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ORIGINAL COMMUNICATION

Potential impact of self-perceived prodromal symptoms on the early diagnosis of Parkinson's disease

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Abstract The detection of Parkinson's disease (PD) at stages earlier than current diagnostic criteria allow for may increase the efficacy of disease-modifying therapies. Here we studied the relationship between retrospectively reported prodromal non-motor and motor features of PD, their pre-diagnostic presentation to physicians, and the extrapolated potential of an earlier diagnosis of PD considering early diagnostic markers detected at presence. One hundred and fifteen PD patients (41 women; age 63.2 ± 8.6 years) underwent a structured face-to-face interview on 22 prediagnostic symptoms. Present olfactory function, motor symptoms, and substantia nigra hyperechogenicity (SN-h) were assessed using standardized tools. Most frequently self-perceived symptoms in the early and very early prediagnostic phase (>2, >7 years prior to diagnosis) were hyposmia (23, 10 %), musculoskeletal pain (21, 9 %), and depression/anxiety (14, 11 %). In the late prediagnostic phase (≤2 years) mild motor signs, especially asymmetric bradykinesia and rest tremor, increasingly dominated the self-perception. In the prediagnostic phase, 99 % of patients consulted a physician because of motor symptoms but only 36 % with non-motor symptoms, mostly pain (20 %), depression/anxiety (9 %), constipation, bladder urgency, insomnia, REM sleep behaviour disorder, sexual dysfunction, and malignant melanoma (each, <6 %). Assuming the potential detectability of present hyposmia, asymmetric motor slowing and SN-h, a triad highly specific for PD, as early as 5 years prior to diagnosis, up to 84 (73 %) patients could have been identified in the prediagnostic phase using their or their physicians' awareness of early symptoms. We conclude that educating the general population and physicians on the importance of distinct prodromal features and applying symptom-specific diagnostic programs can improve the early detection of PD.

Keywords Parkinson's disease · Prodromal phase · Hyposmia · Pain · Substantia nigra hyperechogenicity

Introduction

When Parkinson's disease (PD) is diagnosed according to current clinical criteria, about or even more than 50 % of the dopaminergic cells in the substantia nigra (SN) have degenerated [1]. The time span between the onset of neurodegeneration and manifestation of parkinsonism fulfilling the diagnostic criteria is referred to as the prediagnostic or prodromal phase of PD [2, 3]. A number of studies have shown that this phase lasts for years or even decades [2, 4–6]. The upcoming disease-modifying and neuroprotective therapies should be applied to patients in the earliest stages of the disease, ideally before motor features develop, with the goal of delaying and even preventing the onset of the motor syndrome [7]. Therefore, there are increasing efforts to develop strategies to diagnose PD already in the premotor disease stages. An increased risk of PD has been shown for a

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number of characteristic non-motor symptoms, especially hyposmia, constipation, anxiety, depression and idiopathic REM sleep behaviour disorder (RBD) [3, 7–9]. Also, musculoskeletal pain and skin tumours have been reported to be more frequent in prodromal PD patients compared to age-related normal population [10, 11]. SN hyperechogenicity (SN-h) on transcranial sonography represents an additional risk marker of PD which is already present in prediagnostic disease stages [12, 13], persists during the course of PD [12], and was found to be independent from severity of motor features or hyposmia in PD [14]. Previous and ongoing prospective studies on the use of prodromal symptoms for the early detection of PD focused at specific risk groups such as first-degree relatives of PD patients, subjects with hyposmia or RBD, and asymptomatic LRRK2 mutation carriers who, however, represent only a minority of all subjects developing PD [3, 15–17]. Other studies addressed unselected populations at ages >50 years which may be too costly if applied as a general approach [13]. A promising strategy to screen for subjects at risk is the application of scores combining frequently occurring, self-perceived prodromal symptoms of PD [8, 18]. Olfactory and motor function testing combined with transcranial sonography of SN also detects persons at high risk of PD [14, 15, 19].

The goal of the present interview-based study was to assess retrospectively the potential value of patients' and physicians' awareness of previously reported prodromal features for the early detection of PD. For this, we investigated the frequency, time of onset, and presentation to physicians of a broad range of self-perceived non-motor and motor symptoms and their relation to current olfactory and motor function and SN-h in 115 patients with PD.

