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SM Journal of Neurology and Neuroscience

Review Article

Anxiety and its Features in Parkinson's Disease

Perri Carlson-Hawke[1,2]*, Belinda Brown[2] and Simon Hammond[1]

[1]*Central West Neurology & Neurosurgery, Australia*
[2]*School of Psychology & Exercise Science, Murdoch University, Australia*

Article Information

Received date: Jul 31, 2017
Accepted date: Aug 07, 2017
Published date: Aug 11, 2017

***Corresponding author**

Perri Carlson-Hawke, Central West Neurology & Neurosurgery, 93 Byng Street, ORANGE NSW 2800, Australia, Email: perri@cwnn.com.au

Abstract

Anxiety is one of the most clinically significant psychiatric syndromes in Parkinson's Disease (PD). It is estimated to affect up to 50% of individuals with PD and is associated with higher levels of dependency and poorer quality of life. Although it is common, it remains widely under recognised by patients, carers and clinicians, and has not been extensively studied [1]. Therefore, in spite of its significant impact, the symptomatology, chronology, and neurobiology of anxiety in PD are not well understood.

Recently, anxiety in PD has been associated with increases in motor fluctuations and gait disturbances including freezing. Freezing of gait (FOG) is the temporary inability to walk and is one of the most debilitating symptoms of PD. It is associated with an increase in falls, injuries and dependency. The associations with motor symptoms have significant consequences for the quality of life of people living with PD. This review summarizes the most recent data on the epidemiology, associated features and possible mechanisms underlying anxiety in PD.

Anxiety is one of the most clinically significant psychiatric syndromes in Parkinson's Disease (PD) and is associated with higher levels of dependency and poorer quality of life. Although anxiety in PD is common, it remains widely under recognized by patients, careers and clinicians, and has not been extensively studied [1]. Anxiety in PD frequently goes undetected due to symptom overlap with the motor and autonomic disturbances present in the disease. Recently, anxiety in PD has been associated with increases in motor fluctuations and gait disturbances including freezing, one of the most debilitating symptoms of PD [2]. A greater awareness of the phenomenon of anxiety in PD is needed to improve the accuracy of diagnosis and to direct effective and targeted treatment strategies. This review summarizes the most recent data on the epidemiology, associated features and possible mechanisms underlying anxiety in PD.

Prevalence and Epidemiology of Anxiety in PD

The prevalence of anxiety disorders within the general public falls between 1.9% and 18%, depending on the specific disorder [3]. For those with PD, anxiety it is thought to be far more common. One study by Pontone and colleagues [4] utilised a sample of 127 North American participants with PD who underwent psychiatric and neurological assessments. Current and lifetime prevalence of at least one DSM-IV anxiety disorder was found to be 43% and 49%, respectively. In a multinational, cross-sectional study of 342 patients with PD, 34% met the DSM-IV criteria for at least one anxiety disorder [5]. In an Australian study of the prevalence of anxiety in PD, Dissanayaka and colleagues assessed 79 people with PD recruited from Neurology outpatient clinics, and diagnosed 25% with an anxiety disorder according to DSM-IV criteria [6].

The most common sub classifications of anxiety in PD are Generalized Anxiety Disorder (GAD), social anxiety disorder and panic disorder [7]. Recent studies reporting prevalence of GAD in PD vary between 3% and 21% [4,8]. Some degree of social anxiety is thought to be common amongst those with PD, with a recent review of reporting prevalence of the disorder to be approximately 14% [1]. Many people with PD can perceive themselves as 'disfigured', and find social interactions distressing, leading to the development of social anxiety [9]. One study Kummer[10] diagnosed social phobia in 50% of a sample of 90 PD patients. However, this high prevalence is thought to be an artifact of the inclusive diagnostic criteria used.

Reported rates of panic disorder in PD range between 1.8% and 25% and this often presents with agoraphobia [11]. Other types of anxiety, such as obsessive-compulsive disorder and posttraumatic stress disorder, are thought to be less prevalent in PD and more consistent with the morbidity rates of the general population [1,7].

Many of these estimates vary widely between studies and are dependent upon the measures and diagnostic criteria used. For example, the DSM-III defined GAD as having symptoms for at least 1 month, whereas the DSM-IV and DSM-5 requires symptoms to be present for at least 6 months. Other studies focus less on diagnosis, using clinical measures to determine clinically significant

anxiety symptoms. In the PD literature, the classification of Anxiety disorder 'not otherwise specified' is often used to describe clinically relevant anxiety symptoms which do not fit DSM criteria [11].

