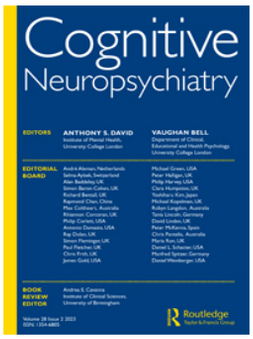

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Neuropsychiatric features of Parkinson's disease in the era prior to the use of dopaminergic therapies

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ABSTRACT

Background: Psychosis in Parkinson's disease includes hallucinations and delusions. Other non-psychotic neuropsychiatric features include depression, anxiety and apathy. There is currently controversy over whether psychosis in Parkinson's is an intrinsic part of the disorder or the result of dopaminergic medications. This study aimed to examine a historical cohort of individuals with Parkinson's prior to the use of dopaminergic therapy to assess the prevalence of psychotic and other neuropsychiatric features.

Methods: The case notes of patients with Parkinson's disease admitted to the National Hospital for Neurology and Neurosurgery, London between 1924 and 1946 were examined. Demographic and clinical variables were extracted along with any neuropsychiatric features. Cases meeting criteria for encephalitis lethargica were excluded.

Results: 115 cases of individuals with Parkinson's disease were identified. 58 (41.7%) were female. Mean age was 54.0 (SD 9.6) years and mean time since Parkinson's diagnosis was 5.3 (SD 5.7) years. No individuals met criteria for encephalitis lethargica. No cases of hallucinations or delusions were reported. There was one case of an illusion in a patient who was using anticholinergic medication. Other neuropsychiatric features reported were sleep disorder (present in 10, 8.7%), depression (8, 7.0%), memory impairment (5, 4.3%), impulsivity (4, 3.5%), bradyphrenia (4, 3.5%), impaired attention (3, 2.6%), anxiety (1, 0.9%), fatigue (1, 0.9%) and apathy (1, 0.9%).

Conclusions: Prior to the use of dopaminergic therapies, patients with Parkinson's disease admitted to hospital rarely, if ever, reported psychotic symptoms, although other neuropsychiatric symptoms were more prevalent. The main limitation is that a lack of systematic enquiry about psychotic symptoms may have resulted in underreporting.

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Key messages

What is already known on this topic

Hallucinations and delusions are common features of Parkinson's disease. However, it is unclear whether they are due to the disease itself or the result of dopaminergic medications.

What this study adds

Before dopaminergic medications were used, patients with Parkinson's rarely, if ever, reported psychotic symptoms, although sleep disorders and depression were more common.

How this study might affect research, practice or policy

Researchers and clinicians should be aware that medications in Parkinson's disease may be at least as important as the disease process in the generation of psychotic symptoms.

Introduction

Psychotic symptoms are common in Parkinson's disease (PD), especially at a late stage in the disease progression (Riedel et al., 2010). Visual hallucinations are most common with a prevalence of up to 75% over a 20-year course of the disease, far higher than the 6-15% prevalence of hallucinations reported in the general population. Auditory hallucinations and delusions are also more common in PD, though they occur less frequently (Diederich et al., 2009; Fénelon & Alves, 2010; Linscott & van Os, 2013).

There are two main explanations for the presence of psychosis in Parkinson's disease. The first is that psychosis is a direct result of the neurodegenerative process. The second is that psychosis results from the action of dopaminergic medications. Disentangling these hypotheses has been challenging, as patients with Parkinson's disease of at least several years' duration in high income countries are almost invariably on medications. This lack of certainty contributed to what was acknowledged to be the most controversial aspect of the 2007 consensus diagnostic criteria for psychosis in Parkinson's disease (Ravina et al., 2007). This stands in contrast to the literature on dementia with Lewy bodies, a disorder closely linked to Parkinson's disease, where it is clear that psychosis is a common feature of the disorder itself (Ballard et al., 2001; Nagahama et al., 2007).

