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Epidemiology of Psychiatric Symptoms in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a multifaceted disease characterized by motor symptoms, and often accompanied by autonomous and psychopathological symptoms. This comorbid psychopathology may take the form of affective, motivational, perceptual, and cognitive symptoms, as well as sleep disturbances and sexual problems. **Aim:** To review the prevalence, impact and risk factors of psychopathology in PD. **Methods:** Review of the literature. **Results:** The prevalence and cumulative incidence of psychopathological symptoms is high. The reported prevalence is 17% for major depressive disorder, 34% for anxiety disorder, 17% for apathy, 14% for impulse control disorders, 88% for sleep disturbances and 60% for sexual problems. The cumulative incidence of hallucinations is 60%. Mild cognitive impairment is present in at least 50% with a cumulative incidence of 66% for dementia after 12 years. All psychopathological syndromes have a strong negative impact on a number of disease parameters, other psychiatric comorbidity, and quality of life. All psychopathological syndromes tend to occur with higher frequency in patients with the hypokinetic rigid type of PD. Other risk factors divide into general and disease-specific risk factors, and may vary between the different syndromes. **Conclusion:** Given the prevalence and impact, clinicians need to be constantly aware of the possibility of psychopathology in their PD patients.

Nowadays, Parkinson's disease (PD) is generally considered a multifaceted disease with a broad spectrum of symptoms. According to the Queens Square Brain Bank diagnostic criteria, motor symptoms such as tremor, rigidity, hypokinesia, and postural instability are obligatory for a diagnosis of PD [1]. In addition to motor symptoms, the disease is often accompanied and sometimes preceded by non-motor symptoms including autonomic and psychopathological symptoms [2]. Autonomous symptoms include orthostatic hypotension, impaired cardiovascular regulation, dysphagia, delayed gastric emptying, urinary incontinence, constipation, dry mouth, disturbed thermoregulation with drenching sweats and sexual problems. Psychiatric symptoms include depression and anxiety, apathy, visual hallucinations and psychosis, impulse control disorders (ICDs), cognitive dysfunction and dementia. Additional symptoms include sleep disturbances, fatigue and pain.

Cluster analyses have shown that all forms of psychopathology occur more frequently in PD patients suffering from hypokinesia and rigidity than in PD patients suffering predominantly from tremor or from postural instability and gait difficulties [3, 4].

The broadness of the spectrum of symptoms can be understood by the disease's widespread pathophysiology in the brain. Braak et al. [5] proposed a staging system for this pathophysiology based on the presence of intraneuronal α-synuclein deposits, known as Lewy bodies. Different cerebral regions that are part of different functional neuroanatomic circuits and different neurotransmitter systems are affected sequentially, with pathology first affecting the olfactory tract and lower brainstem regions, then proceeding upwards to the midbrain, and finally to the basal forebrain and cerebral cortex. In this hypothesis, substantia nigra damage, which is associated with the characteristic motor symptoms of PD, occurs only in mid-stage disease. The diversity of systems affected, and the fact that some of these systems are affected before involvement of the substantia nigra, may explain the diversity of symptoms as well as the fact that some of the non-motor symptoms may precede motor symptoms. The neurobiology of neuropsychiatric symptoms in PD is discussed in the separate chapters. This chapter will provide a brief overview of the basic epidemiology of the psychiatric syndromes in PD that will be discussed in more detail in the other chapters of this volume.

Mood Disorders: Depression and Anxiety

Depression in PD has been the subject of study for a long time. The prevalence rates of depressive syndromes in PD reported in different studies vary widely, ranging from 2.7% to more than 90%, depending on the population studied, the way the diagnosis is established, and the type of prevalence reported (point prevalence, period prevalence) [6]. A recent systematic review of the prevalence rates of the different depressive disorders defined in DSM-IV depression in PD reported an average prevalence across studies of 17% for major depressive disorder, 22% for minor depression and 13% for dysthymia. In addition, 35% of patients showed a clinically relevant level of depressive symptoms without meeting the criteria for any specific depressive disorder [6]. As expected, the prevalence of major depressive disorder in PD patients is lower in the general population (8.1%) than in outpatient and inpatient hospital settings (24.0 and 21.7%, respectively). This is the same for the prevalence of clinically relevant depressive symptoms without a formal diagnosis of depressive disorder, which affects 10.8% in the general population versus 40.4 and 54.3% in hospital outpatients and inpatients, respectively [6].

