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ORIGINAL COMMUNICATION

Non-motor symptoms in Huntington's disease: a comparative study with Parkinson's disease

Tatiana Aldaz[1] · Pasquale Nigro[1] · Almudena Sánchez-Gómez[1] · Celia Painous[1] · Lluís Planellas[1] · Pilar Santacruz[1,4] · Ana Cámara[1] · Yaroslau Compta[1,2,3] · Francesc Valldeoriola[1,2,3] · Maria J. Martí[1,2,3] · Esteban Muñoz[1,2,3,4]

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Abstract

Background/aims The presence of non-motor symptoms in Huntington's disease (HD) has not been systematically assessed so far. Our objective was to know their prevalence and to compare it with a cohort of patients with Parkinson's disease (PD).

Materials and methods Participants were consecutively recruited from our outpatient clinic. They were assessed through the motor part of the Unified Huntington's Disease Rating Scale, the motor part of the Unified Parkinson's Disease Rating Scale, the total functional capacity scale and the PD non-motor symptoms questionnaire.

Results We enrolled 123 participants: 53 HD, 45 PD and 25 healthy controls (HC). Non-motor symptoms were significantly more prevalent in HD patients than in HC. The most frequent non-motor symptoms in HD, involving more than 50% of patients, were attentional deficits, apathy, dysphagia, memory complaints, depression falls, insomnia and urinary urgency. The total score of non-motor symptoms correlated with disease duration, total functional capacity and disease stage. HD scored significantly higher than PD in 11 items (dysphagia, constipation, bowel incontinence, faecal tenesmus, weight loss, memory, apathy, attention, falls, nightmares, delusions) and in four domains (cognitive, hallucinations and delusions, digestive and cardiovascular). PD did not score significantly higher than HD in any domain.

Conclusions HD patients have a high prevalence of non-motor symptoms, which is even higher than in PD, and correlates with disease progression.

Keywords Huntington's disease · Parkinson's disease · Non-motor symptoms · PD NMSQuest

Introduction

Huntington's disease (HD) is an autosomal-dominant inherited neurodegenerative disease that results from expanded CAG triplet repeats in the *HTT* gene on the short arm of chromosome 4 [1]. Usually, the disorder becomes clinically detectable between 35 and 45 years of age, although it can manifest at any time between infancy and senescence [2]. HD has an insidious progression and is mainly characterized by involuntary movements such as chorea and dystonia, motor slowing and clumsiness, gait and balance disturbances, behavioural alterations, and progressive cognitive decline. According to neuropathological studies, the loss of medium spiny gabaergic striatal neurons is the most characteristic finding of the disease [3]. However, there is growing evidence that the disease not only involves the striatum but also other areas of the central nervous system including the cerebral neocortex and allocortex, thalamus, hypothalamus, pallidum, brainstem and cerebellum [4], and even the autonomic nervous system [5], the skeletal and cardiac systems [6, 7], and the gastrointestinal tract [8], among others [9, 10].

HD patients can complain of other non-motor symptoms (NMS) different from behavioural and cognitive abnormalities. However, their clinical assessment is often limited to individual symptoms rather than addressing the whole picture. In addition, there are no specific instruments for the

✉ Esteban Muñoz
jemunoz@clinic.cat

1 Parkinson's Disease and Movement Disorders Unit, Department of Neurology, Hospital Clinic of Barcelona, Villarroel 170, 08036 Barcelona, Catalonia, Spain

2 Institut de Neurociències, University of Barcelona, Barcelona, Spain

3 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

4 European Huntington's Disease Network (EHDN), Barcelona, Spain

screening of NMS in HD. For these reasons, their prevalence is not well known in contrast to what happens with Parkinson's disease (PD), where available evidence indicated that over 90% of patients can suffer from NMS. Otherwise, NMS in PD have been recognized as an important cause of poor quality of life for both patients and caregivers [11].

The aim of the present study was to assess, through a standardized questionnaire, the PD non-motor symptoms questionnaire (NMSQuest) [12], the prevalence of NMS in HD patients and to compare it with that found in age-matched healthy controls (HC), and patients affected by PD to get a global view on the magnitude of the problem.

Methods

Participants

Patients were consecutively recruited from our outpatient clinic of Parkinson's disease and other movement disorders at Hospital Clinic of Barcelona. Most of the HD patients were participants of the ENROLL-HD study. HC, age-matched to HD patients, were recruited from volunteers including non-mutation carrier belonging to the same family of HD participants, partners, caregivers or acquaintances.

