

Review Article

Neurobiology of Depression and Anxiety in Parkinson's Disease

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Depression and anxiety are common in Parkinson's disease (PD) and have important consequences on quality of life. These have long been recognized as frequent accompanying syndromes of PD, and several reports suggest that these are the causative process or risk factors that are present many years before the appearance of motor symptoms. The neurochemical changes in PD involving dopamine, norepinephrine, and serotonin might be related to the pathophysiology of depression and anxiety, but this is still not clear. Several studies showed that anxiety in PD patients occurs earlier than depression, during premotor phase, suggesting that there may be a link between the mechanisms that cause anxiety and PD. Whereas a recent study reported that PD patients with depression and anxiety were associated with different demographic and clinical features.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that results in progressive extrapyramidal motor dysfunction primarily related to loss of dopaminergic nigrostriatal function. The loss of dopamine leads to difficulty with movement, including slowness or lack of movement, rigidity, and resting tremor. Though less acknowledged, non-motor symptoms (NMSs) in PD are common and were recognized by Parkinson himself [1]. He referred to urinary incontinence, constipation, sleep disturbance and delirium. PD patients also suffer from a variety of NMSs, including significant changes in emotional well-being that deleteriously impact their quality of life [2]. O'Sullivan S. S. et al. attempted to correlate NMSs in PD by reviewing medical histories of pathologically identified patients. Twenty-one percent of patients presented with NMSs including pain, urinary dysfunction, depression, and anxiety [3]. In addition, premorbid personality traits consisted of cautiousness, inflexibility, introversion, and

lack of novelty seeking, which also persist after the onset of motor illness. It has been suggested in the general population study that these traits, as well as the low premorbid rates of coffee drinking and alcohol consumption, may reflect an underlying damage to the mesolimbic dopaminergic pathways among individuals predisposed to PD [4].

However, the NMSs of PD are not well recognized in clinical practice and one US study reported that existing depression, anxiety, and fatigue are not identified by neurologists in 50% of consultations, and sleep disturbances are not identified in over 40% of consultations [5]. Psychiatric symptoms may be missed if a clinician's interest is mainly focused on motor impairment. Patients' reluctance to report psychological symptoms may also contribute to the limited detection of these disorders.

This paper is a review of current data on psychiatric features in PD, specifically depression and anxiety, which are important determinants of quality of life, and, therefore, requires early detection and intervention.

2. When Do Depression and Anxiety Occur in PD?

PD cannot be clinically diagnosed until motor symptoms appear, and it is commonly thought that NMSs occur only in late or advanced PD. However, NMSs can indeed present at any stage of the disease, including the early and pre-motor phase [6–9]. Several case-control or cohort studies suggest that anxiety may be one of the earliest manifestations in PD. In a population-based, case-control study, PD patients' historical medical records were examined for depression and anxiety in pre-motor phase of PD (Table 1). This finding held true even when the analysis went as far back as 20 years before the onset of motor symptoms [10]. In addition, the Health Professionals Follow-up study showed that “phobic anxiety” was a significant risk factor for the development of PD [11], and the composite Minnesota Multiphasic Personality Inventory of neuroticism also showed that patients with high anxiety were at an increased risk for PD [12].

While the previously mentioned articles do not look at or show a link between depression and PD, there are several supporting articles. One study found that the initiation of any antidepressant therapy was associated with a higher risk of PD within 2 years after the start of treatment, suggesting that depressive symptoms could be an early manifestation of PD [14]. The second study used a self-report of depression and use of psychotropic medication to identify a link between depression and PD [15]. The third study looked at a database of medical histories in the Netherlands and found a positive association between depression and subsequent incidence of PD [13]. While there are some disparities between depression and PD during the pre-motor phase, all the articles that have looked at anxiety and PD have shown a link, suggesting that there may be an association between the mechanism that causes anxiety and PD. In summary, these reports show that anxiety and depression are associated with PD and suggest that the causative process or risk factors underlying PD may be present many years before the appearance of motor symptoms.