Depression is linked to other PD symptoms and their severity. In cross-sectional studies, depressed patients have worse motor function and more limitations in activities of daily living (ADL) [7–10]. In addition, depressed PD patients exhibit more

cognitive symptoms [11, 12] and report a lower quality of life [13, 14]. In one study, depression was identified as the most important determinant of quality of life in PD patients [14]. Moreover, depression in the patient not only affects the patient, but is also a predictor of depression in the caregiver [15].

Depression is generally considered the result of multiple interacting risks – and protective factors. These can be divided into general risk factors for depression in the population and specific PD-related or treatment-related factors. In one of the few studies addressing general risk factors for depression in PD, a model consisting of five risk factors for depression in the general population, including age, (female) sex, a history of depression, a family history of depression and somatic comorbidity (other than PD), was able to predict major depressive disorder correctly in 75% of a sample of PD patients [16]. In addition, cognitive decline is associated with a higher prevalence of depressive disorder [17–20]. Specific PD-related variables associated with an increased risk for depression are the presence of motor fluctuations [18], a higher level of disability [19, 21] and more impairment of ADL functions [18, 20, 22]. The use of higher levodopa doses has been associated with increased levels of depression [20, 23], while some studies suggest that dopamine agonists may alleviate depressive symptoms [24, 25]. Depressive symptoms are more prominent in PD patients suffering from non-tremor-dominant forms of the disease [3, 4]. Several studies found an association between right-sided symptoms and the occurrence of depression [16, 21, 22], while one study found an association with left-sided symptoms [26].

Depression preceding the diagnosis of PD occurs with higher frequency than in control patients without a diagnosis of PD [27–29]. Odds ratios for depression preceding the diagnosis of PD vary from 1.2 to 3.1 [27]. In one study, 9% of PD patients suffered from depression in the last 3 years prior to diagnosis. Depression sufferers have a higher chance of being diagnosed with PD later [30].

Unlike depressive disorders, anxiety disorders have long been neglected in the research of psychopathology in PD. Fortunately, this is changing and in the past few years a number of larger scale epidemiological studies have been published. Again, prevalence rates for the different anxiety disorders vary widely across studies. Estimates suggest that up to 40% of PD patients experience substantial anxiety, and up to 34% have a circumscribed anxiety disorder as defined by DSM-IV criteria [31–35]. While earlier studies have described panic disorder as the most frequent anxiety disorder in PD, the more recent larger studies indicate that non-episodic anxiety disorders may occur more frequently. These recent studies report that 4–8% of patients suffer from panic disorder, 2–16% from agoraphobia without panic, 3–21% from generalized anxiety disorder, and 8–13% from social phobia (or social anxiety disorder) [31, 32, 34]. One single study reports on the prevalence of specific phobia (13%) and posttraumatic stress disorder (0%) [34]. In addition, 11.4% of patients suffer from significant anxiety symptoms without meeting the criteria for any DSM-defined anxiety disorder [32], while 12–20% meet the criteria for more than one disorder [32, 34]. This may be an indication of limited construct validity of DSM-defined anxiety

disorders in PD patients. There is a large overlap between depression and anxiety, which is reflected in the fact that 36–65% of PD patients suffering from an anxiety disorder also meet the criteria for a major depressive episode, while only 8% of those not suffering from an anxiety disorder meet these criteria [32, 34].