The inclusion criteria for HD patients were the existence of a positive HD genetic test (CAG repeats > 40) associated with unequivocal motor symptoms of the disease with a score ≥ 10 in the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) [13]. For PD patient inclusion, the diagnosis of idiopathic PD according to MDS Clinical Diagnostic Criteria [14] was considered mandatory. As age-matching of HD with PD was not possible because of their different age at disease presentation, we decided to match them according to disease duration.

Subjects with concomitant cardiovascular, prostatic or gastrointestinal diseases that could be associated with any of the NMS assessed were excluded.

The study was approved by the Hospital Clinic Ethical Committee and all participants signed the informed consent before being included.

Evaluations

The design of this study was cross-sectional. Demographic and clinical data of patients and HC were collected. The clinical condition was assessed through the UHDRS-TMS [13] for HD, the Movement Disorders Society-Unified Parkinson's Disease Rating Scale part-III (MDS-UPDRS-III) [15] and the Hoehn & Yahr stage for PD patients, and the Total Functional Capacity (TFC) [13] for the three groups.

The HD stage was classified according to the TFC score as follows: stage 1: TFC = 13 − 11; stage 2: TFC = 10 − 7; stage 3: TFC = 6 − 4; stage 4: TFC = 3 − 1; and stage 5: TFC = 0 [16, 17]. Stages 1–2 were considered slight–mild stages and stages 3–5 were considered moderate–severe stages of the disease [17].

Non-motor symptoms were evaluated using the PD NMS-Quest, a standardized 30-item instrument, featuring "yes or no" responses. The questionnaire covers nine NMS domains: digestive (seven items), urinary (two items), apathy/attention/memory (three items), hallucinations/delusions (two items), depression/anxiety (two items), sexual function (two items), cardiovascular (two items), sleep disorder (five items) and miscellaneous (five items) [18]. In patients with cognitive impairment, the responses were obtained through their caregivers. Although the NMSQuest is recommended in PD assessment by many learned societies and patient groups [19], the items cover a broad area of non-motor domains that may also be affected in HD [20].

Data analysis

The prevalence of NMS was calculated using the percentage of "yes" responses for each item. To analyze the prevalence for domains, the sum of positive responses of the items of each domain was transformed to a percentage on the maximum number of possible positive responses [18]. Mann–Whitney or Kruskal–Wallis tests were used for comparisons between groups. Categorical variables were analyzed using the chi square. Significance was set at $p < 0.05$. Correlations of the NMS total score with different variables, including treatment, were assessed through the Spearman rank correlation coefficient. Correlations were considered weak for coefficient values < 0.30; moderate, for 0.30–0.59; and strong when coefficient values were 0.60 or higher [18]. Statistical analysis was performed using IBM SPSS Statistics software, version 24.0 (Armonk, NY: IBM Corp).

Results

A total of 123 participants were consecutively assessed (53 HD, 45 PD, and 25 HC). Demographic and clinical features of participants are included in Table 1. Mean age was not different in HD and HC ($p = 0.34$), but PD were older than HD ($p < 0.000$). There was no difference regarding disease duration between HD and PD groups ($p = 0.703$). The mean score of TFC was 6.85 ± 4.0 in HD and 8.84 ± 2.93 in PD ($p = 0.007$). The median of Shoulson and Fahn stage in HD patients was 2, and the median of Hoehn and Yahr stage in PD was also 2. The distribution of patients by disease stage is included in Table 1. Thirty HD patients were in slight–mild stages (Shoulson and Fahn 1 or 2) and 23 in moderate–severe stages of the disease (Shoulson and Fahn > 3).

Table 1 Demographic and clinical features of patients and controls

	HD	PD	HC	P^a
Number	53	45	25	–
Female/male	29/24	22/23	14/11	0.796
Age (mean ± SD)	52.3 ± 12.15	66.13 ± 9.95	55.4 ± 15.15	< 0.000
Disease duration (mean ± SD)	9.62 ± 5.34	10.11 ± 6.7		0.703
TFC (mean ± SD)	6.85 ± 4.03	8.84 ± 2.93		0.007
UHDRS-TMS (mean ± SD)	42.08 ± 19.8	–		–
UPDRS-III "on" (mean ± SD)	–	29.07 ± 16.3		–
Median of disease stage (interquartile range)	2 (2–4)[b]	2 (2–2)[c]		–
Distribution of patients by disease stage (%)	1: 17[b]	1: 4.4[c]		–
	2: 39.6	2: 73.3		–
	3: 13.2	3: 13.3		–
	4: 22.6	4: 6.7		–
	5: 7.5	5: 2.2		–
Treatment				
Amantadine	19	7	0	0.02
Tetrabenazine	15	0	0	0.000
Atypical neuroleptics	21	3	0	0.000
Antidepressants	27	9	0	0.001
Benzodiazepines	21	13	2	0.237
Antiepileptics	11	1	0	0.005
Levodopa	1	41	0	0.000
Dopamine agonist	0	24	0	0.000
MAO-B inhibitors	0	20	0	0.000
COMT inhibitors	0	13	0	0.000

