Correlates of psychiatric and psychological distress in patients with Parkinson’s disease

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Abstract
Parkinson’s disease is the second most commonly diagnosed neurodegenerative disorder worldwide and the physical manifestations of the disease are well documented in the literature. However, in excess of 60% of patients with the disease report having one or more psychiatric symptoms which worsen as the disease progresses. These symptoms arise differentially from the same pathology which underlies the disease or from the treatment with dopaminergic drugs. Psychiatric and psychological difficulties tend to be under-recognised and undertreated yet cause great disability, significantly impact the quality of life of patients and add to greater burden on their caregivers. These symptoms can be relieved through adjusting the doses of anti-Parkinson’s drug therapy and success in improving psychological distress has been found using adjuvant psychotherapeutic intervention, most notably with Cognitive Behavioural Therapy.

Keywords: Psychiatric symptoms; Dopaminergic treatment; Non-motor effects; Parkinson’s disease; Caregiver burden

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Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder worldwide, affecting an estimated 0.4%-1% of people between the ages of 60 to 79 and rising to approximately 2% of people over the age of 80 [1]. Disease onset is typically after age 50. The primary pathology involves the destruction of dopaminergic neurons in the substantia nigra pars compacta within the midbrain and the consequent decrease in transmission of dopamine with both motor and non-motor sequelae; circuits related to emotion and cognition are also variably negatively affected [2-4].

PD is classified as a movement disorder but motor problems form only part of the symptomatology of the disease [5]. The physical aspects of PD, such as tremor, rigidity, and postural imbalance, are the defining characteristics of the disease and diagnosis is generally made on the basis of movement impairment [6]. However, PD is a complex neurodegenerative progressive disease process which has a much greater effect on patients’
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quality of life than solely physical impairment and deficits in mobility. Neuropsychiatric symptoms are intrinsic to and disabling in PD. The neurobiological bases of these symptoms are complex, partly because of the disease itself and partly because of the effects of dopaminergic treatment such as dopamine agonists, which stimulate dopamine receptors and levodopa, the immediate precursor of dopamine. For some PD patients, the neuropsychiatric burden of the disease causes greater morbidity than motor dysfunction [5,7].

Many non-motor aspects of PD, such as depression, anxiety, drug-induced psychosis, impulse control disorders, cognitive impairment, and sleep disturbances are commonplace but under-recognised and undertreated [2,6]. This may be due to lack of awareness among healthcare providers or a greater emphasis being placed on treating motor deficits. However, these symptoms can significantly limit the patient's ability to take part in their usual activities of daily living and participate in social and recreational interests, thereby adversely affecting quality of life. Evidence also suggests that presence of psychiatric morbidity is an independent predictor for poorer outcome, i.e., institutionalization and increased mortality rates [5,8].

The insidious onset of disability often necessitates that people with Parkinson's require care in multiple settings. They may receive outpatient occupational, physical, speech, and recreational therapies coupled with care provided by family members and friends at home. These informal caregivers play an important role in keeping individuals with Parkinson's disease engaged in life, which ultimately can improve their quality of life. Informal caregivers of Parkinson's patients are often called “care-partners” to highlight the fact that the disease process has an impact on the caregivers as well [9].

Psychological features of PD

Research demonstrates that in excess of 60% of PD patients report experiencing one or more persistent psychological and/or psychiatric symptoms [6]. These features may stem from the pathophysiology which underlies the disease and include depression, anxiety and apathy which deteriorate with disease progression. Dementia is also a well-documented sequel of PD [10].

Other aspects are related to the pharmacological treatment of PD, of which the primary intervention is dopamine replacement therapy. This effectively relieves motor impairments but may elicit non-motor sequelae including vivid dreams, visual or tactile hallucinations, delusions and confusion. The management of treatment-related psychosis is complicated by the fact that the necessity to reduce dopaminergic drugs may exacerbate motor symptoms and require the application of antipsychotics [11].

