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Dag Aarsland, Kolbjørn Brønnick, Guido Alves, Ole-Bjørn Tysnes, Kenn Freddy Pedersen, et al.. The spectrum of neuropsychiatric symptoms in patients with early, untreated Parkinson's disease.. Journal of Neurology, Neurosurgery and Psychiatry, 2009, 80 (8), pp.928. 10.1136/jnnp.2008.166959 . hal-00552740

HAL Id: hal-00552740

<https://hal.science/hal-00552740>

Submitted on 6 Jan 2011

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**The spectrum of neuropsychiatric symptoms in patients with early, untreated
Parkinson's disease.**

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Key words

Parkinson's disease, neuropsychiatric symptoms, apathy, depression, cluster analysis

Word count

1705 words

ABSTRACT

Background: Neuropsychiatric symptoms are common in Parkinson's disease (PD), and have important clinical consequences for patients, caregivers and society. Few studies of neuropsychiatric symptoms in early, untreated PD exist.

Objective: To explore the range, clustering and correlates of neuropsychiatric symptoms in an incidence-cohort of untreated subjects with PD.

Methods: All cases with incident PD identified during a 22-months period in four counties of Western and Southern Norway were included. Standardized criteria were employed to diagnose PD. The Neuropsychiatric Inventory (NPI) was administered to 175 PD and 166 healthy control subjects with similar age and sex distribution. Cluster analysis was used to investigate the inter-relationship of NPI items.

Results: The proportion with any symptom and severity of NPI symptoms was higher in PD (56%) than in controls (22%) ($p < .001$). Depression (37%), apathy (17%), sleep disturbance (20%) and anxiety (17%) were the most common symptoms. Clinically significant symptoms occurred in 27% of the PD group, compared to only 3% in the control group ($p < .001$). Subjects with clinically significant neuropsychiatric symptoms had more severe parkinsonism than those without. Two neuropsychiatric clusters were identified, one characterised by mood symptoms and one by apathy.

Conclusions: Although the majority of patients with early, untreated PD do not have clinically significant neuropsychiatric symptoms, these symptoms are more common in patients than in people without PD. Both psychological stress and brain changes associated with PD are likely to contribute to the higher frequencies.

INTRODUCTION

A wide range of neuropsychiatric symptoms have been described in PD, with important clinical consequences both for patients, caregivers and society.[1] However, no population-based studies of the spectrum of neuropsychiatric symptoms exist in patients with early unmedicated PD. Since antiparkinsonian drugs have the potential to influence a range of psychiatric symptoms, including affective symptoms, cognition, impulsivity, and psychotic symptoms,[2] studying drug-naïve patients is required to explore behavioural changes that are related to the disease itself.

Therefore, we administered the Neuropsychiatric Inventory (NPI)[3] to a large, unselected sample of patients with incident, non-demented, untreated PD and matched controls, derived from the Norwegian ParkWest project, a multicentre population-based longitudinal cohort study.

METHODS

Patients and controls

Case ascertainment, patient selection and diagnosis are described in an accompanying paper. From 206 subjects who were spouses or friends of the patients, or unrelated persons from the study area, the 175 subjects who provided the best possible match regarding age- and sex-distribution and years of education to the eligible patients with PD were included as a control group.

Neuropsychiatric assessment

The NPI was used to assess frequency and intensity of 12 neuropsychiatric symptoms. The maximum possible score is 12, and a score of ≥ 4 is usually considered to represent clinical significant severity. In two subjects with missing data on one or two

items, a score of 0 was recorded on the missing item, whereas subjects with missing data on more than two items were excluded. Motor symptoms were rated using the Unified Parkinson's Disease Rating scale (UPDRS) subscale III.[4]

Neuropsychological assessment included the Mini-Mental State Examination (MMSE) [5], a battery of neuropsychological tests and standardised history of cognitive impairment, and subjects with probable dementia associated with PD at examination were excluded. See [6] for a detailed description of procedures and criteria to diagnose dementia.

Statistics

Due to non-linearity of NPI subscores, non-parametric analyses (Spearman correlation and Mann-Whitney test) were used to estimate associations between NPI and demographic and clinical features. To explore how the different psychiatric symptoms clustered in individual patients, we performed cluster analyses. The NPI subscores of each patient were standardized to z -score values based on the mean and standard deviation of each NPI variable. This was performed in order to ensure equal weighting of the different symptoms in the clustering procedure. A similarity matrix was calculated using a Euclidean distance measure.[3] A Ward-method cluster-analysis was used on the similarity matrix. For validation purposes we also employed an average-linkage cluster analysis. The material was considered too small to perform a split-sample validation procedure. To identify the appropriate number of clusters, we plotted the overall within-group sum of squares over all the included variables and investigated the plot for an "elbow". P-values below 0.05 were considered statistically significant.