3. Depression

According to DSM-IV criteria, a major depressive disorder is defined as a person who must either have a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period in addition to fatigue, insomnia, weight loss, and so on. It is estimated that between 30–45% of PD patients are depressed, which reduces both subjective and objective quality of life independent of motor deficits [16–19]. By contrast, the average prevalence of clinically relevant depression in an age-matched group of the general population is roughly 13.5% [20].

One potential explanation for this increased prevalence of depression is the damage that PD has on the dopaminergic, serotonergic, and noradrenergic systems [21]. Remy et al. [22] used [¹¹C]RTI-32 PET, an *in vivo* marker of both dopamine and noradrenaline transporter binding, to localize differences between depressed and nondepressed PD patients. Depressed PD patients had lower [¹¹C]RTI-32

binding than nondepressed PD patients in the limbic system, but also in locus coeruleus, which is the noradrenergic nucleus. They suggested that depression in PD might be associated with a loss of dopamine and noradrenaline innervations in the limbic system. A randomized, controlled trial of paroxetine CR (selective serotonin reuptake inhibitor (SSRI)), nortriptyline (Tricyclic antidepressant (TCA)), and placebo in patients with PD and depression showed that Nortriptyline was efficacious in the treatment of depression and paroxetine CR was not [23]. However, Atomoxetine (selective norepinephrine reuptake inhibitor (SNRI)) was not efficacious for the treatment of depression in PD [24]. TCA is a dual (serotonin and noradrenaline) reuptake inhibitor, SSRI inhibits only serotonin, and SNRI inhibits only noradrenaline; therefore, it is possible that the mechanism of the apparent superiority of nortriptyline is its effect on norepinephrine besides serotonin.

The first randomized study done by Rektorova et al. showed possible antidepressive effects, not dependent on motor improvement of pramipexole (PPX) as compared to pergolide [25]. PPX, a D₂/D₃ receptor agonist, preferentially acts on D₃ receptors in the brain, while pergolide preferentially acts on D₂ receptors. We found that PPX has benefits for depressive symptoms in PD patients, and antidepressant effects did not depend on motor functional improvement [26]. These results suggest that the original serotonergic and noradrenergic hypotheses of depression do not fully account for the neurobiology of depression or mechanism of action of effective antidepressants. In addition, there is an efficacious difference among dopamine receptor agonists. Roy et al. [27] found lower cerebrospinal fluid levels of homovanillic acid (HVA), which is a dopamine metabolite found at lower levels in depressed subjects. In addition, direct measurement of brain monoamine metabolites from the internal jugular vein of patients resistant to depression treatments revealed low HVA levels that were highly correlated with illness severity [28]. These results support the monoaminergic theories of depression, which hold that dysregulation of PD system, involving dopamine in addition to serotonin and norepinephrine, may also be involved in depression.

Ropinirole, another D₂/D₃ agonist, acts on D₃ preferentially and showed effects on NMSs in PD patients with motor fluctuations and/or dyskinesias [29]. In addition, Pahwa et al. reported in a double-blind placebo-controlled study, that Ropinirole improved NMSs in PD patients [30]. When comparing other dopamine agonists which act on D₂ preferentially, bromocriptine worsened psychotic symptoms in patients suffering from schizophrenia, other psychotic disorders, or psychotic depression [31]. Pergolide works well to treat PD, but this dopamine agonist has no efficacy on depression in PD [25]. In contrast, PPX, which is a nonergot dopamine agonist showed an antidepressant effect in the double-blind study with Placebo [32]. These effects may relate to PPX's preference for D₃ versus D₂ receptors and neurotrophic properties. In addition, D₃ receptors are more abundant in limbic system than D₂ receptors and play an important role in neuronal circuits implicated in depressive states.

TABLE 1: Depression and anxiety in pre-motor phase of PD.