Depression

Depression is a frequent comorbid disorder of Parkinson's disease and may result from the disease process; however, little is known about its pathomechanisms. It is likely that a greater degeneration of dopaminergic neurons which mediate cognition, emotions and reward-seeking behavior, in addition to a reduction in other neurotransmitters such as noradrenaline and serotonin, may give rise to depression.

Diagnosis is complicated by the fact that many features of depression, such as low affect, anhedonia, hopelessness, suicidal ideation, mimic those of PD [11,12]. Although depression is an important factor negatively affecting the quality of life of parkinsonian patients, it often remains undiagnosed and therefore untreated. Furthermore, antidepressant therapy is problematic because of the need to combine antidepressant drugs with antiparkinsonian treatments [13].
Depressive symptomatology in PD may manifest across a broad range of severity, chronicity and etiology. This includes major depression, dysthymia, subsyndromal depression or depressive disorder due to PD.

In terms of pathophysiology, changes in dopaminergic, noradrenergic, and serotonergic systems are seen as primary causes of depression in patients with PD. However, psychological reactions to the diagnosis or disability associated with PD are also instrumental in precipitating depressive reactions [12].

Risk factors for depression in PD patients are female gender severity of motor symptoms, dosage of dopaminergic medication, anxiety and sleep disturbances, psychotic episodes such as hallucinations and cognitive decline and dementia [12].

**Anxiety**

Anxiety disturbances are common non-motor psychiatric comorbidities in (PD) with a prevalence shown to be as high as 60% [14,15]. The neuropathology of PD gives rise to anxiety and the patient’s response to progressive disease symptoms may additionally evoke or exacerbate mood dysfunction.

Anxiety may occur independently of motor symptoms or may occur simultaneously, with some studies suggesting that anxiety disorders may begin up to 20 years before any motor symptoms become apparent [16]. These studies indicate that patients with PD are at greater risk of developing anxiety disorders before the diagnosis of PD which suggests that anxiety may be an early non-motor constituent of PD. This, in turn, suggests that disability may contribute to the experience of anxiety but is not the only determinant. The reason that anxiety and depression may be precursors of the appearance of motor symptoms in PD may be due to the finding that the parkinsonian disease process begins in the brainstem and advances towards the midbrain. The brainstem contains serotonin and adrenergic neurons which may contribute to the experience of anxiety and depression, whereas the midbrain contains dopaminergic neurons which contribute to the motor symptoms of PD [14].

Disease-specific anxiety can develop, for example, apprehension toward physical symptoms (freezing of gait) or the stigma of being perceived as physically disabled [17]. These contribute to reductions in quality of life, high levels of care dependency and greater caregiver burden but may be under-recognized and undertreated in patients with PD due to several factors, inter alia, diagnostic imprecision, the overlap of motor and cognitive symptomatology which are features of PD, the complexity of diagnosis, access to healthcare and resources, as well as under-reporting of symptoms by patients and caregivers [14].

Studies have demonstrated that anxiety and depressive syndromes frequently co-occur [14]. In addition, panic attacks and social phobia appear to be a feature in an estimated 30% of PD patients. Anxiety may exacerbate mental and somatic distress and existing motor symptoms; patients may report that episodes of anxiety worsen existing tremor. Similarly, fear of falling is associated with impaired postural stability [14].

Thus, anxiety in PD may be related to a combination of medical, neurochemical and psychosocial factors. In certain patients, anxiety disorders may be seen as a reactive response to the diagnosis of PD. However, when compared with other patients with chronic illnesses and similar levels of disability, anxiety in patients with PD appears to be significantly more severe. Psychosocial factors are related to fear of inability to function or embarrassment brought about by the exhibition of motor symptoms. Neurochemical factors are related to the brain and the chemical pathways associated with the degeneration of subcortical nuclei and ascending dopamine, as well as norepinephrine and serotonin pathways which may be responsible for symptoms of anxiety [12]. Several studies have shown a significantly
higher rate of family history of anxiety conditions in PD patients which suggests there may be genetic links between anxiety and PD in some individuals [16].