Evidence for the first hypothesis – that psychosis develops from Parkinson's disease pathology itself – arises from epidemiological studies that have managed to identify patients with Parkinson's disease at an early phase in their illness when they were medication-naïve. One such study found that minor hallucinatory experiences were reported in 42% of drug-naïve Parkinson's patients, compared to only 5% in controls (Pagonabarraga et al., 2016). A study in Tanzania of 33 patients with Parkinson's found 4 cases of visual hallucinations among medication-naïve individuals (Dotchin et al., 2009). However, another contemporary study using systematic symptom ascertainment found that only two out of 175 patients with untreated Parkinson's disease experienced hallucinations (Aarsland et al., 2009). Moreover, a longitudinal study found that the

incidence of hallucinations was strongly related to the dose of dopaminergic medication administered (Onofrj et al., 2002). Two large studies identified doses of dopaminergic medications as risk factors for psychosis in PD (Forsaa et al., 2010; Morgante et al., 2012). In the pre-dopaminergic era, a review of the literature found that there were reports of hallucinations occurring in individuals with parkinsonism, but cases of true Parkinson's disease were often not sufficiently differentiated from encephalitis lethargica or dementia with Lewy bodies (Fénelon et al., 2006). Encephalitis lethargica is a neurological condition that affected more than one million people worldwide in an epidemic from 1916 onwards (Ravenholt & Foege, 1982). In addition to parkinsonism, patients with encephalitis lethargica also commonly exhibited hypersomnia and oculogyric crises with some exhibiting psychiatric features such as mood dysregulation, personality change and psychosis (Hoffman & Vilensky, 2017).

A study of levodopa administration in healthy individuals found that it resulted in a marked reduction in the ability to discriminate between relevant and irrelevant stimuli, a potential trait marker of psychotic symptoms (Schmack et al., 2018). There have also been reports of psychosis induced by dopamine agonists in the treatment of prolactinoma and for lactation inhibition (Bernard et al., 2015; Pérez-Esparza et al., 2017). However, a small study found that intravenous administration of high doses of levodopa in individuals with Parkinson's disease did not acutely induce hallucinations or delusions (Goetz et al., 1998).

Evidence for the role of dopamine in psychosis is also provided from the schizophrenia literature. Striatal F-DOPA uptake is increased in schizophrenia and in those with prodromal schizophrenia-like clinical features compared to healthy controls (Howes et al., 2009). The effect of antipsychotic drugs is proportional to their binding at the dopamine D_2 receptor (Seeman et al., 1976). Beyond schizophrenia, elevated striatal dopamine activity also seems to underlie psychotic symptoms in individuals with Alzheimer's disease (Reeves et al., 2009). Amphetamine, which increases synaptic dopamine, can induce psychosis, (Bramness & Rognli, 2016) and stimulation of mesostriatal dopaminergic neurons in mice can induce hallucination-like perceptions (Schmack et al., 2021).

Current evidence suggests that striatal dopaminergic hyperactivity is a key underlying mechanism of psychosis. However, it remains unclear whether psychosis in Parkinson's disease is due to the pathophysiology of the disorder, or a consequence of dopaminergic medications. This study aimed to investigate the prevalence of neuropsychiatric symptoms in dopaminergic medication-naïve PD patients by examining historical medical records from the pre-levodopa era. As a secondary objective, we aimed to investigate the prevalence of other neuropsychiatric symptoms in the absence of dopaminergic therapies.

Methods

Setting

The study was conducted using the case notes in the Queen Square Archives of the National Hospital for Neurology and Neurosurgery (NHNN), London. These case notes contain the medical assessments on admission for all patients admitted to the

National Hospital for Neurology and Neurosurgery, the UK's largest clinical neurosciences centre, from 1863 to 1946. As the first dopaminergic medication for Parkinson's disease (levodopa), was used in 1961 (Tolosa et al., 1998), none of the cases included for the present studies were on any dopaminergic medication. Further, chlorpromazine, the first conventional antipsychotic, was only synthesised in 1951, so it is unlikely that drug-induced parkinsonism occurred (Ban, 2007). Approval was obtained from the Queen Square Archives to undertake the project. Because archived casebooks are accessible to the public, formal ethical approval was not required.

Case identification

Clinical diagnoses were searched for terms containing "Parkinson", "Parkinsonian" and "paralysis agitans" from 1924 to 1946. Diagnoses other than Parkinson's disease were excluded. Only a patient's first admission was included. The reason for excluding subsequent admissions was that the clinical records of re-admitted patients were abbreviated, assuming knowledge of the previous admission and not including full assessment of the range of symptoms. Including subsequent admissions could potentially underestimate important neuropsychiatric features. Incomplete case notes, including those with page damage, blank pages, and missing important data were excluded. Due to similarities in the clinical presentation of Parkinson's disease and encephalitis lethargica, additional screening criteria were applied to exclude cases of encephalitis lethargica.