Anxiety in PD is associated with increased subjective motor symptoms, more severe gait problems and dyskinesias, freezing and on/off fluctuations [35–38]. Anxiety symptoms in PD patients also have a negative impact on health-related quality of life [34, 39]. There are not many studies of risk factors for anxiety disorders, and results from different studies are not always in line. In PD patients, female sex, severity of PD symptoms, the presence of motor fluctuations, as well as a previous history of an anxiety or depressive disorder have been identified as markers for anxiety disorders [31, 32, 34]. The use of a MAO-B inhibitor was associated with a reduced prevalence of anxiety disorders [32].

Anxiety may also precede the diagnosis of PD. One study reports an odds ratio of 2.2 for anxiety disorders and 2.4 for comorbid anxiety and depressive disorder in PD patients compared to control subjects in the years prior to diagnosis [40]. Whereas for depression such an association could only be made in the last few years preceding diagnosis, the increased risk of anxiety disorders was significant even up to 20 years prior to diagnosis of PD.

Apathy

Apathy is commonly observed in PD patients, but unfortunately it lacks a clear definition. Only recently has a set of diagnostic criteria for apathy as a syndrome been proposed. Based on earlier proposals by individual researchers [41–43], a workgroup endorsed by several professional associations, including the European Alzheimer's Disease Consortium and the European Psychiatric Association reached consensus on proposed diagnostic criteria. They defined apathy as a syndrome of reduced motivation, characterized by a deficiency in three symptom domains: activities, cognition and emotion [44]. The proposed diagnostic criteria have recently been validated in patients suffering from a range of neuropsychiatric diseases and in PD patients, where they showed good reliability and validity [45, 46]. So far, only one study involving PD patients has used these criteria and reported a prevalence of apathy of 17% [45]. In earlier studies, 'apathy' is usually diagnosed on the basis of an above threshold score on one of the apathy rating scales, or on the apathy section of the neuropsychiatric inventory (NPI). In these studies frequencies varying from 17 to 70% have been reported, depending on the population characteristics and assessment procedures [43, 47, 48].

In PD, apathy is associated with more severe cognitive deficits, more severe depressive symptoms, and a decreased quality of life [47–50]. Apathy is also considered a predictor of cognitive decline and dementia in PD patients [47].

Psychosis: Delusions and Hallucinations

Psychotic symptoms occur frequently in patients with PD and may affect up to 60% of the patients [51–53]. Psychosis in PD has a wide spectrum of presentations, ranging from 'lively dreams' to illusions or 'misinterpretation of objects', 'feelings of the presence or the passing of others', visual hallucinations, hallucinations in other sensory modalities, and delusions. Of those patients suffering from hallucinations, 64% suffer from illusions or sensations of presence or passing of people, 56% have visual hallucinations and 23% have auditory hallucinations [51]. Although longitudinal studies are scarce, it is clear that psychosis in PD tends to be persistent and progressive [54–56]. There is only one report of an increased incidence of psychosis prior to the diagnosis of PD [57].

The impact of psychosis in PD is considerable. It is associated with more severe depression, increased cognitive decline, and earlier nursing home placement [58, 59]. Psychosis is associated with a negative influence on quality of life of the patient [60], and increased caregiver strain [15].

Psychosis in PD is often seen as a 'drug-induced' psychosis due to dopaminergic treatment. However, the relation between medication and psychotic symptoms is not a simple one. Psychosis has been described in the pre-levodopa era, and infusion of levodopa in PD patients is not readily associated with incident hallucinations [61, 62]. Some studies find a correlation with higher levodopa equivalent medication doses [52], but most studies do not find such a relation [51, 63, 64]. Risk factors of psychosis in addition to medication are: higher age, higher age at onset, more advanced stage of disease, and disease duration. Moreover, comorbid conditions such as reduced vision [65], depression, cognitive decline and sleep disturbances predispose to psychosis [51, 52, 63, 64, 66].

Sleep Disturbances

Sleep disturbances are common in PD, and may affect up to 88% of patients [67]. They may take different forms. Rapid eye movement (REM) sleep behavioural disorder (RBD), excessive daytime sleepiness and 'sleep attacks' have received most attention. Other types of sleep disorders described in PD are insomnia, sleep apnoea, and restless legs syndrome (RLS). These types of sleeping disturbances are not mutually exclusive and may co-occur [68, 69].