Subsyndromal anxiety describes anxiety symptoms that do not meet the complete Diagnostic and Statistical Manual Fifth Edition (DSM-V) [18], diagnostic criteria but still have a significant effect on patient quality of life. Research suggests that 2%-25% of PD patients experience subsyndromal symptoms of anxiety. One recent study suggests that subsyndromal anxiety does not necessarily present with comorbid depression, and that subsyndromal anxiety may be a unique characteristic of PD [15]. Risk factors for anxiety are female gender, young age at onset and onset of periods of freezing or immobility [12].

Apathy and anhedonia

The definition of apathy is not consistent in the literature but may be primarily defined as a marked loss of motivation and decreased interest in daily activities which are not associated with emotional distress or cognitive impairment [19]. It is a common feature of neurocognitive disorders. Changes in subcortical structures and function in Parkinson’s patients manifest as a spectrum of abnormalities in goal-oriented behaviours which is termed apathy, and can affect the quality of life of not only the patient but caregivers as well [20]. There is an overlap between symptoms of apathy and depression in that both feature loss of, inter alia, interest and pleasure, indifference, decreased initiation and persistence and hypersomnia. Apathy differs from depression in that symptoms such as suicidality, excessive guilt, despair and loss of appetite are not present. Apathy is common phenotype of depression, but whereas depression is regarded as an affective disorder, apathy is termed a motivational disorder not co-occurring with affective disorders [21]. Risk factors for apathy are more severe motor symptoms, which suggests it may be due to dopamine depletion, and cognitive decline [12]. Anhedonia which is defined as the inability to experience social or physical pleasure, is a common symptom in PD patients [22]. It is often confused with depression, but may rather be regarded as a core symptom of major depression [23]. Differences between these two constructs exist in terms of mechanisms, therapeutic management and prognoses related to patients with PD [12,24]. Independently of the presence of depression in patients with PD, anhedonia is explained by the dysfunction of the dopamine pathway which occurs secondary to the degenerative process of PD and is related to depression, severity of apathy and frontal lobe dysregulation [23,25].

The treatment of anhedonia in PD patients may be confounded by the presence of impulse-control disorders such as pathological gambling, sexual behavior, buying or eating which have been observed in patients with PD. Apathy and anhedonia are closely related [25]. Studies show that where apathy is observed, anhedonia is also significantly present. No relationship between apathy and depression has been observed so their conclusion is that apathy and anhedonia are considered to have similar mechanisms and morbid states [21].

Dementia

The prevalence of dementia in patients with PD is estimated to be high, in the order of 83%, with PD patients at a 5-6-fold greater risk of developing dementia than the general population. This prevalence increases with age and the time elapsed since diagnosis of PD. Its development impacts negatively on daily functioning and is related to a significant increase in morbidity and mortality [26].

The clinical diagnosis of dementia due to PD (Parkinson’s disease dementia; PDD) is determined on the basis that dementia occurs in the context of established PD [1]. It is associated with depression, anxiety, hallucination, apathy and irritability [12]. Current treatments offer modest symptomatic relief and new treatments are slow to emerge because while the pathological processes which
underlie the motor deficits of PD are well understood, the neural mechanisms underlying the process of dementia and the associated cognitive deficits are less well known. The complexity of the neuropathological factors which underlie the development of PDD renders positing a generalized pathophysiological mechanism across all patients difficult [26].

Dementia in PD patients may manifest as a combination of cortical or subcortical features. Cortical features comprise impaired memory and language dysfunction, whereas subcortical features consist of executive dysfunction, that is, difficulties with planning and organizing, problem solving, strategy development, slowness of thought and impaired working memory. However, deteriorating memory is typically not an initial symptom of dementia in PD and often diagnosis of dementia is delayed [12].