HD Huntington's disease, *PD* Parkinson´s disease, *HC* healthy controls, *SD* standard deviation, *TFC* total functional capacity scale, *UHDRS-TMS* Unified Huntington's Disease Rating Scale Total Motor Score, *UPDRS-III* Unified Parkinson's Disease Rating Scale part III

[a]HD vs. PD

[b]Shoulson and Fahn stage

[c]Hoehn and Yahr stage in "on" state

HD versus HC

The mean NMS total score was significantly higher in HD patients (10.22 ± 5.54) than in HC (1.8 ± 2.6) ($p < 0.000$). At least one NMS was present in 56% of HC and in 100% of HD. The frequency of "yes" responses was also significantly higher in HD than in HC in 21 items (Table 2). The assessment by domains showed that HD patients scored higher than HC in all the domains (Table 3). The most frequent NMS, observed in more than 50% of the HD patients, were dysphagia (swallowing), urinary urgency, memory complaints (remembering), apathy (loss of interest), attentional deficiencies (concentrating), depression (sad, blues), falls and insomnia.

Correlations of NMS in HD

In HD patients, NMS total score showed a moderate positive correlation with disease duration ($r = 0.34$; $p = 0.015$) and disease stage ($r = 0.32$; $p = 0.023$), and a moderate negative correlation with the TFC score ($r = -0.4$; $p = 0.004$) (Fig. 1). We found no correlation between NMS total score and age or UHDRS-TMS.

None of the treatments showed correlation with the NMS total score. However, we searched for the presence of correlations between treatment and individual items to assess the possibility that some of these items could be related to treatment. Thus, amantadine treatment showed a weak negative correlation with the presence of nausea and vomiting ($r = -0.278$; $p = 0.048$), apathy (r=-0.287; $p = 0.039$), depression ($r = -0.289$; $p = 0.038$) and diurnal somnolence ($r = -0.299$; $p = 0.031$). Tetrabenazine treatment correlated moderately with constipation ($r = 0.417$; $p = 0.002$) and showed a weak negative correlation with insomnia ($r = -0.278$; $p = 0.048$). Treatment with neuroleptics correlated weakly with libido-related symptoms (r=-0.283; $p = 0.044$). Antidepressant treatment correlated moderately with nausea and vomiting ($r = 0.330$; $p = 0.017$), and

Table 2 Comparison of the presence of non-motor symptoms between slight–mild and moderate–severe stages of HD, and between HD, HC and PD groups

Non-motor symptoms	HD Stages 1–2 ($n=30$)	HD Stage ≥ 3 ($n=23$)	p^a	HD ($n=53$)	HC ($n=25$)	PD ($n=45$)	p^b	p^c
Dribbling	7	7	0.561	14	0	14	0.005	0.608
Taste/smelling	4	3	0.728	7	2	27	0.5	0.000
Swallowing	10	23	0.000	33	1	10	0.000	0.000
Vomiting	3	3	0.728	6	2	4	0.65	0.691
Constipation	8	12	0.057	20	1	7	0.002	0.014
Bowel incontinence	3	10	0.005	13	1	3	0.084	0.019
Bowel emptying incomplete	11	6	0.413	17	1	4	0.006	0.006
Urgency	13	14	0.205	27	4	15	0.003	0.079
Nocturia	13	9	0.758	22	4	31	0.026	0.006
Pain	5	3	0.714	8	0	8	0.04	0.720
Weight lost	5	11	0.014	16	0	5	0.002	0.021
Remembering	18	15	0.033	33	4	13	0.000	0.001
Loss of interest	18	16	0.471	34	0	18	0.000	0.029
Hallucinations	2	6	0.050	8	0	4	0.04	0.350
Concentrating	21	18	0.499	39	2	13	0.000	0.000
Sad/blues	17	13	0.992	30	5	20	0.002	0.230
Anxiety	9	9	0.486	18	4	9	0.1	0.123
Sex drive	11	6	0.413	17	2	16	0.019	0.766
Sex difficulty	11	5	0.240	16	3	10	0.074	0.343
Dizziness	9	5	0.498	14	1	7	0.019	0.191
Falling	13	14	0.744	27	0	9	0.000	0.001
Daytime sleepiness	6	1	0.095	7	0	9	0.057	0.364
Insomnia	16	11	0.691	27	2	19	0.000	0.340
Intense vivid dreams	16	6	0.046	22	2	9	0.002	0.009
Acting out during dreams	14	5	0.060	19	1	15	0.002	0.726
Restless legs	8	3	0.225	11	1	10	0.056	0.860
Swelling	1	8	0.002	9	1	5	0.110	0.407
Sweating	6	8	0.226	14	0	16	0.005	0.327
Diplopia	0	0		0	0	0	-	
Delusions	7	7	0.561	14	0	0	0.005	0.000