RBD is characterized by abnormal behaviour during REM sleep due the absence of the usual atonia of voluntary muscles. Patients may enact their dreams, by which they may bring themselves or their partner in danger. Bruises, lacerations, fractures, etc. have all been reported as a result. The disorder may be present in 15–50% of patients [68, 70]. RBD is probably a predictor of hallucinations [71, 72].

Excessive daytime sleepiness occurs in 15–50% of patients [73]. It often co-occurs with fatigue and is significantly correlated with more severe motor symptoms, more disability, cognitive decline and depression [74]. Sleep attacks occur in up to 30% of

all patients [75]. They have been linked with the use of (any) dopamine agonist, but probably are associated with all dopamine replacement therapy [69]. Due to their occurrence without warning, sleep attacks may have considerable consequences if patients engage in potentially dangerous behaviour, such as driving.

Insomnia may take the form of problems with sleep initiation, sleep maintenance and early awakening. Insomnia may be due to physical discomfort, such as stiffness or muscle aches, nocturia or restless legs. Some 74–88% of patients report a degree of insomnia [67, 76]. Obstructive sleep apnoea syndrome (OSAS) is usually associated with obesity. Polysomnographic studies have shown that 20–50% of PD patients suffer from OSAS [68], often despite normal weight [77], which is tenfold the prevalence in the general population. RLS is a recently recognized syndrome that can occur in patients with PD. The prevalence of this coexistence is uncertain: some studies report a prevalence of 15% [78], while others report that patients may have restlessness, but fail to satisfy diagnostic criteria for RLS [79]. Apart from low serum ferritin, no other predictors of RLS are known [80].

As expected, disturbed sleep may have a great impact on the quality of life of patients [81, 82]. It is a risk factor for cognitive deterioration and dementia [83, 84], more frequent hallucinations [51] and a predictor for nursing home placement [59]. Sleep disturbances in patients also affect caregiver sleep to a great degree [85–87].

Sexual Dysfunction

Sexual dysfunction in patients with PD may take the form of impaired function or as hypersexuality. Hypersexuality can be defined as excessive sexual thoughts or behaviours that constitute an *atypical change from premorbid* sexual behaviour of the patient. It may take the form of inappropriate or excessive requests for sex from the partner, promiscuity, compulsive masturbation, the use of telephone sex lines or (online) pornography, or paraphilias [88]. These behaviours are usually associated with use of dopamine agonists or subthalamic deep brain stimulation, and will be discussed below under ICDs.

Sexual dysfunction is more common than hypersexuality. Although sexual dysfunction increases with age, there is evidence for PD-specific factors since impaired sexual dysfunction was reported in 60% of PD patients, as compared to 37% of matched controls [89]. Men with PD are more likely to report sexual problems than women [90]. Impaired sexual dysfunction in men may take the form of erectile dysfunction or impairment of ejaculation (up to 70%) or diminished libido (44%); reduced libido is reported in 44% of women [91–93]. In men, sexual dysfunction has been associated with testosterone deficiency [94].

Many factors may affect sexual function in PD patients: motor impairment, pain, fatigue, sweating, salivary drooling, side-effects of medication, as well as the changed roles in the relationship [95]. The epidemiology and aetiology of sexual dysfunction in PD has not been extensively studied.

Impulse Control Disorders

ICDs are a range of maladaptive behavioural patterns that are characterized by impulsiveness or compulsiveness. ICDs may take the form of pathological gambling, compulsive shopping, hypersexuality, binge eating, and compulsive medication use (the latter is often called 'dopamine dysregulation syndrome' or 'hedonistic homeostatic dysregulation'). The exact psychopathological nature of ICDs is still under debate. If accompanied by elated mood, hyperactivity and reduced sleep, the behaviour may resemble a hypomanic state; if the behaviour is not associated with hedonic gratification, it may resemble a compulsive disorder; moreover, behaviour in ICDs may resemble that seen in addictive disorders and is sometimes viewed as a behavioural addiction [96].