Methods

Subjects

We enrolled patients with clinically definite idiopathic PD who were age <75 years or, if older, had a PD duration of <15 years [20, 21]. They were seen as inpatients at the Parkinson Clinic Bernburg between January 2009 and August 2010. Inclusion criteria were Hoehn & Yahr stage 1–3, fluency in German language, and transcranial insonability. Exclusion criteria were dementia according to the DSM-IV criteria assessed by an experienced clinician and a score ≤26 in the Mini-Mental State Examination, evidence of atypical parkinsonian syndromes, severe head trauma or other central neurological disorders. The study was approved by the ethics review board at Rostock University. All subjects gave written informed consent.

Structured interview and clinical assessment

All patients underwent an expanded, structured face-to-face interview on a range of non-motor and motor prodromal symptoms of PD, including the presence and self-perceived age at onset of the following: hyposmia, parosmia, depression, anxiety, dysphoria/personality change, cognitive dysfunction, problems with falling and/or staying asleep, vivid dreams, RBD symptoms (acting out during dreams), chronic musculoskeletal pain including its laterality and localisation (neck/shoulder, back, arm, leg, generalized), constipation (difficulty in bowel emptying and <3 bowel movements per week) [22], bowel incontinence, bladder urgency, sexual dysfunction (reduced sex drive, sex difficulty), excessive sweating, skin tumours, hypophonia, hyperkinesia, lateralized/symmetric bradykinesia, micrographia, lateralized rest tremor, and repeated falls. The earliness of symptom perception was classified as follows: very early, >7; early, >2; and late, ≤2 years prior to diagnosis of PD. The patients were asked if they had consulted a physician for reported prodromal symptoms, and if causes other than PD could be related to their symptoms, e.g. head trauma or chronic sinusitis in hyposmia. The information on reported pain characteristics and other possible causes of the pain was used to judge whether the pain was, at least partly, related to PD or not [23]. Smoking habits and history of PD in first-degree relatives were recorded. A patient who had not or rarely smoked in the last 10 years prior to diagnosis of PD was classified as non-smoker.

In an adaption from the non-motor symptoms questionnaire (NMSQuest) [24], the information obtained in the interview was used to calculate a modified score (mNMS, score 0–15) containing the following items: hyposmia, constipation, bowel incontinence, bladder urgency, pains, remembering and/or concentrating difficulty, depression, anxiety, dysphoria/personality change, sexual dysfunction, falling, insomnia, intense vivid dreams, acting out during dreams, sweating. To evaluate the discrepancy between self-perception and verifiable presence of current symptoms, the patients were assessed on the Beck Depression Inventory (BDI; depression considered present at score >13) [25], the Urge-Urinary Distress Inventory (U-UDI; bladder urgency present at score >0.5) [26], and the 12-item Sniffin' Sticks test (SS-12; age-related cut-off values for hyposmia) [27]. The off-medication severity of motor symptoms was quantified on the UPDRS-III [21].

Transcranial sonography

Transcranial sonography was performed bilaterally through the preauricular acoustic bone windows using a 2.5-MHz phased-array ultrasound system (Acuson Antares; Siemens, Erlangen, Germany) [14, 28]. SN echogenic size was

Table 1 Findings in PD patients with and without potential detectability in the prodromal phase according to the strategies proposed here