[a]Slight–mild stages vs. moderate–severe stages of HD

[b]HD vs. HC

[c]HD vs. PD

Table 3 Comparison of the domains of the PD NMSQuest between HD, HC and PD groups

	Digestive	Urinary	Attention/apathy/memory	Hallucinations/delusions	Depression/anxiety	Sexual	Cardiovascular	Sleep	Miscellany
Between groups	0.000	0.001	0.000	0.001	0.017	0.041	0.000	0.000	0.000
HD vs. HC	0.000	0.003	0.000	0.002	0.005	0.035	0.000	0.000	0.000
HD vs. PD	0.043	0.538	0.000	0.007	0.113	0.810	0.002	0.921	0.405
PD vs. HC	0.000	0.000	0.001	0.127	0.142	0.009	0.013	0.000	0.000

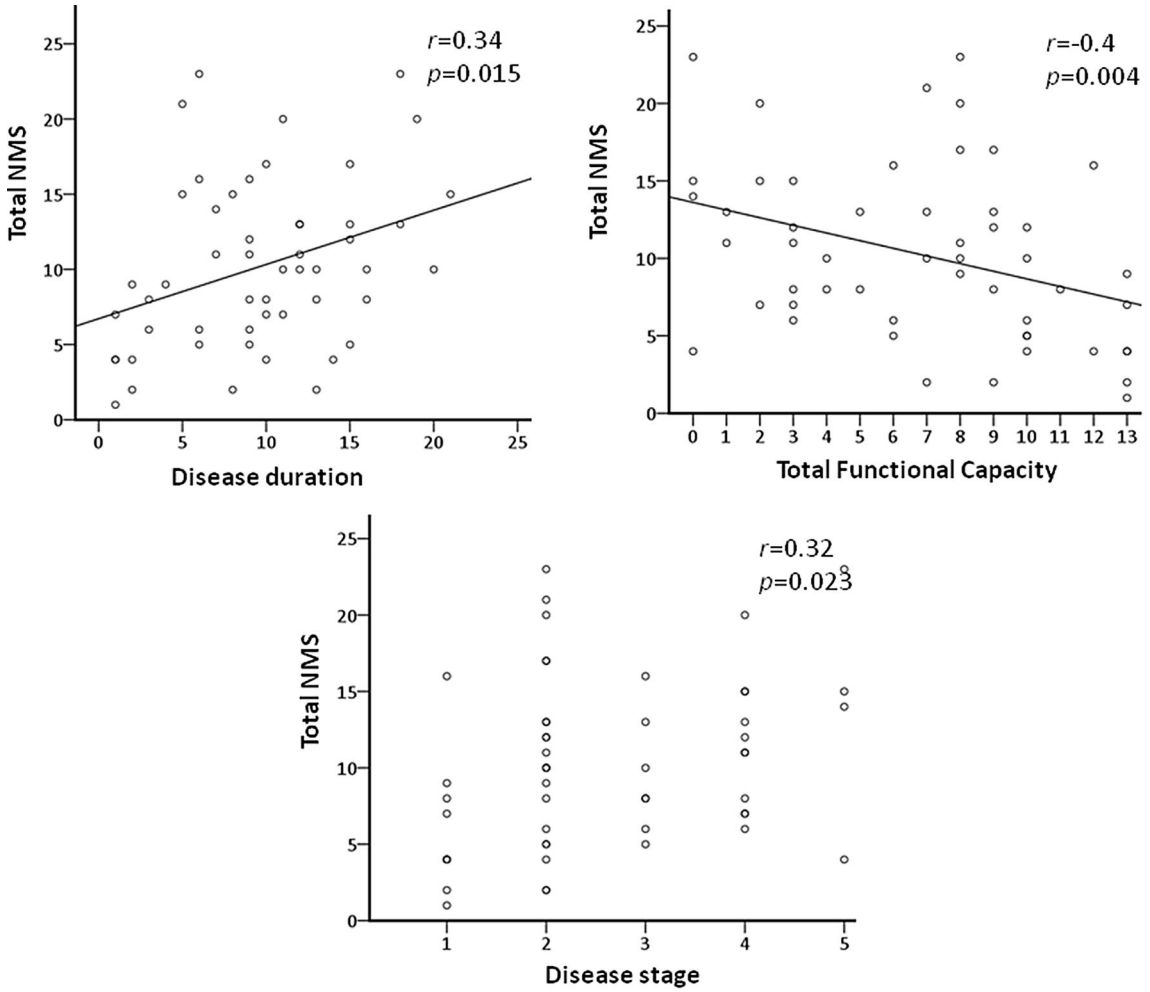

Fig. 1 Correlation of NMS total score with disease duration, total functional capacity score and disease stage

dizziness ($r=0.307$; $p=0.027$), but not with the presence of depressive symptoms. Benzodiazepine treatment showed a moderate correlation with drooling ($r=0.364$; $p=0.008$) and nocturia ($r=0.409$; $p=0.003$), and a weak correlation with libido ($r=0.283$; $p=0.044$). However, it did not correlate with anxiety or insomnia. Finally, treatment with antiepileptic drugs as mood stabilizers correlated weakly with the presence of nausea and vomiting ($r=0.291$; $p=0.036$), and hallucinations ($r=0.299$; $p=0.031$).

Comparison of HD patients by stages

When comparing slight–mild with moderate–severe HD stages, dysphagia, bowel incontinence, memory complaints and swelling of legs resulted significantly more frequent in the latter, and weight changes and intensive vivid dreams in the former subgroup ($p<0.05$) (Table 2). Nevertheless, the mean NMS total score did not reach statistical significance between slight-mild (9.5 ± 6) and moderate-severe (11.17 ± 4.82) stages ($p=0.229$).

HD versus PD patients

The mean total score of the NMSQuest in HD patients (10.22 ± 5.54) was higher than in PD patients (7.4 ± 4.29) ($p=0.002$). Eleven items out of the 30 that make up the NMSQuest were significantly more prevalent in HD than in PD patients (Table 2). These items were in the order of frequency: attentional deficiencies ($p<0.000$); apathy ($p=0.03$); memory complains ($p=0.001$); dysphagia ($p<0.000$); falls ($p=0.001$); intense, vivid or frightening dreams ($p=0.009$); constipation ($p=0.014$); bowel emptying incomplete ($p=0.006$); weight changes ($p=0.022$); delusions ($p<0.000$); and bowel incontinence ($p=0.02$).

