases. Finally, a possible ceiling effect of cognitive measures (FAB and MMSE) cannot be excluded. Indeed such measures mainly cover memory, language and executive skills, but they are not sensitive enough to detect many cases of mild cognitive impairment, which is common in PD patients despite normal MMSE scores [21]. Keeping these limitations in mind, MMSE and FAB were chosen because they are standardised and easy-to-administer screening tools.

Conclusions

This survey of a large population of unselected patients with different forms of parkinsonism confirms that VP is possibly the most common type after PD, while atypical parkinsonian disorders are much rarer, and generally more severe than PD and VP. NMS, a specific aspect of parkinsonism evaluated by the PRIAMO study, have a diverse domain distribution across the different diagnoses, generally consistent with the prevalent clinical features of the disease. Atypical parkinsonism patients report the worst QoL, with no significant differences among the various forms, whereas PD and VP patients have a better QoL. This seems to mirror the ranking of severity of parkinsonism. Novel and currently under evaluation therapeutic approaches in atypical forms may warrant further investigation, in the near future, taking into consideration also the different NMS profile in each of the atypical parkinsonian patient populations.

Acknowledgments This study was supported by an educational grant issued by Boehringer-Ingelheim, Italy. L. Simoni is an employee of Medidata s.r.l.

Appendix I: The PRIAMO study group

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