Data extraction

Data on demographics, diagnosis, admission date, discharge date, core features of Parkinson's disease (tremor, rigidity and bradykinesia), clinical outcome, history of psychotic illness, presence of eye disease, acuity for both eyes, time window since the first onset of Parkinson's symptoms, presence of key Parkinson's clinical features, medication history and anticholinergic medication use were extracted by the first author. The neuropsychiatric symptoms that were identified *a priori* were hallucination, delusion, illusion, depression, anxiety, apathy, fatigue, impulsivity, sleep disorder, memory impairment, bradyphrenia and impaired attention. An additional category for other neuropsychiatric symptoms was also included. Neuropsychiatric symptoms were coded as present, absent or insufficient information.

In order to exclude cases of encephalitis lethargica, the clinical criteria developed by Howard and Lees were used (Howard & Lees, 1987), which require the presence of three of the following seven clinical features: basal ganglia involvement, oculogyric crises, ophthalmoplegia, obsessive-compulsive behaviour, akinetic mutism, central respiratory irregularities, and somnolence and/or sleep inversion. Data on these clinical features were also extracted.

Interrater reliability

To establish the reliability of the data extraction, data for 10 of the cases were also extracted by the senior author and interrater reliability was calculated using Fleiss' kappa for the 12 neuropsychiatric symptoms.

Data analysis

Data on demographics, disease-related variables and neuropsychiatric symptoms were summarised with descriptive statistics. Analysis was conducted using SPSS version 25.

Results

Cohort description

Case selection is illustrated in Figure 1. No cases were excluded due to damaged records, though 6 records were excluded due to being incomplete. 115 cases were identified