Only two NMS were more frequent in PD patients than in HD patients: nocturia ($p=0.006$) and loss of smell or taste ($p<0.000$).

The analysis by domains, performed as previously described [15], showed that HD scored higher than PD in four of the nine domains of the NMSQuest: the cognitive (apathy/attention/memory) ($p < 0.000$), hallucinations and delusions ($p = 0.007$), digestive ($p = 0.043$) and cardiovascular domains ($p = 0.00$) (Table 3; Fig. 2). PD did not score higher than HD in any domain.

Discussion

There is growing awareness that HD patients may suffer from different NMS, but their prevalence is not well known. This fact could be related, at least in part, with the lack of a comprehensive screening instrument addressing the range of NMS in HD. For this reason, and to be able to compare HD with PD, we have used the PD NMSQuest to evaluate the presence of NMS in both diseases.

The results of our study suggest that a wide range of NMS occurs across all stages of HD, with dysphagia, urinary urgency, memory complaints, apathy, attentional deficiencies, depression, falls and insomnia being the most frequent symptoms. The recognition of these symptoms is important because some of them are treatable, which may contribute to improve the quality of life of the patients. In addition, we have found that NMS score correlates with disease duration, TFC score and disease stage, supporting that the prevalence of these symptoms increases as disease progresses. When comparing HD to PD, the prevalence of NMS was higher in HD, despite PD being older than HD. Older age has been associated with a higher prevalence of NMS in PD independently of disease duration [18]. NMS in PD are currently considered an integral part of the clinical spectrum of disease [21]. However, except for cognitive and behavioural disturbances, this consideration has not been made in HD so far.