RESULTS

Among the 201 eligible PD patients and 175 normal controls, 19 PD and 9 control subjects were not administered the NPI or had missing data on more than two items. Further seven patients were excluded due to dementia, leaving 175 PD patients and 166 healthy control subjects for inclusion. The patients had lower mean MMSE score (27.8, SD 2.3) than the control subjects (28.6, SD 1.5) ($p=0.001$), and slightly less years of formal education (10.9 (2.3) vs 11.6 (3.5), $p=0.04$), but did not differ significantly regarding age (67.8 (9.0) vs 67.3 (9.1), ns) and sex distribution (58% vs 60% male, ns).

Table 1. Composite scores and proportions with positive and clinically significant item scores on the Neuropsychiatric Inventory in early PD and control subjects

	Mean score		% with a positive score		% with a clinically significant score*	
	NC	PD	NC	PD	NC	PD
Delusions	0.0	0.06	0	1.1	0	0.6
Hallucinations	0.01	0.04	0.6	1.2	0	0.6
Agitation	0.02	0.15	1.2	5.7	0	1.1
Depression	0.11	1.06	7.8	34.3	0.6	10.3
Anxiety	0.07	0.59	2.4	16.4	0.6	6.9
Euphoria	0	0	0	0	0	0
Apathy	0.03	1.06	1.2	27.4	0	11.4
Disinhibition	0	0.08	0	4.0	0	0.6
Irritability	0.14	0.22	5.4	8.6	1.2	1.7
Motor behaviour	0.02	0.14	0.6	2.3	0.6	1.7
Sleep disturbance	0.2	0.69	9.1	17.8	1.8	7.5
Appetite disturbance	0.09	0.70	1.8	14.9	0.6	8.0

**clinically significant neuropsychiatric symptoms defined as a NPI score of ≥ 4*

PD=Parkinson's disease; NC=normal controls

The NPI item scores and proportion with symptoms are shown in table 1. The total NPI score, number of symptoms and number of symptoms with a clinically significant severity differed significantly between the groups (Mann-Whitney test, all p values <0.001). Ninety-eight (56%) of the PD group had a positive score on at least one item, compared to 36 (21.7%) in the control group (chi square=42.0, $p<0.001$). In the PD group, depression (34.3%), apathy (27.4%), sleep disturbance (17.8%) and anxiety (16.4%) were the most common symptoms. The number of positive NPI items was higher in PD patients than control subjects ($Z=-7.2$, $p<0.001$), with 61 (34.9%) patients having more than one symptom compared to only 10 (6.0%) in the control group.

Forty-seven (26.9%) PD patients had at least one symptom of clinical significance, the most common being apathy (11.4%), depression (10.3%), appetite (8%), and sleep (7.5%) disturbances, compared to only 5 (3.0%) in the control group having a symptom of clinically significant severity ($p<0.001$). PD patients had more symptoms of clinically significant severity than control subjects ($Z=-6.1$, $p<0.001$), and 22 (12.6%) PD patients had more than one clinically significant symptom, compared to only 2 (1.2%) in the control group.

Patients with at least one clinically significant score had higher UPDRS motor subscale score (29.5 (13.7)) than those without clinically significant neuropsychiatric symptoms (21.5 (9.7), $t=4.3$, $p<0.001$), whereas the MMSE score or sex distribution did not differ significantly.

Antidepressant drugs were used by 23 (13.1%), one (0.6%) used an antipsychotic, and a benzodiazepine was used by 21 (12%) (regularly by 19, intermittently by 2). The proportions taking antidepressants (35.6% vs 5.8%; chi square 26.1, $p<0.001$) and

benzodiazepine (26.7% vs 5.5%; chi square 15.3, $p < 0.001$) were higher among those with at least one significant neuropsychiatric symptom compared to those without significant neuropsychiatric symptoms.

Cluster-analysis was performed to explore whether groups with specific neuropsychiatric syndromes could be identified. Five clusters were identified, based on the finding of a very clear "elbow", indicating that there was little added benefit of increasing the cluster count from 5 to 6. When dividing in two samples, 166 of 175 patients (94.8%) were classified in the same clusters, supporting the validity of the cluster solution. Two of the clusters contained only 1 and 2 patients and were discarded, with three clusters remaining: The majority of patients ($n=158$, 90.3%) fell into a cluster with no or very mild symptoms (Cluster 1). Cluster 2 consisted of patients with mood symptoms ($n=10$; 5.7%), ie high scores on the depression, anxiety, and apathy items, and a final small cluster 3 ($n=4$, 2.3%) consisted of patients with predominant high apathy score. The three clusters differed significantly in cognition and motor impairment, with the patients in the apathy cluster being more impaired than the other groups (table 2).