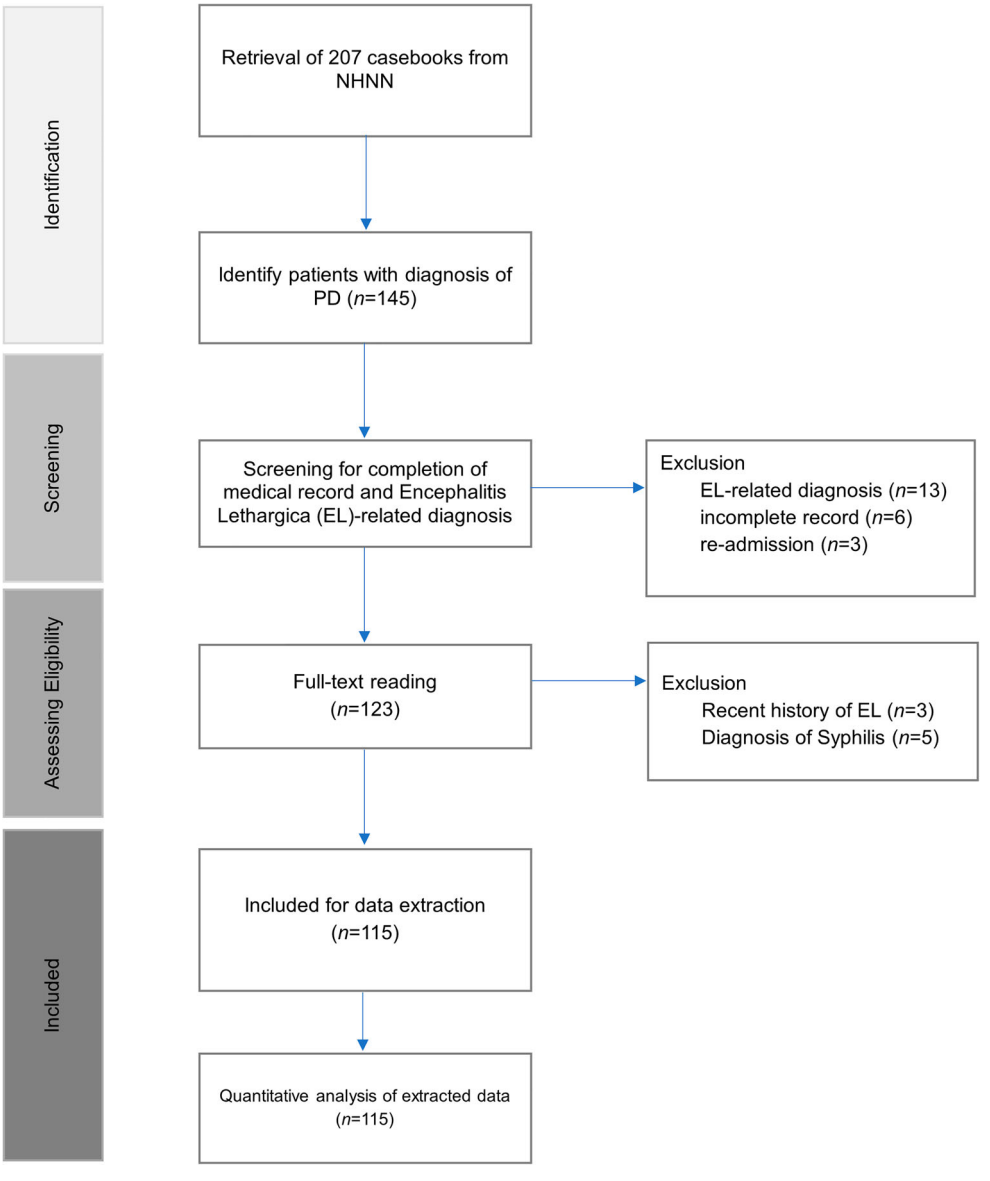

Figure 1. Process of eligibility screening.

between 1924 and 1946. 58 subjects (41.7%) were female and 67 (58.3%) were male. The mean age at presentation was 54.0 (SD 9.6) years. Mean age at onset of symptoms of Parkinson's disease was 48.8 (SD 10.8) years. Mean duration of PD symptoms was 5.3 (SD 5.7) years and the median was 3.3 (IQR 4.0) years.

Prevalence of PD clinical features, encephalitis lethargica features, eye disease and medication use are shown in Table 1. In terms of encephalitis lethargica, all patients had basal ganglia involvement by virtue of having parkinsonism and 11 cases had one additional feature, but no patients met the Howard and Lees criteria by having three or more of the diagnostic features. The median length of admission duration among patients was 43 days (IQR = 36). In terms of admission outcome, as judged by the patient's neurologist on hospital discharge, 55 (47.8%) were considered improved, 3 much improved (2.6%), 11 (9.6%) slightly improved, 39 (33.9%) unchanged and 1 (0.9%) worse, while 2 patients (1.7%) died during admission. Outcome was unrecorded in 4 cases (3.5%).

Interrater reliability

Across all neuropsychiatric symptoms, interrater reliability was calculated as kappa = 0.37 (95% CI 0.28–0.46, $p < .0001$), which corresponds to fair interrater reliability (Landis & Koch, 1977). Given that it was harder to distinguish the absence of symptoms from there being insufficient information, kappa was calculated where the only options were to state that a symptom was clearly present or not, giving $\kappa = .89$ (95% CI 0.76–1.01, $p < 0.0001$), corresponding to almost perfect agreement.

Neuropsychiatric symptoms

The prevalence of each neuropsychiatric symptom is shown in Figure 2. The most prevalent neuropsychiatric symptoms were sleep disorder ($n = 10$, 8.7%), depression ($n = 8$, 7.0%) and memory impairment ($n = 5$, 4.3%). Sleep disorder was specified in 3 cases (2.6%) as initial insomnia and was unspecified in the remainder. Symptoms of anxiety, fatigue, and apathy were reported relatively rarely, with only 1 case (0.9%) for each

Table 1. Frequency of clinical features of cases.

Clinical features	Frequency (%), $N = 115$
Parkinson's disease features	
Tremor	99 (86)
Rigidity	104 (90)
Bradykinesia	57 (50)
Encephalitis lethargica features	
Somnolence/sleep inversion	2 (1.7)
Central respiratory irregularities	1 (0.9)
Akinetic mutism	0 (0)
Obsessive-compulsive behaviour	1 (0.9)
Ophthalmoplegia	7 (6.1)
Oculogyric crises	0 (0)
Basal ganglia involvement	115 (100)
Eye disease	12 (10.4)
Medication use	2 (1.7)
Anticholinergic medication	1 (0.9)