In the clinical setting, dysphagia is a frequent complaint of patients with HD and can lead to aspiration pneumonia, that is one of the main causes of death in HD [22]. Nevertheless, there are few studies addressing this topic. Thus, the real prevalence of dysphagia and in what stage of the disease it becomes clinically apparent are not well known [23]. In our study, dysphagia was present in 62% of HD patients and was more frequent in advanced stages of the disease, but it was also reported in 33% of patients in early stages. We also found that dysphagia was more frequent in HD than in PD, suggesting that deglutory mechanisms [23] are more severely affected in HD. Other digestive symptoms such as constipation, bowel incontinence and rectal tenesmus were also significantly more frequent in HD than in PD patients. Studies in animal models of HD have demonstrated that mutant huntingtin is expressed in nearly all tissues, including the gastrointestinal tract, and accumulates, similar to what happens with alpha-synuclein in PD [24], in the form of aggregates in the enteric neurons of stomach, duodenum and rectum [8, 25]. This finding may explain, at least in part, some of the gastrointestinal symptoms that HD patients can suffer [8]. Constipation is a well-known adverse effect in patients treated with tetrabenazine [26], neuroleptics [27], antidepressants [28] and amantadine [29]. Although constipation only correlated with tetrabenazine treatment in our HD patients, we cannot rule out that other drugs might also play a role. No treatment used in PD correlated with constipation (data not shown). Hyposmia is another NMS included in the digestive domain of the PD NMSQuest. In our study, the prevalence of hyposmia was lower in HD than in PD. Previous studies in HD have found that odour recognition, and discriminative intensity and quality are affected [30, 31]. Hyposmia in PD has to do with loss of olfactory

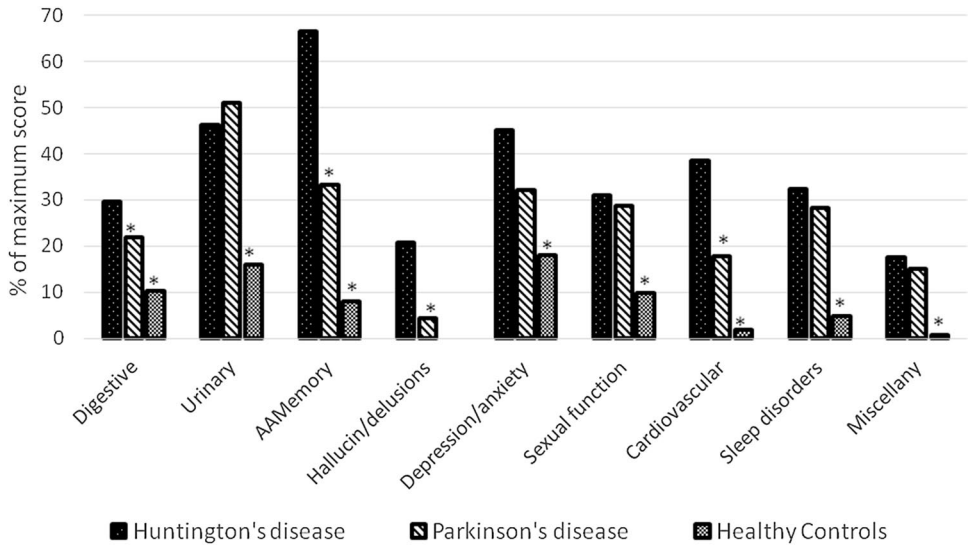

Fig. 2 Percentage of positive answers for NMS grouped by domains. Comparison between HD and PD and HC (*$p \leq 0.05$)

bulb neurons, whereas in HD not only reduced olfactory bulb neurogenesis [32] but also the entorhinal cortex, thalamus, parahippocampal gyrus, and caudate nucleus seem to be involved in the smell alterations [31].

Urinary disturbances were reported frequently in our HD patients. Although functional disability and depression have been associated with the presence of dysautonomic symptoms [33], bladder dysfunction could precede the onset of motor symptoms or appear early in the course of the disease [33, 34] as we have also found in our study, where 43% of patients in stages 1–2 complained of urinary urgency. Urgency seems to be more prevalent in early stages, whereas incontinence became increasingly common with disease progression [34]. Nocturia is a well-recognized NMS in PD, with a prevalence described up to 62% [18]. Older age, men and advanced stages are significant predictors of nocturia in PD [35]. In our study, nocturia was significantly more frequent in PD than HD (69% vs. 41.5%). As PD patients were older than HD patients, we cannot rule out an age-effect for this finding. We found a moderate correlation between nocturia and treatment with benzodiazepines in HD but not in PD (data not shown). However, we cannot rule out that such an association in HD could be due to a confounding factor as nocturia is a reason for awakening [36] and benzodiazepines are used frequently as hypnotics. In fact, in our study, 14 of the 21 HD patients under treatment with benzodiazepines were taking them at night due to sleep problems.