Feature		All	Potentially detected		*p*
		($n = 115$)	No ($n = 31$)	Yes ($n = 84$)	
Gender, F/M	[n]	41/74	12/19	29/55	0.68[a]
Age (years), mean ± SD	[y]	63.2 ± 8.6	60.8 ± 7.8	64.1 ± 8.7	0.06[b]
Age at diagnosis of PD	[y]	55.9 ± 8.7	53.5 ± 8.6	56.8 ± 8.6	0.07[b]
PD duration since diagnosis	[y]	7.6 ± 5.6	7.6 ± 6.2	7.6 ± 5.5	0.99[b]
PD motor subtype, AR/MT/TD	[n]	45/61/9	11/17/3	34/44/6	>0.6[c]
Hoehn & Yahr stage, median, IQR		2.5 (2, 3)	2.5 (2, 3)	2.5 (2, 3)	0.68[d]
UPDRS-III score, off-medication		31 (24, 40)	35 (23, 41)	30 (24, 40)	0.31[d]
BDI score, range 0–63		5 (3, 9)	5 (3, 8)	5 (3, 9)	0.81[d]
U-UDI score, range 0–4		1.1 (0.3, 2.0)	1.0 (0.2, 1.9)	1.2 (0.3, 2.0)	0.42[d]
SS-12 score, range 0–12		6 (5, 8)	9 (5, 10)	6 (5, 7)	**0.004**[d]
mNMS score, range 0–15		6 (4, 7)	5 (3, 7)	6 (4, 7)	0.51[d]
mNMS score, prediagnostic[e]		1 (0, 3)	1 (0, 2)	1 (0, 3)	0.15[d]
Malignant melanoma	[n]	3	0	3	0.56[c]
Non-smoker (since >15 year), Y/N	[n]	100/15	24/7	76/8	0.07[a]
First-degree relative with PD	[n]	3	1	2	1.0[c]

AR akinetic-rigid, *BDI* Beck Depression Inventory, *mNMS* modified Non-motor Symptom Score, *MT* mixed-type, *UPDRS-III* Unified PD Rating Scale, motor part, *SS-12* 12-item Sniffin' Sticks test, *TD* tremor-dominant, *U-UDI* Urge-Urinary Distress Inventory

[a] χ^2 test

[b] *t* test

[c] Fisher's exact test

[d] Mann–Whitney *U* test

[e] Non-motor symptoms with reported onset at 6 months or longer prior to the diagnosis of PD

measured on axial scans automatically after manually encircling the outer circumference of SN's echogenic area [28]. With the ultrasound system applied, SN echogenic sizes of <0.24 cm^2 are considered normal, and sizes of ≥ 0.24 cm^2 hyperechogenic (SN-h) [14]. For classification of a patient's SN echogenicity the greater of bilateral measures was used. All examinations were performed by an experienced investigator blinded to the patients' anamnesis and clinical data. The sonographic examinations were digitally stored as video sequences, made anonymous, and off-line re-analyzed by a second investigator. SN-h was only regarded as present if both readings agreed.

Statistical analysis

For comparison of non-normally distributed data the Mann–Whitney *U* test was used, of means the *t* test for independent samples, and of categorical data the χ^2 test or Fisher's exact test. Analyses were performed with SPSS 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

Study cohort

One hundred and fifteen patients who had been diagnosed with PD 0.5–31 (median, 7.0; IQR, ± 3.5) years before met the inclusion criteria (Table 1). Only nine patients had a PD duration of >15 years.

Self-perception of prodromal symptoms

One hundred and thirteen (98 %) patients reported one or more (3.1 ± 2.0; range 1–12) prodromal symptoms preceding the diagnosis of PD at least 6 months (Table 2; Fig. 1). Of the remaining two patients, bradykinesia was observed in one patient by a treating physician and the other consulted the neurologist one month after self-perceived onset of rest tremor. Seventy-nine (69 %) patients reported one or more (median, 2; range 1–10) non-motor symptoms. The six patients who reported parosmia also had experienced hyposmia. Depression and anxiety coincided in three patients in the prodromal phase. Patients with bowel incontinence usually later developed constipation, except for two in the prodromal phase. Eighty (70 %) patients reported chronic musculoskeletal pain which was judged as PD-related in 71 (62 %). Of those, 35 had pain in one body part, and 36 in multiple locations or generalized. Of the 36 patients with pain as a prodromal symptom, 26 had pain of neck and shoulder, 21 of back, nine of arm, and eight of leg. Of 33 patients with lateralized pain, 31 had motor symptom onset on the side of pain (χ^2 test, $p < 0.001$). Malignant melanoma was reported by three patients (prodromal in two), and basal cell carcinoma by six (prodromal in one). Since the incidence rates of basal

Table 2 Frequency and onset of self-perceived prodromal symptoms in 115 PD patients