Starkstein and colleagues proposed various presentations of anxiety in PD, distinct from those listed by current classifications. The authors examined the syndromal profiles of 342 patients with PD in an international, multicentre study utilising latent class analysis. Their results outlined 3 clinical profiles including 'episodic anxiety-without depression', 'persistent anxiety with depression' and 'both persistent and episodic anxiety with depression'. These clinical phenotypes may correspond better to the anxiety syndromes encountered in clinical practice than those listed current DSM classifications [8]. Certainly, there is evidence to suggest that the features of anxiety in PD are not easily defined by current criteria.

Features of Anxiety in PD

There are a number of epidemiological and clinical observations which suggest the features of anxiety in PD may be unique to this population [4,5,8]. Anxiety is also a common feature of wearing-off and is known to trigger increased bodily awareness, leading to increased anxiety, and in some cases panic attacks [12]. Wearing-off is a term used to describe the phenomena associated with the wearing-off of short-acting levodopa medications used to treat PD symptoms. The state in which the patient is in need of a new dose of dopamine replacement therapy and experiences intensified PD symptoms is typically referred to as the 'off' state. The period where a patient shifts from an "on" state to an "off" state, and experiences symptoms re-emerging, is referred to as "wearing-off". This is often referred to as 'wearing-off' anxiety. Like other forms of anxiety, wearing-off anxiety is accompanied by physical complaints including shortness of breath, sweating and abdominal discomfort [13].

The severity and duration of anxiety associated with wearing-off is not always found to be congruent with motor fluctuations however, suggesting a possible increased sensitivity and reactivity to the wearing-off symptoms or potentially an increase in the awareness of bodily sensations in these patients [13]. Hypervigilence to physical sensations can be maladaptive and is also related to anxiety and panic [12]. Brown & Fernie surveyed a sample of 106 PD patients from the UK. Their study found metacognitive factors were significantly associated with anxiety in PD. Specific worries which have been associated with anxiety in PD include worry about potential negative comments from others about physical disabilities and embarrassment arising from parkinsonian motor symptoms, such as tremor [5,9,14] fear and worry about the effects of wearing-off periods (e.g. panic or freezing symptoms) and a fear of falling which is frequently observed in PD patients with anxiety and has been shown to have a substantial impact on quality of life [4,5]. In addition to anxiety resulting from these PD specific worries and symptoms, social anxiety or social withdrawal can manifest as an additional consequence of having PD, leading to an increase in social isolation, dependency and decrease in quality of life [15].

Anxiety in PD frequently goes undetected due to symptom overlap with the motor and autonomic disturbances present in the disease. Symptom similarity with depression contributes to this, in addition to the complexities associated with the diagnosis of PD, access to healthcare and resources, and the under-reporting of symptoms by patients and caregivers. Recently, anxiety in PD has been associated with increases in motor fluctuations and gait disturbances including freezing of gait (FOG) [16,17]. As a result, anxiety in PD may have a particular relevance for quality of life and as an avenue for further investigations into the neurobiological mechanisms in PD.

The literature reveals mixed results regarding the chronology of anxiety in PD. In an Australian sample, one study found anxiety is more common in younger patients than in older patients [6]. In a case-series of 79 patients with PD, those under the age of 62 were found to be nine times more likely to experience anxiety symptoms than older patients with PD [6]. Other studies however, have found no significant association between anxiety and age [18]. Similar variability is reported in the literature regarding the relationship between anxiety and disease duration, with no relationship found in the Australian study [6] and anxiety associated with younger disease onset in a Chinese study [19].

The literature points to several factors which indicate anxiety in PD may be distinct from that found in the other populations [1,8]. Epidemiological studies, including those conducted by Dissanayaka and Pontone and colleagues, found anxiety disorders to be equally distributed between males and females with PD [4,6]. This is in contrast to the distribution in the general population where anxiety is found to be more prevalent in women [3].