Table 2. Demographic and clinical features of early PD patients in the two neuropsychiatric clusters and in those with no or mild neuropsychiatric symptoms

	No/mild symptoms	Mood cluster	Apathy cluster	Statistic	<i>p</i>
Age	67.5 (9.0)	69.0 (9.1)	75.1 (8.7)	1.5	0.24
Male/Female (n)	90/58	7/3	3/1	1.1	0.3
Education, years	11.0 (3.3)	10.0 (4.0)	8.4 (1.8)	1.6	0.21
MMSE score	27.9 (2.4)	28.0 (2.1)	24.5 (1.7)	4.0	0.02
UPDRS motor score	22.8 (11.2)	31.7 (9.7)	35.3 (11.5)	5.1	0.007

Numbers represent mean and SD if not otherwise indicated.

UPDRS motor=Unified Parkinson's Disease Rating Scale, motor subscale

MMSE=Mini-Mental State Examination Scale

DISCUSSION

This study demonstrates for the first time that a characteristic neuropsychiatric symptom pattern can be found in early, drug-naïve patients with PD. More than half of the patients exhibited at least one symptom, and more than a quarter had at least one symptom of clinically significant severity. Several patients had two or more symptoms, and 13% had two or more clinically significant symptoms. Depression, anxiety, sleep disturbances and apathy were the most common symptoms, whereas psychotic symptoms were very rare.

The cluster analysis identified two neuropsychiatric syndromes, one with mood symptoms and one with predominantly apathy. This observation is consistent with previous studies. Studies of medium staged PD, ie Hoehn & Yahr stage 3-4, have reported neuropsychiatric clusters, including depression, anxiety, and apathy clusters and a psychosis cluster.[7] In a cohort consisting of patients with advanced PD and dementia, a group with agitation and a variety of symptoms was added to mood, apathy, and psychosis groups.[8] Thus, the spectrum of neuropsychiatric symptoms tends to widen with more advanced disease. In early PD, mood and apathy are the predominating neuropsychiatric symptoms. Subsequently, with advancing disease, a group with hallucinations occurs, and in later stages with dementia, a group of patients exhibit multiple and severe neuropsychiatric symptoms including agitation.

The aetiology of neuropsychiatric symptoms in PD is most likely multifactorial, with possible contribution from both psychological stress and brain changes associated with PD. At this early disease stage, the motor symptoms are usually mild with little functional impairment, but the knowledge of having been diagnosed with a chronic, progressive and debilitating brain disease with potentially negative effect on their job

situation, economic security and quality of life [9] may induce mood symptoms such as sadness and anxiety. On the other hand, both depression and anxiety can develop before the onset of motor symptoms and the diagnosis of PD,[10] strongly suggesting that brain changes occurring early in disease may render the patients more likely to develop psychiatric symptoms.

Neuropsychiatric symptoms were associated with cognitive impairment. Care was taken to exclude any patient with dementia, and thus this finding adds to previous studies in demonstrating a relationship between psychiatric and cognitive disturbance even in early, non-demented patients. This provides further support for distinguishing PD patients with mild cognitive impairment from those with normal cognition, as a harbinger of dementia, as has been shown in imaging [11] and longitudinal [12] studies.

We found a relationship between motor severity and psychiatric symptoms in PD, consistent with previous studies.[7,13] The demonstration of such a relationship in drug-naïve patients is a novel finding, and suggests that to some degree, brain changes leading to motor symptoms and psychiatric morbidity develop in parallel, or have similar underlying brain substrates, ie dopaminergic, nigro-striatal disturbance.

The possibility of studying patients with early, drug-naïve PD allows us to rule out the potential confounding effect of dopaminergic treatment on neuropsychiatric symptoms, which may affect a wide range of behavioural, motivational and emotional functions.[2] Antidepressants and anxiolytics were used by some patients, which might have influenced the findings by reducing the severity and frequency of depression and anxiety. Other limitations of the study include the cross-sectional

design, precluding conclusions as to aetiology and course of neuropsychiatric symptoms.

In addition, important psychiatric symptoms such as obsessive-compulsive or impulse control disorders were not assessed. Although the NPI inquires about psychotic phenomena, it does not provide a systematic way of capturing the presence or character of the “minor” forms of psychosis in PD, such as illusions, passage and sense of presence hallucinations. Thus, such symptoms may have been present but not detected. Finally, the NPI assesses only severity of depression and anxiety, but provides no formal diagnosis, which would require a structured psychiatric interview.

Although the majority of patients with early untreated PD did not have clinical significant neuropsychiatric symptoms, this study shows that such symptoms are clearly more prevalent than in controls. We recommend that a screening of neuropsychiatric symptoms should be performed already at time of diagnosis of PD. Longitudinal studies are required to explore the predictive significance of neuropsychiatric symptoms, and how the profile of these symptoms evolve with time.

COMPETING INTERESTS

No competing interests.

FUNDING

This study was funded by the Western Norway Regional Health Authority (grant# 911218) and the Research Council of Norway (grant# 177966).

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