Prodromal symptom[a]	Incidence (cumulative) %	Time of onset prior to diagnosis of PD		Onset age
		Mean ± SD, *y*	Median, *y*	Mean ± SD, *y*
Autonomic				
Constipation	7.8	16.7 ± 16.6	11.0	44.8 ± 17.6
Bowel incontinence	4.3	16.2 ± 23.5	4.0	52.2 ± 17.5
Sexual dysfunction	6.1	6.4 ± 8.4	4.0	56.5 ± 9.2
Excessive sweating	13.0	5.7 ± 10.0	2.0	48.4 ± 14.2
Bladder urgency	6.1	5.6 ± 5.0	4.0	56.1 ± 7.5
Mental and sleep				
Anxiety	7.0	11.7 ± 12.8	9.5	43.3 ± 10.0
Depression	13.0	10.9 ± 11.6	8.0	43.6 ± 10.6
Vivid dreams	6.1	8.6 ± 13.1	2.5	43.4 ± 12.9
Problems with staying asleep	11.3	8.4 ± 9.8	5.0	47.5 ± 12.1
Problems with falling asleep	5.2	6.5 ± 6.3	6.0	50.7 ± 6.8
Dysphoria/personality change	4.3	4.9 ± 4.8	3.5	47.6 ± 10.1
RBD symptoms	8.7	4.5 ± 5.4	2.0	48.1 ± 6.1
Cognitive dysfunction	1.7	1.0 ± 0	1.0	48.3 ± 4.6
Sensory				
Hyposmia	28.7	8.7 ± 10.9	3.5	49.8 ± 10.2
Pain	31.3	5.2 ± 6.1	2.8	50.6 ± 8.4
Skin				
Malignant melanoma	1.7	6.3 ± 6.8	4.0	50.0 ± 13.4
Motor				
Hypophonia	7.8	3.2 ± 4.4	1.0	57.1 ± 8.1
Symmetric motor slowing	2.6	2.8 ± 3.6	1.0	55.2 ± 2.3
Falling	9.6	2.4 ± 2.1	2.0	56.1 ± 7.6
Asymmetric rest tremor	50.4	1.8 ± 1.9	1.0	54.8 ± 9.6
Asymmetric motor slowing	60.0	1.7 ± 1.8	1.0	53.5 ± 8.8
Micrographia	19.1	1.7 ± 1.7	1.0	55.2 ± 10.4
Hyperkinesia	0.9	1.0	1.0	59.0

PD Parkinson's disease, *RBD* REM sleep behaviour disorder, *SD* standard deviation, y years

[a] Symptom with time of onset at 6 months or more prior to diagnosis of PD

cell carcinomas in our patients were equal to those reported for mid-European population [29], with manifestation mostly after the diagnosis of PD, we did not regard this feature as a prodromal symptom in the further analysis. However, malignant melanomas occurred mostly prior to diagnosis of PD and were roughly twice as frequent as in the age-related German population [30].

The most frequent symptoms with very early perception (>7 years prior to diagnosis of PD) were depression/anxiety (11 % of patients), hyposmia (10 %), pain (9 %), insomnia (4 %) and constipation (4 %). On the other hand, lateralized rest tremor and lateralized bradykinesia were by far the most frequently self-perceived prodromal symptoms but were usually noticed only in the late prodromal phase.

Presentation of prodromal symptoms to physicians

In 114 (99 %) cases the self-perception of rest tremor or bradykinesia prompted the patient to consult a physician, and usually led to diagnosis of PD within the same year. However, only 41 (36 %) patients consulted a physician because of self-perceived non-motor symptoms in the prodromal phase (Fig. 2), and in none of these cases was the possibility of early PD communicated to the patient. Features most frequently presented were pain (20 % of all patients) and depression/anxiety (9 %; in-patient treatment: 3 %).

Comparison between self-perception and objective measures

In all patients who reported asymmetric motor signs, this could be confirmed in the neurological investigation. Of 96 patients with hyposmia on the SS-12, 17 (18 %) had reported present normosmia (supplementary Table 1). Four (44 %) of nine patients with a BDI score >13 did not regard themselves as currently depressed. Of 78 patients with abnormal U-UDI, 32 (41 %) did not report present urgency.