Anxiety may also be overrepresented in those with PD even when compared to other clinical populations. Menza, Robertson-Hoffman and Bonapace evaluated 42 patients with PD from a North American movement disorders clinic, comparing DSM-III-R criteria with 21 medical matched controls. They found 28% of patients with PD met diagnostic criteria for at least one anxiety disorder and an additional 40% displayed anxiety symptoms but did not meet criteria for formal diagnosis. This was significantly more than the 5% of medical controls who met diagnostic criteria for an anxiety disorder, with none displaying subclinical anxiety symptoms [20]. To date, this is the only study evaluating the prevalence of anxiety in PD against other medical controls and additional evidence is required to support a conclusion that anxiety in PD is distinct from that found in other populations. Indeed, there is a body of research which suggests anxiety may be a distinct symptom of PD, associated with pathophysiological changes in the brain, and in many instancesprecededing the initial motor symptoms.

Anxiety in PD: Risk factor or biomarker?

It is not uncommon for those experiencing anxiety in PD to meet criteria for more than one anxiety disorder [5,11]. Similarly, research shows that a history of anxiety, prior to PD diagnosis, is associated with anxiety in PD [21,22].

In the international study by Stakstein, approximately 70% of those reporting current symptoms of anxiety also had a previous history of anxiety. More conservative findings were reported by Aarsland and colleagues who investigated neuropsychiatric symptoms in 175 newly diagnosed, untreated, PD patients in Norway. They found that overall, participants with clinically significant neuropsychiatric symptoms had more severe parkinsonism. Within this, 17% were reported to have existing anxiety symptoms [21]. The design of this study however, limits interpretation of these results. It could be argued that elevated rates of anxiety in this sample may be due to other factors, e.g. reaction to recent diagnosis, rather than related to PD itself.

Anxiety in PD has also been explored as a preclinical symptom or risk factor. Research has demonstrated that by the time motor symptoms in PD develop, significant loss (approximately 70%) of dopaminergic neurons in the substantia nigra will have already occurred [6]. Preliminary research into the preclinical features of PD has found symptoms and signs may include essential tremor, olfactory dysfunction, sleep disturbances and constipation as well as depression and apathy [23]. Anxiety has also been suggested as a potential preclinical feature in PD and between 1976 and 1995, Shiba and colleagues [24] studied 196 North American participants who later went on to be diagnosed with PD. Using a case-control design, the study looked at the association between preceding psychiatric disorders, including anxiety, and PD. Results suggest that anxiety disorders were associated with later PD diagnosis with an odds ratio of 2.2 (95% confidence interval, CI = 1.4 - 3.4). The literature is unclear as to whether anxiety in PD should be viewed as a risk factor or a prodromal feature in PD. Jacob and colleagues, attempted to determine this in a North American population-based case control study. The study recruited 371 PD patients, 402 population and 115 sibling controls and lifetime depression and anxiety diagnoses recorded. The authors concluded anxiety to be a pre-clinical symptom prior to the onset of PD, rather than an etiologic risk factor.

Overall, the research in this area demonstrates that anxiety often precedes the initial motor symptoms of PD, in some cases up to 20 years prior to somatic PD symptoms and could be viewed as a risk factor in PD or potential biomarker. Identifying the biomarkers for PD is clearly important for the early diangosis and management of the disease.

Motor Fluctuations and Anxiety in PD

Currently, the presence of motor symptom fluctuations is thought to be a principal marker of anxiety in PD [16]. Nissenbaum first described the association in a study reporting symptoms of depression and anxiety in 4 of 9 patients with PD with motor fluctuations. In 1999, Dunn and Hammond conducted an epidemiological study of 101 people with PD in Australia. They found 80% reported anxiety caused a temporary worsening of their symptoms [25]. Soon after, a smaller study described an association between motor fluctuations and general mood symptoms in PD, including anxiety, in 22 out of 47 Italian patients [26]. Five of the 22 patients reported symptoms of anxiety associated with fluctuations of other symptoms.

Richard et al. found fluctuations in both general mood and anxiety symptoms were associated with motor symptoms in 15 of 20 patients with PD [27]. Pontone and colleagues in their epidemiological study of 127 patients with PD, found an association between anxiety symptoms and wearing off in 13 of 38 participants with an anxiety disorder [4].

