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Hypomania and mania related to dopamine replacement therapy in Parkinson's disease

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ABSTRACT

Objectives: To investigate hypomania and mania related to dopamine replacement therapy (DRT) in Parkinson's disease (PD).
Methods: We recruited 108 non-demented PD patients without deep brain stimulation from a movement disorders in and outpatient clinic. Forty-five age- and gender-matched controls were also included. Disease characteristics, cognitive functioning, comorbid psychiatric diseases, dopaminergic and psychiatric medication were evaluated. Diagnosis of DRT-related hypomania and mania was based on DSM-IV-TR criteria with supplementary assessment of two mania self-rating scales. First, patients and controls were compared. Patients with DRT-related hypomania or mania were then compared to the remaining patients. A binary logistic regression analysis was performed to identify correlates of DRT-related hypomania.
Results: Patients scored significantly higher on mania self-rating scales than controls. Twelve patients (11.1%) had DRT-related hypomania and six patients (5.6%) had DRT-related mania. Both groups had significantly higher self-rating mania-scores than patients without these mood states. DRT-related hypomania was significantly related to younger age, younger age at PD onset, dyskinesias, higher levodopa equivalent daily dose, dopamine dysregulation, and amantadine treatment. In contrast, DRT-related mania was significantly associated with hallucinations and delusions, history of levodopa-induced psychosis, quetiapine treatment, higher depression and daily levodopa dose, and cognitive deficits. Regression analysis revealed dopamine dysregulation, dyskinesias, amantadine treatment, and younger age at PD onset as significant correlates of DRT-related hypomania.
Conclusion: DRT-related hypomania and mania are relevant comorbidities in PD. DRT-related hypomania may exist as a distinct psychiatric symptom complex in young patients with early disease onset. Different patient profiles likely underlie DRT-related hypomania and mania.

1. Introduction

Research focusing on hypomania and mania in patients with Parkinson's disease (PD) is scarce. There are numerous publications describing increased goal oriented activity, also known as impulse control disorders (ICDs), which can be considered as symptoms of mania. However, the full spectrum of mood elevation, irritability, inflated self-esteem, flight of ideas, or distractibility has not been well elucidated outside of the immediate post-deep brain stimulation (DBS) setting. One reason for this oversight may be the complicating factors of PD itself and the possible confounding effects of dopamine replacement therapy (DRT). The diagnosis of hypomania or mania, as it is stated in the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision, DSM-IV-TR [1]), requires the exclusion of a general medical condition and substance-induced pathophysiology, but these criteria are usually not applicable for patients with PD under DRT. However, the

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potential antidepressant or mood enhancing effect of DRT has long been speculated on [2], and new onset mania after treatment with dopamine agonists has been reported [3].

Transient hypomanic mood states have been described recently in PD as part of the dopamine dysregulation syndrome (DDS) [4–6] and ICDs [7]. While ICDs are characterized by incentive- or reward-based, repetitive behaviors [8], DDS refers to a compulsive or addictive DRT medication intake [4]. Typical clinical features of DDS are male gender, early onset of disease, levodopa usage, depression, and dyskinesias [4–6], while ICDs have been associated with younger age, treatment with dopamine agonists, and also higher depression-scores [5,9,10]. For both syndromes, the dopaminergic (over-)stimulation of the mesocorticolimbic circuit seems to be crucial, especially in early PD where the relatively intact ventral striatum might suffer from a dopamine overdose leading to behavioral changes [11,12]. Moreover, PD patients treated with subthalamic DBS occasionally demonstrate symptoms of hypomania, possibly caused by the stimulation of the ventral part of the subthalamic nucleus [13,14].

However a systematic psychiatric examination of DRT-related hypomania and mania in non-DBS patients with PD does not exist. It remains unclear how many PD patients experience DRT-related hypomania or mania, may be coexistent with DDS or ICD, or as an exclusive DRT-related mood change. Therefore, the first goal of this study was to compare PD patients with gender- and age-matched controls regarding manic and hypomanic symptoms. We hypothesized that PD patients on DRT have higher mania-scores than controls. The second goal was to analyze the clinical factors associated with DRT-related hypomania and mania in a large sample of non-demented, non-DBS PD patients. Taking the literature of DDS and ICDs into consideration, we hypothesized that patients with DRT-related hypomania and mania would differ from patients without these mood disorders in respect to age, age of PD onset, daily amount of dopamine, depression, and presence of dyskinesias. Finally, a logistic regression model was used to identify clinical correlates for DRT-related hypomania and mania.