Syndrome	Reference	Prevalence	Notes
Depression	Schuurman et al. (2002) [13]	Hazard ratio 3.13	The relative risk of depressed individuals developing PD
	Alonso et al. (2009) [14]	Rate ratio 1.85	The ratio of PD who initiates antidepressant therapy compared with noninitiators
	Shiba et al. (2000) [10]	Odds ratio 2.2	The frequency of preceding anxiety in PD compared with control subjects
Anxiety	Weisskopf et al. (2003) [11]	Relative risk 1.6	Risk of PD relative to use of anxiolytic medication
	Bower et al. (2010) [12]	Hazard ratio 1.63	The relative risk of anxious personality developing PD
Depression and anxiety	Jacob et al. (2010) [15]	Odds ratio 1.42	The frequency of receiving a diagnosis of depression or anxiety prior to PD

SSRI and TCA are two major categories of antidepressants commonly used to treat depression. SSRIs appear to be tolerated; however, an Italian multicenter study reported that the proportion of patients who recovered, as defined by a final Hamilton Depression Rating Scale score ≤ 8 , was significantly higher in the PPX group as compared to sertraline (an SSRI) group [33]. TCAs have been shown to be effective in treating depression in PD patients, while SSRIs have no effect compared to placebo. However, some problems may arise with TCA due to side effects such as sedation and orthostatic hypotension [23, 34].

4. Anxiety

Anxiety is a common NMS among patients with PD and has a reported prevalence of 25–49% [16, 35], which is much higher than what is seen in non-PD subjects. Panic disorder, generalized anxiety disorder, and social phobia are the most common anxiety disorders reported. Anxiety and depression may be difficult to distinguish; however, unlike depression, a core feature of anxiety is the presence of apprehension, fear, or worry. The severity, but not the duration of PD, was positively related to anxiety. In addition, PD patients with postural instability and gait dysfunction symptom clustering were more likely to experience anxiety than tremor-dominant patients. Levodopa dosage had no relationship to anxiety; however, experience of dyskinesias or on/off fluctuations increased the risk of anxiety. Anxiety in PD contributed to a poor quality of life, and younger patients (<62 years) were more likely to experience anxiety disorder. Nortriptyline was significantly better than Paroxetine CR, and placebo in alleviating anxiety [23]. In addition, Atomoxetine, treated patients showed decreased severity of anxiety compared with Placebo group [24]. There was no association between patients who had functional neurosurgery for PD and anxiety; however, history of psychiatric disorders increased the risk for a diagnosis of current anxiety [35].

Anxiety and PD could share some underlying biological mechanisms that lead to them occurring at any stage of disease including pre-motor phase. Abnormalities in dopaminergic transmission are associated with anxiety. Striatal dopamine receptor binding was found to be reduced in both nonhuman primate models of anxiety and humans with anxiety disorders. Humans with anxiety disorders also appear to have reduced levels of dopamine

uptake in the striatum and reduced level of homovanillic acid in cerebrospinal fluid. Other neurotransmitter systems, including those of norepinephrine, serotonin, acetylcholine, and γ -aminobutyric acid, may also play a role in anxiety as suggested by the results of animal experiments and pharmacological studies in humans [36, 37]. These neurotransmitter systems interact with dopaminergic system and might be affected in PD patients.

5. Coexistence of Depression and Anxiety in PD

Depression and anxiety are frequently associated in the same patients, and this can be seen as an argument to support the hypothesis that these two symptoms may share common pathophysiological mechanisms. Dissanayaka et al. reported that comorbid depression with anxiety was observed in 14% of PD patients [35]. While Negre-Pages et al. found that anxiety and depression in patients with PD were associated with different demographic and clinical factors [38]. They also found that PD patients with anxious symptoms were more frequently female and younger than those without such symptoms, whereas those with depressive symptoms had more severe indices of parkinsonism, more comorbidities, and lower cognitive function. These studies support the hypothesis that anxiety and depression may refer to different mechanisms since they are not correlated to the same features in PD. Anxiety may be more related to nonspecific factors, comparable to those observed in the general population, while depression may be more linked to the dopaminergic denervation that characterizes PD.

6. Conclusions

Depression and anxiety in PD can occur at any stage of disease including pre-motor phase and are more frequent in PD patients than in controls. While the link between depression and PD during the pre-motor phase is not clear, all the articles reviewed in this paper support a link between anxiety and pre-motor phase PD. This suggests there may be an association between the mechanism that causes anxiety and PD. However, a recent study reports that PD patients with depression and anxiety were associated with different demographic and clinical features. Further studies are needed to elucidate these differences.

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