In 2012, Leentjens et al. [16] conducted an international multicenter cross-sectional study of 250 people with PD. The study investigated the relationship between anxiety symptoms and motor fluctuations in both 'on' and 'off' dyskinetic states. The findings were multifaceted, failing to find a significant relationship between anxiety symptoms and the pattern or timing of their motor symptoms. However, the study did find that amongst those who did report a relationship between anxiety and motor symptoms, these almost always occurred during "off" periods. More generally, the study found that those with motor fluctuations had more than twice the prevalence of GAD than those without fluctuations. These findings suggest the mechanisms underlying anxiety and motor symptoms are complex. This is further evidenced by the association between anxiety in PD and freezing of gait.

Freezing of Gait

FOG is typically experienced when an individual with PD is in narrow spaces, in the dark, or under time constraints. Research evidence has suggested that anxiety influences gait in PD, and that it is the anxiety-provoking nature of these situations which may be an important factor in triggering FOG [17].

In 2014, Ehgoetz Martens and colleagues conducted a controlled trial with 14 patients who experienced FOG and 17 who did not. Participants' gait was measured whilst they walked in two virtual environments, one specifically designed to be anxiety-provoking. Anxiety was measuredprior to the treatment exposure using the State-Trait Anxiety Inventory [28] and immediately after exposure with a self-assessment manikin scale. Results showed that not only did the FOG group experience significantly more FOG episodes during each trial; they also reported higher levels of anxiety compared to Non-FOG group [17].

In another study, virtual environments were utilised to induce anxiety and evaluate whether it caused FOG in 461 with PD. Participants were grouped into 3 groups, (231 PD without FOG, 180 PD with FOG, 50 PD with only mild FOG) and were assessed using the Freezing of Gait Questionnaire item 3, Hospital Anxiety and Depression Scale, along with a number of other measures. The study demonstrated that anxiety was significantly greater in those reporting FOG compared to those who did not. The study did not measure whether anxiety preceded the onset of FOG. However it did reveal anxiety severity to be significantly correlated to the degree of self-reported FOG, regardless of group [2].

The mechanisms underlying FOG are still unclear; however, this research provides preliminary evidence that anxiety in PD is key. Researchers have suggested that anxiety may contribute to FOG by overloading limbic inputs into the striatum and consequently interfering with competing information processing within the basal ganglia. It has also been argued that those reporting FOG may also experience heightened levels of anxiety-related cognitions, particularly in regard to a fear of falls. This field of study is in its very early stages and continued research into the prevalence of FOG and its relationship with anxiety in PD are required to provide insight into this debilitating condition. Such research may also provide further evidence regarding the neurobiological mechanisms involved in the creation and maintenance of anxiety in PD.

Neurobiological Mechanisms Underlying Anxiety in PD

There is ample evidence that underlying neurobiological mechanisms interact to create a complex and diverse symptomatological profile of anxiety in PD. Anxiety in PD has been associated with a reduction in the neurotransmitters dopamine, noradrenaline and serotonin. Dopaminergic neurotransmitter alterations can be directly related to anxiety symptoms in PD [7]. A decrease in the production and distribution of these neurotransmitters in the structures of the basal ganglia has implications for both motor and non-motor symptoms [29]. The basal ganglia are responsible for

voluntary motor control, procedural learning, eye movement, and are also involved in cognitive and emotional functioning. The primary neural pathways associated with neurodegeneration in PD are the mesolimbic and mesocortical dopaminergic pathways which project to the amygdala, a key structure long associated with triggering and regulating anxiety. These underlying mechanisms would suggest anxiety and motor symptoms in PD would fluctuate corresponding with neurodegeneration. However, the clinical evidence relating to these symptoms indicates a more complex relationship, though this is yet to be definitively defined [16].

Summary

Anxiety is a prevalent non-motor complication in PD and may have a significant negative impact on quality of life [30,31]. Whilst much of the literature to date has focused on depressive mood symptoms, more recent studies have found that anxiety is a clinically significant symptom in PD, with features distinct from that found in other populations [1]. Anxiety disorders are heterogeneous in presentation and the use of DSM criteria for their evaluation in PD can be problematic. Features which are unique to PD, such as wearing off anxiety, complications with medications; and episodic anxiety associated with fluctuations in motor symptoms, all contribute to this. Consistent with this, research indicates that more than half of clinically significant anxiety cases are not currently being recognized by clinicians, and therefore anxiety is undertreated in this population. It is important that future epidemiological research in this area, clearly define the many characteristics of anxiety in PD, to ensure timely, accurate diagnosis and provide effective, targeted treatments.

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