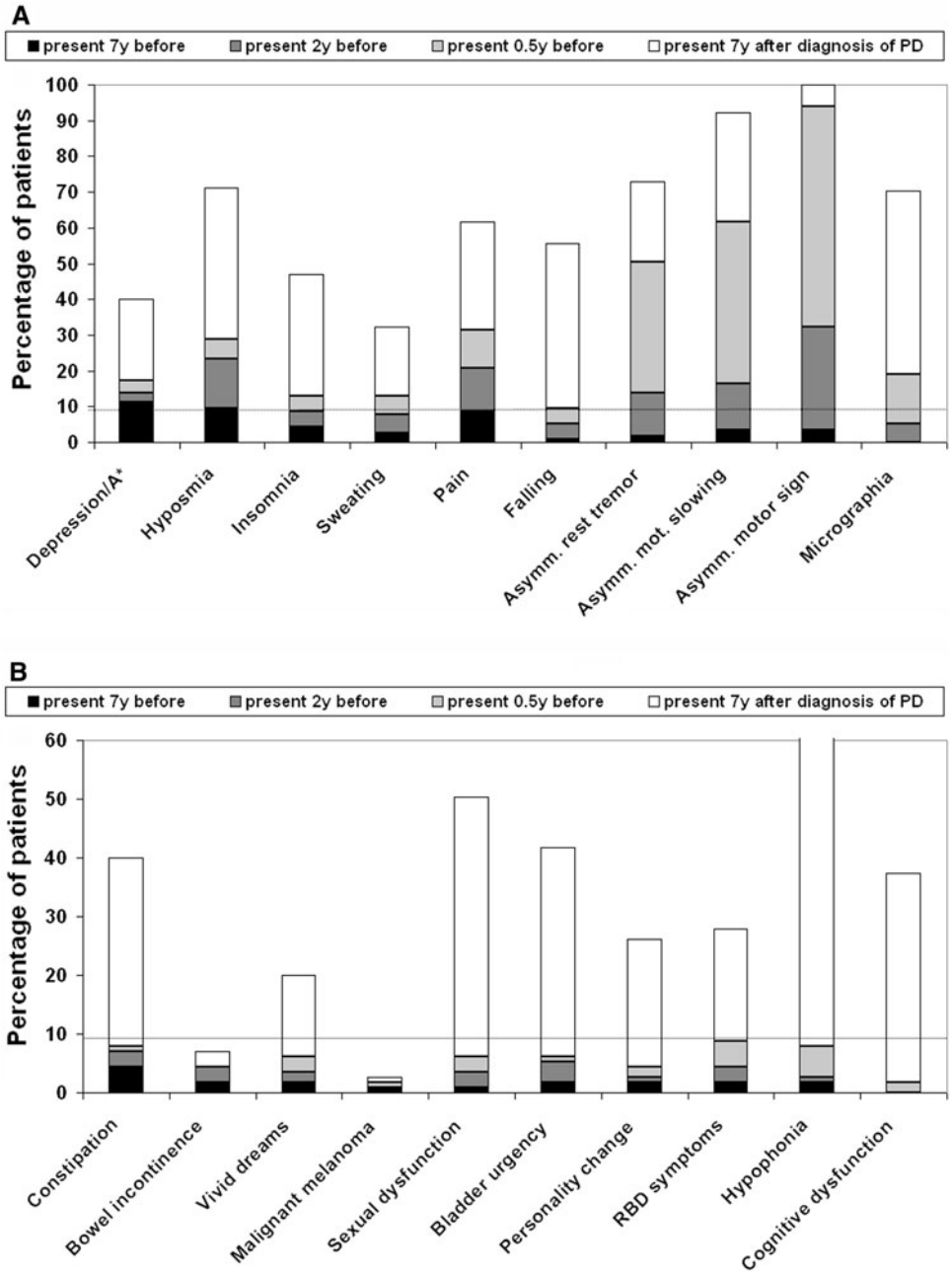

Fig. 1 Frequency of self-perceived prodromal symptoms in 115 patients with PD at different time points of the prodromal and post-diagnostic phase. **a** Diagram showing the more frequently perceived symptoms, present in at least 10 % of patients in the prodromal phase. **b** Diagram showing less frequently perceived symptoms, present in <10 % of patients in the prodromal phase

Transcranial sonography findings

SN-h, found in 109 (95 %) patients, was not related to any motor or non-motor symptom (each, χ^2 test, $p > 0.05$; supplementary Table 2).