It is well known that patients with HD can exhibit deficiencies in several cognitive domains including attentional and visuospatial functions, psychomotor speed, negative emotion recognition, executive functioning, and memory [37, 38]. The cognitive dysfunction can have a significant impact on the life of the individuals touched by the disease affecting their ability to work, handle financial affairs, manage domestic responsibilities and finally to maintain their self-care. Attentional and memory alterations were reported in more than 70% and 60% of our HD patients, respectively. They were more prevalent in moderate–severe stages but were present at any stage of the disease. In fact, cognitive symptoms have been reported to be the first symptom of the disease in 8.4% of the patients [37, 39]. Attentional and memory deficiencies may also be related to treatment with benzodiazepines [40]. Although we did not find a correlation between them in HD, a moderate correlation between attentional problems and benzodiazepines was found in PD ($r = 459$; $p = 0.002$).

The overall prevalence of apathy was 64% in our HD patients. The prevalence of apathy in HD is highly variable, ranging from 32.2 to 76% of patients in different studies [41–46]. It has been suggested that apathy might herald the dementia process [47] and that is associated with disease duration, cognitive impairment and motor deterioration [46]. However, up to 60% of our patients in slight–mild stages complained of apathy, suggesting this finding that apathy can appear early during the course of the disease. We found that amantadine treatment showed a negative weak correlation with the presence of apathy in HD but not in PD (data not shown). Although there are no studies supporting this finding in the literature [48], exploratory outcomes in patients with PD suggest that amantadine might improve apathy and fatigue in such patients [29, 49].

Psychiatric symptoms are common in HD affecting 33–76% of patients [50] and occur as part of the underlying disease process rather than simply as a response to disease diagnosis. These symptoms often cause more distress and disability in patients and their caregivers than motor symptoms [51]. In previous studies [52, 53], the most common psychiatric condition reported was depression followed by anxiety. Depression was present in 56.6% and anxiety in 34% of our HD patients. Although the scores for psychiatric symptoms were higher in HD than in PD, they did not reach statistical significance. Neither were there significant differences between slight–mild and moderate–severe HD stages. In contrast with our results, Paulsen et al. [53] reported that the proportion of HD patients endorsing significant depression diminished with disease progression. These differences may have to do with the different tools used to assess depression in both studies or with the fact to consider only significant depressive symptoms. In this sense, the assessment of depression in our study does not discriminate by the severity of the symptoms. Studies including a large number of patients with HD have reported that around 20% of patients have lifetime suicidal thoughts and about 10% commit an attempt of suicide [54, 55]. Depressed mood, impulsivity and irritability have been identified as risk factors for suicide in HD. Two critical periods of increased risk of suicide exist, one immediately before receiving a formal diagnosis of Huntington's disease and the second in the stage 2 of the disease, when functional independence starts to diminish [54, 55]. These findings highlight the importance to assess systematically the presence of depressive and suicidal ideation in HD patients. Treatment, especially with tetrabenazine [26], is another factor that should be considered for the presence of depressive symptoms in our patients, but the only correlation we found for depression was a weak negative one with amantadine in HD but not in PD (data not shown). Although there are not studies in HD, current evidence for a positive effect of NMDA antagonists on psychiatric symptoms in PD is inconclusive and requires further studies [56].

Delusions were present in 26% and hallucinations in 15% of our HD patients. Hallucinations were more frequent in advanced stages of the disease and delusions were more frequent in HD than in PD patients. The presence of psychotic symptoms in HD ranges from 3 to 12% of patients [57, 58] and has correlated with a longer duration of disease, higher motor score, lower TFC score, positive

psychiatric history for depression and obsessive–compulsive symptoms, and treatment with benzodiazepines and antipsychotics [58]. However, except for the antiepileptic treatment that correlated weakly in HD and moderately in PD with the presence of hallucinations, we did not find correlation of these symptoms with other treatments. The association of hallucinations with antiepileptics, especially the tactile ones, has previously been reported in some patients treated with these drugs for seizures or pain [59, 60]. Although both hallucinations and delusions are considered part of the psychotic spectrum, they can also occur in non-psychotic individuals, in the absence of other psychotic, affective, cognitive and negative symptoms [61].