In the largest study to date, including 3,090 PD patients, ICDs were described in 13.6% of patients. Of these, 5.7% suffered from compulsive buying, 5.0% from compulsive gambling, 4.3% from binge eating disorder, and 3.5% from compulsive sexual behaviour [97]. Of patients suffering from ICDs, 29% suffered from more than one type of ICD simultaneously. The percentages reported in this study are in line with those reported in several smaller studies [88, 97–100]. Compulsive medication use probably occurs in 3.4–4% of patients [96]. Men are more prone to suffer from compulsive sexual behaviour (OR 11.98), and women were more prone to suffer from compulsive buying (OR 1.82) and binge eating (OR 1.75) [97].

The most important risk factor for ICD is treatment with a dopamine agonist. Seventeen percent of patients treated with a dopamine agonist will have ICD. The odds ratio of having an ICD while being treated with a dopamine agonist versus not being treated with a dopamine agonist was 2.72 [97]. The association with dopamine agonists is probably a class effect, since no relevant differences were found between the incidence of inpatients being treated with pramipexole or ropinirole [88, 97, 98]. There was no association with the dose of dopamine agonist [88, 97], but there was an association with the dose of levodopa. When patients were treated with a combination of dopamine agonist and levodopa, compared with a dopamine agonist alone, there was an additional increase in the odds ratio for ICD to 1.42 [97]. Other risk factors for ICDs are younger age, younger age at onset, being unmarried, smoking, a family history of gambling problems, and alcohol use [88, 97].

It is hard to specify the impact of ICD in terms of disease severity, ADL or quality of life. Due to the nature of the syndrome, ICDs can be very disruptive on a relational, financial and social level. Compulsive gambling often leads to serious debts and compulsive sexual behaviours to relational difficulties and separation [88].

Cognitive Impairment and Dementia

Cognitive impairment and dementia are both common in PD. Cognitive impairment may be present early in the course of the disease and be associated with dopaminergic

deficiency in the mesocortical circuit. This 'mild' cognitive impairment (MCI) usually takes the form of mental slowing, attentional difficulties and disturbed executive function, including reduced mental flexibility and planning difficulties, while memory remains spared. About 50% of the patients will have cognitive impairment in at least one domain [101, 102]. MCI is a predictor of later dementia in PD [103, 104].

Dementia in PD is characterized by disturbances in a number of cognitive functions, while behavioural symptoms such as affective changes, hallucinations and apathy are frequent [105]. For a diagnosis of Parkinson dementia, a slow cognitive decline is necessary in at least two out of four core cognitive domains (attention, memory, executive and visuospatial function) [105]. Memory impairment is not obligatory for the diagnosis. A systematic review of dementia in PD reported that 24–31% of PD patients suffer from dementia, and that dementia associated with PD constitutes 3–4% of the cases of dementia in the population [106]. However, the cumulative incidence probably gives a better impression of the risk of dementia. Long-term follow-up studies show that the majority of PD patients will eventually develop dementia. Percentages reported vary from moderate percentages, e.g. 38% after 10 years [107], to high percentages: 52% after 4 years, and 78% after 8 years [108]; another study reports that 66% of patients will suffer from dementia after 12 years of follow-up [109], or even 87% after 20 years [110].

Risk factors associated with the occurrence of dementia are higher age, longer disease duration, more severe disease, hypokinetic forms of the disease, more disability, and probably also the existence of depression or psychosis and male sex [105, 107–111].

As is to be expected, dementia has a negative influence on quality of life [112]. Dementia is also a predictor of nursing home admission and mortality in PD [52, 58].

Conclusion

PD is a multifaceted disease, characterized by motor symptoms, autonomous symptoms and psychopathological symptoms. Among these psychopathological symptoms are affective, motivational, perceptual, and cognitive symptoms, as well as sleep disturbances and sexual problems. The prevalence or cumulative incidence of these symptoms is high, and they generally have a large impact on the general level of functioning and quality of life of patients. Given this prevalence and impact, it is important to be aware of these symptoms in clinical practice.

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