Self-perceived prodromal symptoms and diagnostic criteria

Using the interview data and the test results on bradykinesia, hyposmia, and SN-h, and extrapolating these test results to be present up to 5 years prior to diagnosis of PD [9, 12, 13, 17, 31, 32], we calculated the fraction of patients potentially identifiable within 5 years prior to actual diagnosis of parkinsonism considering three different sets of diagnostic criteria:

1. Considering the combined finding of asymmetric bradykinesia, hyposmia and SN-h as highly predictive of PD [14, 19], 81 (70 %) patients presenting with this triad could potentially have been identified in the late prediagnostic phase by testing for hyposmia and SN-h shortly after the self-perception of asymmetric motor signs. This fraction decreased to 17 (15 %) patients in the early prediagnostic phase. However, in the early

prediagnostic phase up to 23 (20 %) patients could have been identified by immediate testing for hyposmia, bradykinesia and SN-h after they had consulted physicians with non-motor complaints. The potential rate of early PD detection depending on the type of self-perceived prodromal feature is shown in Fig. 3.

2. Considering the combined presence of RBD, hyposmia and SN-h as highly predictive of PD [9, 15, 33], three of these 81 patients could have been detected 2–4 years earlier.
3. In an adaptation of the PD risk score recently proposed [18], with a cut-off criterion of six out of ten anamnestic items (eight non-motor symptoms, non-smoker, relative

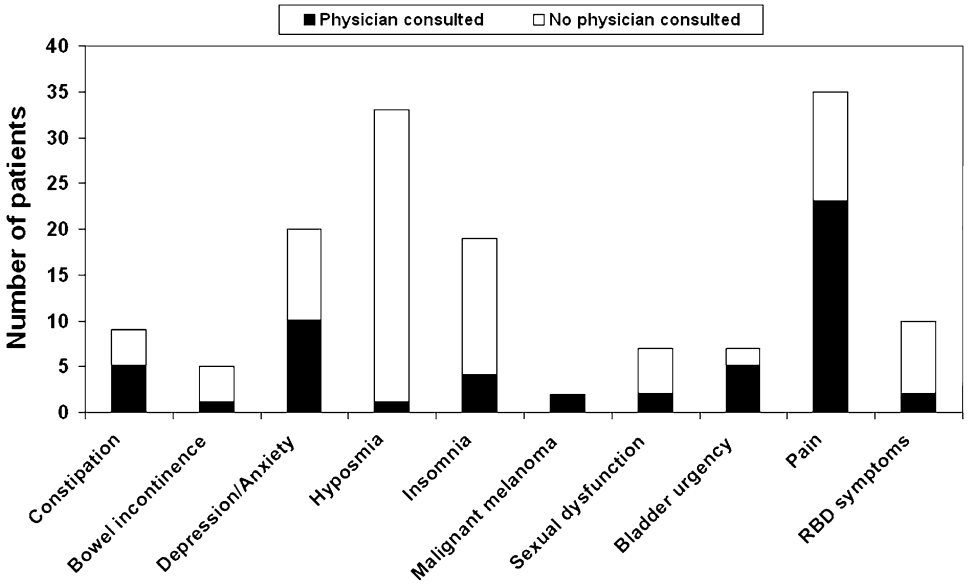

Fig. 2 Frequency of presentation of self-perceived non-motor symptoms to physicians in the prodromal phase of PD. The diagram displays only those non-motor symptoms out of the various features queried in the structured interview that prompted at least one affected patient of the study cohort to consult a physician