It is broadly acknowledged that the clinical phenotype of PDD extends beyond the dysexecutive syndrome apparent in early disease and includes further deficits in recognition memory, attention processes and visual perception in addition to visual hallucinations and cognitive fluctuations. Executive impairment deteriorates with disease progression and has deleterious effects on social functioning [26].

Many PD patients may also experience dementia caused by the presence of Lewy Bodies; abnormal proteins found in the brainstem of patients with PD. In dementia with Lewy Bodies, these abnormal proteins are found throughout areas of the brain including midbrain and the cerebral cortex. Acetylcholine is depleted, causing dysregulation of perception, thinking, and behavior [27]. The diagnosis of Lewy Body dementia is predicated on the presence of three features:

- Fluctuations in cognition with variations in attention span/alertness
- Consistent presence of detailed visual hallucinations
- Parkinsonism movement that occurs spontaneously

In patients presenting with two of these features, a diagnosis of Lewy Body dementia is probable, while in those patients with just one feature, a diagnosis of Lewy Body dementia is possible. In addition, impairments in executive function, visuospatial ability, and attention are often seen in patients with Lewy Body dementia [28]. Risk factors for dementia in PD are older onset of disease, longer duration of PD symptoms, the presence of hallucination, marked postural and gait deficits, the akinetic-rigid form of the disease and smoking [12].

**Psychosis**

PD psychosis (PDP) refers to a spectrum of hallucinations, illusions and delusions that manifest throughout the course of the disease [29]. Susceptibility to psychosis correlates strongly with the patient’s mental status: PD patients not experiencing cognitive decline and not receiving medication to remediate motor symptoms rarely experience hallucinations or delusions [5]. Psychosis may appear as minor phenomena such as illusions (distorted sensory perceptions of real stimuli), passage hallucinations (fleeting visual hallucinations that occur in the peripheral visual field) and presence hallucinations (the sensation of a presence of someone/something nearby where none exists), formed visual and nonvisual hallucinations and delusions [30]. Hallucinations may present as people or inanimate objects. In early stage disease, with preserved insight, the patient may be aware that these are hallucinations [31]. As disease progresses, hallucinations may become nonvisual with delusions. Delusions usually incorporate ideas of persecution, jealousy, theft or grandiosity [12]. Hallucinations are more likely to appear in situations such as at twilight (termed sundowning), where there are few background stimuli, or when the patient is alone.
in a quiet environment [5]. The prevalence of visual hallucination appears to be in the order of 22%-38%, while auditory hallucination occurs from 0%-22%. Overall, psychoses range from 26%-82%. Recent studies point to PDP as a set of symptoms with distinct pathophysiological mechanisms, rather than a single pathophysiological symptom with a range of severity [29].

There is difficulty in differentiating between PDP, drug-induced psychosis and combined forms. Dopamine agonists are more likely to provoke hallucinations than is carbidopa/levodopa [5]. An estimated one third of patients treated with long-term dopaminergic therapy develop drug-induced psychosis [12]. Psychosis with hallucinations and delusions has been found in an estimated 20% of patients without dementia who are receiving PD medication. However, those PD patients with dementia frequently experience visual hallucinations, delusions and paranoid ideation even when not receiving anti-parkinson’s medication. Commencing dopaminergic therapies commonly triggers or exacerbates the underlying susceptibility to psychosis in patients who have dementia with Lewy Bodies or PDD. Hallucinatory experiences in PD become increasingly vivid and frightening for the patient as the symptoms develop into psychosis. Psychotic symptoms can occur early after starting treatment for PD, although much less frequently than in the later stages of the disease [5]. If reduction in PD medication fails to bring about improvement in symptoms, atypical (second-generation) antipsychotics, must be considered [4,12,32].