2. Methods

2.1. Participants

The patient sample consisted of PD patients, prospectively and consecutively recruited from the Department of Neurology, University Hospital Cologne. Only patients with idiopathic PD (Queen's Square Brain Bank criteria) [15], who received DRT and who had no history of neurosurgery were included. Patients participated either during an elective inpatient stay on the neurology ward or during an outpatient appointment. Emergency hospitalizations were not included. In Germany, unlike in North-American countries, it is common for PD patients to be hospitalized for DBS screening, adjustment of medication, or clarification of PD diagnosis. Hence, in general, inpatients are not necessarily more severely impaired than others managed as outpatients.

Additionally to the patients, gender- and age-matched controls without neurological disorders were examined. Controls were recruited from a general practitioner practice. Present or history of psychiatric disorders was no exclusion criterion for both patients and controls. Patients and controls with dementia (DemTect score < 9 [16]) were excluded. The study was approved by the local ethics review board (study number 11–261) and all study participants gave written informed consent before participation.

2.2. Clinical assessment

Patients were examined by a neurologist, a neuropsychologist, and a psychiatrist. All tests were administered while patients were on their regular daily DRT. Motor impairment was evaluated by two trained movement disorder neurologists (C.E., D.P.) using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III, range 0–108) [17]. Disease stage was determined with the Hoehn and Yahr scale (range 0–5) [18]. The levodopa equivalent daily dose (LEDD) was calculated according to the guidelines of the German Neurological Society [19]. Additionally, the daily levodopa dose and the dopamine agonist LEDD were registered separately. Gender, age, disease duration, age at PD onset, body side of onset, neurological and psychiatric medication, and presence of dyskinesias, hallucinations and delusions were recorded.

The criteria of the DSM-IV-TR [1] were applied for a diagnosis of DRT-related hypomania or mania. The presence of PD and use of dopaminergic medication were not used as exclusion criteria to making psychiatric diagnoses. The DSM-IV-TR distinguishes mania from hypomania by the presence of psychotic features (delusions, hallucinations), the duration of symptoms (hypomania $\geq$4 days versus mania $\geq$7 days), marked impairment in social or occupational functioning, and required hospitalization. Patients also filled out two mania-related questionnaires: the Self-Report Manic Inventory (SRMI) [20,21], to examine patient's manic/hypomanic state and the Hypomanic Personality Scale (HPS) [22,23], to assess more stable hypomanic traits. Both scales consist of 48 items with a dichotomized answering profile, are used internationally, and have validated German versions [21,23]. Higher scores equal more severe impairment. To our knowledge, these scales have never previously been used to assess PD patients. The diagnosis of DRT-related hypomania and mania was made by two clinical neuropsychologists (F.M., C.L.) and a psychiatrist (J.K.), and was based on standard scales, clinical interviews and behavioral observations. All patients were examined regarding current DDS (according to Giovannoni [4]), current ICDs (criteria by Voon and Fox [8]), current and lifetime history of major depression (MD) and lifetime history of bipolar disorder (both DSM-IV-TR [1]), and lifetime history of hallucinations and levodopa-induced psychosis. Moreover, the Beck Depression Inventory-2 (BDI-2) [24] was completed by all patients. Punding was not explicitly evaluated in our patients.

Controls filled out the same self-report questionnaires (SRMI, HPS, BDI-2) and were assessed with respect to current and lifetime history of psychiatric disorders. Cognitive functioning was measured using the DemTect (dementia screening, range 0–18, 13–18 no cognitive impairment, 9–12 mild cognitive impairment (MCI), 0–8 dementia) [16] and the Brief Test of Attention (BTA, auditory divided attention) [25] in all study subjects.

2.3. Statistical analysis

Statistical analysis was conducted using IBM SPSS version 20.0 (IBM Corp, Armonk, NY, USA). Statistical significance was defined as $p < .05$. The chi-squared test for categorical variables, the independent samples *t*-test for parametric and the Mann–Whitney-U-test for nonparametric variables were first used to compare patients and controls. This analysis was Bonferroni corrected by the number of tests performed. Patients with PD were then divided into three groups: patients with DRT-related hypomania, patients with DRT-related mania, and patients without DRT-related hypomania/mania. The three groups were compared using the chi-squared test for categorical values, and the Fisher's exact test for two groups, when a value was not applicable for the third group. Analysis of variance (ANOVA) was applied for parametric and the Kruskal–Wallis test for nonparametric values. Thereafter, post-hoc Bonferroni tests were used to assess significant group differences in the ANOVAs. Post-hoc Fisher's exact tests were performed for significant chi-squared test results, and Mann–Whitney-U-tests were