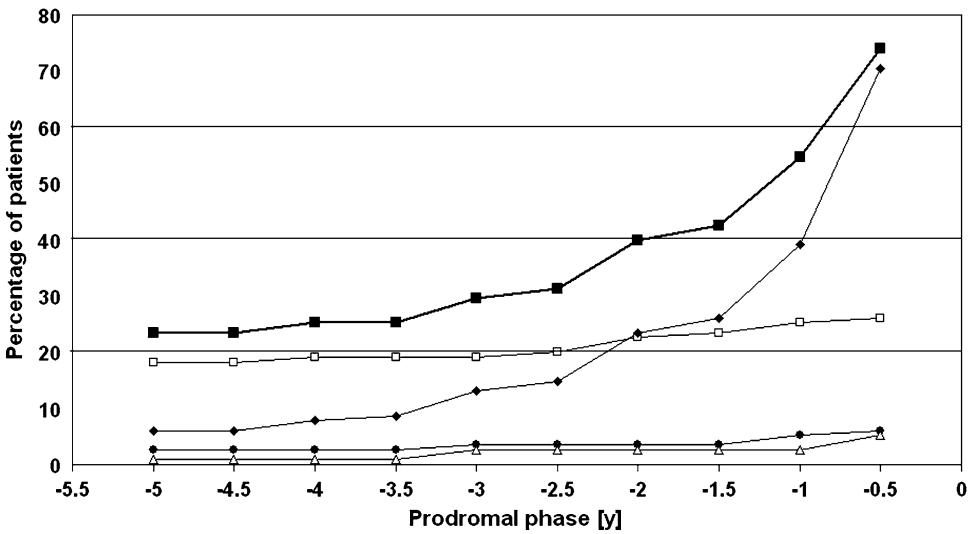

Fig. 3 Diagram showing the retrospectively calculated fractions of patients of the present study cohort that could potentially have been detected as subjects at high risk of developing PD, depending on the type of self-perceived prodromal symptom. The calculation of this model was performed using the assumption that both triads, i.e. (i) of (lateralized) bradykinesia, hyposmia and SN hyperechogenicity, and (ii) of RBD, hyposmia, and SN hyperechogenicity are highly specific for PD, and that bradykinesia, hyposmia and SN hyperechogenicity can be detected at least five prior to the diagnosis of parkinsonism (for details, see text). *filled circle* self-perceived RBD symptoms in combination with positive test results for hyposmia and SN hyperechogenicity; *unfilled triangle* prediagnostic mNMS score >5 (including 15 non-motor symptoms plus the items 'non-smoker' and 'positive family history of PD'; for details, see text); *unfilled square* self-perceived non-motor symptoms that led to consultation of a physician, in combination with positive test results for bradykinesia, hyposmia and SN hyperechogenicity; *filled diamond* self-perceived asymmetric motor slowing or asymmetric rest tremor, in combination with positive test results for hyposmia and SN hyperechogenicity; *filled square* fraction of patients potentially detected if combining all four approaches

with PD), we considered the 15-item mNMS instead of the eight non-motor symptoms. Still, <10 % of our patients would retrospectively have met this cut-off criterion due to the low frequency of patients reporting at least five prodromal non-motor symptoms (supplementary Fig. 1). Nevertheless, the application of this risk score further increased the number of patients potentially detected in the prodromal phase (Fig. 3).

Combining the detection strategies 1–3, 84 (73 %) patients could potentially have been identified in the prediagnostic phase. The remaining 31 were characterized by higher frequency of normosmia (55 %/2 %; χ^2 test, $p < 0.001$), normal SN echogenicity (16 %/1 %; $p = 0.001$), and by trend, smokers (23 %/10 %; $p = 0.065$) and young-onset PD (onset age <40 years; 10 %/2 %; $p = 0.089$) (Table 1).

Discussion

Our aim was to identify the potential value of self-perception of various prodromal features for the early detection of PD. Previous neuroimaging and clinical studies suggested a prodromal (prediagnostic) phase with a probable duration of 10–13 years [2, 4–6]. Data obtained in this study show that in the early prodromal phase the most frequently self-perceived symptoms are depression/anxiety, hyposmia, and axial musculoskeletal pain not explained by other causes. In the late prodromal phase mild motor signs of PD, especially asymmetric rest tremor and asymmetric bradykinesia, increasingly dominate the self-perception. In 99 % of cases, troublesome motor symptoms led to the consultation of a physician. In contrast, non-motor prodromal symptoms were only partly brought to a physician's attention, most often pain, depression/anxiety, bladder urgency and constipation, and if so, these had not been linked to the possibility of early PD. Present findings may have important implications for the design of screening programs and educational strategies addressing the general population and physicians.

Because of the retrospective design of our study the reported frequency and duration of prodromal symptoms may be underestimated. Many of the queried prodromal symptoms develop slowly, and are often still mild in incident PD [34]. Hence, not all symptoms are perceived immediately at their first occurrence. On the other hand, systematic overestimation of predominant symptoms can also be of issue with a well-informed patient population that recognizes current symptoms and projects that they began prior to diagnosis. We aimed to minimize these limitations by performing a structured face-to-face interview in a stress-free, patient-friendly setting. The patients were informed several days in advance on the content of the interview. Therefore, we are confident that the major fraction of self-perceived symptoms could be identified. The present study did not include a healthy control group to confirm that the symptoms studied here were more frequent in prodromal PD patients since this has been demonstrated in a number of earlier studies [6–11, 19].