Risk factors are female gender, dopamine agonist therapy, cognitive decline and anticholinergic drug therapy. The presence of psychosis poses an increased risk of dementia while cognitive decline is a risk factor for psychosis in PD and vice versa (Han et al., 2018). Older age at onset, the presence of sleep disorders, other psychiatric symptoms and medication are also factors likely to influence the development of PDP [31].

**Impulse control disorder**

Dopaminergic medication-related impulse control disorders (ICDs), also termed “behavioral addictions,” include features such as pathological gambling, compulsive shopping, hypersexuality (including paraphilias), and binge eating. The inability to resist engaging in these behaviors rises to the level where it is termed a disorder when it causes distress or impaired functioning [33]. Studies show that there may be a “Parkinson personality” characterized by caution and a decreased tendency to indulge in pleasurable activities which when treated with dopaminergic medication, may become obsessive in the pursuit of gratifying experiences. ICDs appear to be more common in patients who are receiving treatment with a dopamine agonist than in patients treated only with the dopamine precursor levodopa.

Risk factors for ICDs include treatment with dopamine agonists, treatment with very high doses of levodopa, with patients receiving treatment with both at the highest risk, a personal or family history of ICDs or addiction and the presence of premorbid impulsive traits. Gender differences exist for particular ICDs. Studies have shown that men are more likely to engage in hypersexual behaviours where women are more likely to engage in impulsive buying or binge eating [3].

**Effects on caregivers of patients with PD**

The primary goal in the management of PD is to treat the symptomatic motor and non-motor features of the disorder, with the objective of improving the patient’s overall quality of life. Appropriate management requires an initial evaluation and diagnosis by a multidisciplinary team consisting of neurologists, primary care practitioners, nurses, physical therapists, social workers, and pharmacists. It is also important that the patient and his or her family have input into management decisions [34]. PD imposes significant demands on patients but the psychological effects on those people living and
caring for these patients, who also often have a reduction in their quality of life (QOL), has not been extensively studied. Significant demands may be placed on caregivers, as they assume more daily tasks and provide increasing physical, emotional, and economic support [35].

What is termed Caregiver Burden (CB) is a negative psychological state in caregivers induced by the demands of caring for a person with an illness or disability. The management of CB in PD is significant because informal caregivers contribute substantially to the well-being of patients with PD, often at the expense of their own financial, social and personal well-being. Failure to identify and manage CB may lead to burnout and consequently to premature institutionalization of the patient with PD [36]. CB increases in those caring for relatives with PD and a significant correlation has been established between increasing CB and a reduction in a caregiver's QOL and level of depression. Studies have shown that PD caregivers have greater psychological distress than the general population which may manifests as higher levels of depression, anxiety, and stress, which correlate with increasing disease progression [9,35].

As PD is classified as a motor disorder, the burden of providing physical care would appear to be the greatest stressor. However, some studies show that patient psychological issues are experienced by caregivers as particularly stressful [9]. Other studies suggest that patients’ physical dependency correlates more significantly than psychological behavior, with caregiver distress [37].

Recent studies suggest that greater CB is more likely in patients with progressed disease, poorer therapeutic control of motor symptoms and experiencing more frequent and more severe mood symptoms. These studies further identify early signs of CB which may include an increase of patient self-reported mobility issues, daily activity dependency and fatigue [38].

Further, it appears that the PD patient’s sleep symptoms influence levels of distress in caregivers of patients with PD. A recent study found that sleep quality and depression better predicted caregivers’ well-being than motor disability. Since sleep disorders appear in 80-90% of patients with PD, this has significant consequences for the well-being of both patient and caregiver [39]. Other factors associated with increased CB include severity of patient psychiatric symptoms and falls [40]. A recent study found that caregiver self-efficacy and social support were mediating variables affecting CB, caregiver anxiety, and depression [41].