Sexual problems were higher in HD than in HC but no differences were found between HD (31%) and PD (29%) or between early and advances stages in our study. Sexuality and partnership have an important influence on the quality of life of patients with chronic disorders and should not be under-evaluated. The prevalence of abnormal sexual behaviour in HD disease varies from 30% to more than 80% of the patients, including hypoactive sexual disorder in some cases and increased sexual interest and paraphilia in others [62–65]. The disease itself, psychiatric treatment, depression or dementia may play a role in sexual dysfunction in HD [65]. In our study, libido alterations showed a weak positive correlation with neuroleptics and benzodiazepine treatment, and with the presence of depressive symptoms (data not shown) in HD. PD patients also showed a moderate correlation between libido and treatment with benzodiazepines ($r = 0.346$; $p = 0.02$). All together, these findings may suggest a role for benzodiazepines on the libido alterations that our patients can suffer.

Neurophysiological and pathological studies have shown an imbalance between sympathetic and parasympathetic control of the heart [66], and a possible vulnerability to early death from cardiac causes in HD [67]. Cardiovascular symptoms in the PD NMSQuest include two items: feeling light-head, dizzy or weak when standing from sitting or lying, and falling. In our study, the frequency of cardiovascular symptoms in HD (39%) was higher than in PD (18%). This difference was due to a higher prevalence of falls in HD (51% vs 20%). However, we cannot assure that HD patients have more cardiovascular problems than PD patients because it was very difficult to ascertain whether falls in our patients were related to dysautonomic causes. In addition to postural instability, motor deficits (chorea and bradykinesia), cognitive decline and behavioural disturbances seem to contribute to falls in HD [68]. Although treatment with neuroleptics, antidepressants and amantadine may induce dizziness and falls due to orthostatic hypotension [29, 69], we only found a moderate correlation of antidepressants with dizziness in HD and with falls in PD ($r = 0.444$; $p = 0.002$).

Sleep disorders were reported in more than 50% of our patients with HD. Although a progressively worsening of sleep disorder has been reported in HD patients [70], we did not find differences in frequency between early and advanced stages. Insomnia was reported in 51% of HD and 42% of PD patients, but it did not reach statistical significance. Only the item of nightmares was higher in HD than in PD. However, no differences were found regarding the sleep disorder domain between both groups. Sleep disorders in HD mainly include diurnal somnolence, insomnia, periodic leg movements and in some instances REM sleep behaviour disorder [71]. When asked directly about the quality of their sleep via an HD-targeted questionnaire, up to 90% of patients report to have sleep problems [72]. Insomnia has been related to amantadine treatment in PD patients [29]. Although we did not find a correlation between amantadine treatment and insomnia, a weak negative correlation was found with diurnal somnolence in HD but not in PD (data not shown).

Finally, weight change, sweating, swelling of legs, diplopia and pain are items included in the miscellaneous domain. Except for weight loss, all these symptoms have barely been described in HD. In our study, the prevalence of pain in HD (15%) was similar to that found in PD (18%), and there were no differences between early and late stages of the disease. In contrast with our findings, it has been reported that pain can affect, in some degree, more than 40% of patients [73], being a common symptom in advanced HD [74]. We found that weight loss was more frequent in HD (30%) than in PD patients (11%). Weight loss leads to general weakening, affects disease progression [75] and contributes substantially to both morbidity and mortality [76, 77]. Weight loss in HD has been related to the CAG repeat length [78] and chorea severity [79]. Although the intrinsic mechanisms contributing to weight loss in HD are not totally known, metabolic changes [77, 78, 80], hypothalamic and endocrine dysfunctions involving the thyrotropic and somatotropic axis [20, 81], dysphagia, gastrointestinal dysfunction including malabsorption of nutrients and bacterial overgrowth [8] may play a causal role.

Our study may have some limitations such as that we have compared different diseases involving basal ganglia functioning using a specific scale for PD, the different age between HD and PD patients, the relative small number of patients included in each group, the cross-sectional design with an only exploratory data analysis, and, finally, the possible confounding effect of some treatments on the presence of NMS, because correlations in HD were not always found in PD, and to attribute a causal effect of treatment was difficult in some instances. Despite these limitations, we consider our study is of interest as a first approach to assess globally the prevalence of NMS in HD. We believe that, similar to what happened with PD several years ago, further studies are needed to design and validate specific

tools for the assessment not only of the prevalence, but also the severity of NMS, and their impact on the quality of life of HD patients and their caregivers.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The authors state that this study has been approved by the ethic committee of Hospital Clinic of Barcelona and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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