The frequency, age at onset and duration of prodromal symptoms assessed here are in line with the findings of a recent telephone interview study on 93 PD patients [6]. The lower frequency of constipation in our study can be explained by the applied stricter Rome criterion (<3 bowel movements per week) [22]. The high rate of prodromal motor symptoms conforms to findings of the prospective Rotterdam study where early motor signs were reported by more than 70 % of those individuals in whom PD was diagnosed after a mean follow-up of 5.8 years [35]. An increased risk of developing PD has been demonstrated for distinct non-motor symptoms, especially hyposmia, constipation, anxiety, depression and idiopathic RBD [3, 7–9]. The relevance of pain and malignant melanoma, both suggested previously to be associated with an increased risk of PD, is still a matter of debate [3, 7, 10, 11, 36]. We found a surprisingly high fraction of patients with musculoskeletal pain in the prodromal phase, most often of neck/shoulder and back, and with significant correlation to the side of onset of PD motor symptoms. Shoulder pain occurring before the onset of PD symptoms and typically at the side of maximum PD symptom severity was reported earlier [37, 38]. Our finding that depression and pain were the non-motor symptoms most often presented to physicians in the prodromal phase is in line with previous reports [37–39]. It has been shown that patients in the first 6 years after diagnosis of PD perceive pain as the most bothersome non-motor symptom [40]. Present results imply that this holds true also for the prodromal phase. It may, therefore, be worthwhile educating physicians who are regularly consulted by patients suffering from pain of neck, shoulder and back (e.g. general practitioners, orthopaedists) to consider the possibility of early PD if the pain in a patient can not be sufficiently explained by other causes.

Malignant melanomas occurred in our patients mostly prior to the onset of PD, and more frequently than in a comparable general population [30]. There is growing evidence suggesting a pathogenic link between malignant melanoma and PD [41]. Since, however, the role of malignant melanoma as a possible prodromal feature of PD is not yet substantiated [36], it remains to be elucidated whether it might be worthwhile to regularly search for early PD symptoms in patients with malignant melanoma.

The results of previous studies suggest that the triad of early motor signs of PD, hyposmia and SN-h is highly predictive of PD [14, 19]. Considering their principal

detectability as early as 5 years prior to diagnosis of parkinsonism in the vast majority of cases [9, 12, 13, 17, 31, 32], more than two-thirds of our patients could potentially have been identified as high-risk subjects within 5 years prior to actual diagnosis of PD, presuming these features were also antecedent by at least 5 years in our population. This, however, would require that all these subjects had perceived at least one early prodromal symptom and communicated this to a physician who, in turn, should have linked this feature to the possibility of early PD. Since some of the prodromal non-motor symptoms of high relevance for the early detection of PD (RBD, hyposmia) only rarely caused the patients to consult a physician, it might be worthwhile educating the general population of the potential relevance of these prodromal symptoms, provided that early diagnosis and treatment strategies exist. On the other hand, as less specific but more bothersome symptoms often prompt the patients to consult a physician (pain, depression/anxiety, bladder urgency, malignant melanoma), it might be a promising concept to educate the treating physician specialists to consider the possibility of prodromal PD, and to refer these subjects to specialized diagnostic centres.

Other frequent prodromal non-motor symptoms of PD are disturbance of color vision [9], dizziness/orthostatic hypotension [3, 6], and increased saliva/drooling [34]. The latter two features are, together with the mNMS items studied here, included in the NMSQuest [24]. Considering the data of the present and previous reports [18, 42], a non-PD subject with an NMSQuest score >5 could be regarded as being at an increased risk of developing PD.

In conclusion, our findings suggest that for the early detection of PD in the prodromal phase different patient-related and physician-related detection strategies depending on the nature of the first prodromal symptom may be adequate. However, the attempts in antedating the diagnosis of PD need to be accompanied by updated ethical and treatment concepts addressing the management of patients diagnosed with a very early stage of PD.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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