**Pharmacological interventions**

It is well documented in the literature that antidepressant therapy may benefit PD patients who are depressed and can be effective in improving the quality of life of patients and even relieve motor symptoms with few adverse effects. In addition, certain medications used to relieve sleep disorders have been found to exert a positive effect on PD patients. Some success has been achieved in remediating the memory deficits which commonly appear as PD progresses, with drugs commonly used to treat Alzheimer’s disease [42].

Studies have demonstrated that many antipsychotics given to PD patients for hallucinations or delusions may eliminate the symptoms, but inhibit the action of dopaminergic drugs given to control motor symptoms. This may result in a deterioration of the patients’ motor symptoms. Newer antipsychotics have been developed which are to remediate psychotic symptoms without exerting a deleterious effect on the patients’ motor symptoms [14]. Current research is aimed on finding pharmacological treatment that will slow down disease progression. There is a strong focus on neuroprotective treatments...
such as nonsteroidal inflammatory drugs as there is significant evidence that inflammation may be involved in the PD process [2]. Physical activity (PA) is also increasingly recommended as an adjunct intervention for patients with PD and can be seen as complementary to pharmacological treatment in managing the inherent decline of progressive disease. Studies suggest that physical and cognitive capacity improve with PA, particularly in the spheres of limb strength, metabolic functions, gait, mobility and balance in relation to physical effects and some improvement was found in relation to depressive symptoms [43].

Psychotherapeutic intervention

Besides standard pharmacological treatments, psychiatric symptoms can be treated by means of non-pharmacological approaches including various types of psychotherapies, the most widely used of which is cognitive behavioral therapy (CBT). CBT has been found by studies to be beneficial in improving mood in both patients with PD and their caregivers [44]. Several factors point towards CBT being particularly useful in treating psychiatric symptoms associated with movement disorders as these disorders are often associated with mood disorder, Obsessive Compulsive Disorder (OCD), and fatigue. These are pathological conditions in which CBT has been shown to be effective.

CBT is a psychotherapeutic approach that challenges dysfunctional beliefs and emotions, maladaptive behaviors and cognitive processes through a number of goal-oriented and systematic procedures. CBT focuses on the patient’s thoughts, appraisals, and beliefs in shaping feelings and actions, and on the identification and modification of dysfunctional thoughts to improve mood. The theoretical foundation on which CBT is based assumes that emotional reaction and behavior depend on cognitive processing in specific situations. CBT aims to introduce change in the patient’s subjective experience through cognitive and emotional restructuring of thoughts, beliefs, memories and emotions. Various techniques, each of which is specific to different disorders, may be utilised [45].

Changes in attitudes and behaviors through psychotherapy may allow caregivers to be more sympathetic to patients. Reduction in the caregivers’ stress in turn reduces stress, anxiety, and depression in the PD patients as well. It has also been shown that increases in executive functioning in caretakers result from CBT [44]. Studies have shown significant effects of CBT on depression and anxiety in PD patients and treatment gains were demonstrated to continue and further improve over time [46]. Many studies examining the psychiatric sequelae of PD emphasise the need for greater liaison between neurologists and psychiatrists in identifying patients at risk for mood disorders. There is evidence to suggest that this may also lead to a better understanding of other diseases are based in the brain, such as attention-deficit/hyperactivity disorder, bipolar depression, and schizophrenia [2,47].

Conclusion

Parkinson’s disease has a significant negative impact on patients, not only in terms of their physical deficits but also in terms of the effects of both disease and its treatment on their psychological functioning. These effects are largely under-observed and a majority of patients experience psychiatric symptoms. These deteriorate with disease progression and have a significant impact on the quality of life of not only the patient but caregivers as well. Given the prevalence of PD as the second most commonly diagnosed neurodegenerative disorder worldwide, it is important for those healthcare professionals treating PD patients to be aware of the prevalence of psychiatric and psychological symptoms and to refer patients for adjuvant psychotherapeutic care in order to optimise the quality of life of patients and caregivers.
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