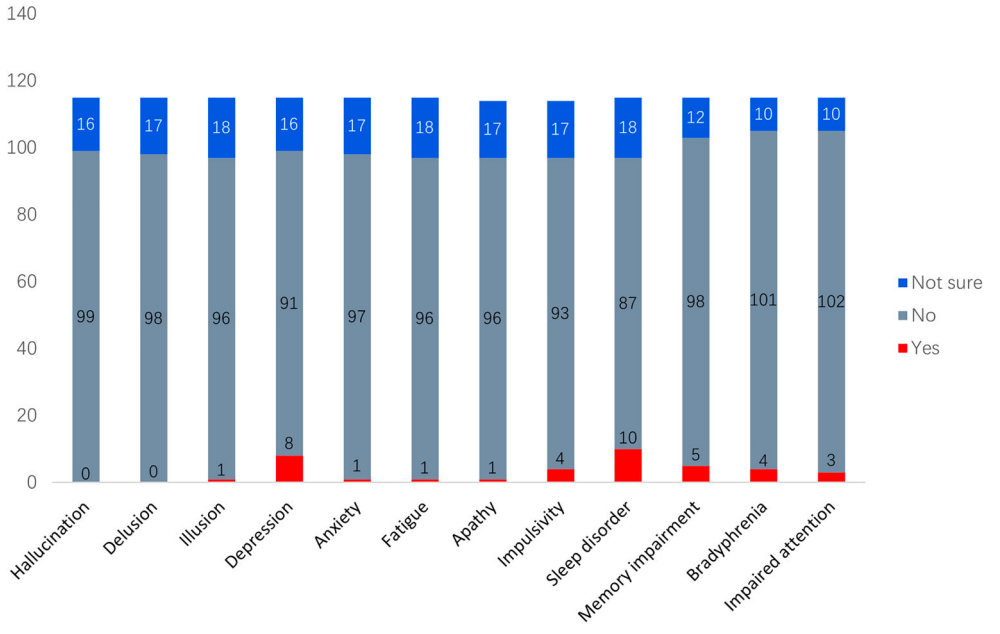

Figure 2. Frequencies of neuropsychiatric features.

symptom. There were 4 cases (3.5%) who exhibited bradyphrenia, and 3 cases (2.6%) with impaired attention.

In terms of psychotic symptoms, there were no cases of hallucination or delusion. There was one case of illusion, where a patient presented with misperception of temperature, which occurred in an individual who had long-term use of anticholinergic medications.

Discussion

The present study is – to our knowledge – the largest historical case review of the prevalence of neuropsychiatric symptoms in PD patients in the pre-dopaminergic therapy era to date. Out of 115 patients, there was not a single reported case of hallucination or delusion. The one patient who reported illusions had a history of long-term anticholinergic use. Other neuropsychiatric features, such as sleep disturbance, depression and cognitive impairment were more common, however.

The current finding supports several previous studies that have found psychotic symptoms, especially hallucinations and delusions, are associated with the use of dopaminergic medications (Carey et al., 1995; Factor et al., 1995; Park & Stacy, 2011; Poewe, 2008). A lack of cases with hallucinations or delusions might indicate that psychotic symptoms occur only after the use of dopaminergic medication. However, several studies were inconsistent with the current findings. A review of cases in the 18th and 19th centuries did find sporadic cases, but many also had dementia and others may have included cases of encephalitis lethargica, which were strictly excluded from the current study (Fénelon et al., 2006).

The findings of this study are limited by several issues. The sample size of the study, though the largest of its kind, was relatively small. The main limitation is that there was

not systematic elicitation of neuropsychiatric symptoms, so it is possible that some cases of hallucination or delusion were missed because they were not volunteered and not enquired about. Some medical histories were provided by family members, rather than the patient, so this may also have underestimated the prevalence of psychotic symptoms that did not cause overt functional impairment. It is possible that patients with overt psychosis would have been diverted to asylums rather than a neurological hospital, although the National Hospital for Neurology and Neurosurgery did admit patients for primary psychiatric disorders at the time as well. Another limitation is that fewer than 10% of cases were included for interrater reliability assessment. It would be beneficial for future studies to assess interrater reliability on a larger sample of cases. Moreover, since the present study included the records only of each patient's first admission, most of the cases of PD were relatively young compared to contemporary Parkinson's patients. Therefore, it is possible that psychosis later in Parkinson's disease could be missed in this cohort.

This study found no cases of hallucinations or delusions among 115 individuals with Parkinson's disease in the pre-dopaminergic era. Other neuropsychiatric features such as sleep disorders, depression and cognitive impairment did occur, however. There is likely to be some underreporting of psychotic features, but this study highlights the important role of dopaminergic medications in the generation of these symptoms. It also serves to emphasise the importance of other neuropsychiatric symptoms.

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