

Editorial

NEUROPSYCHIATRIC ISSUES IN PARKINSON DISEASE (PD) PATIENTS: CLINICAL FEATURES AND GENETICS PREDISPOSITION

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Editorial Note

Neuropsychiatric symptoms are common and bothersome to both the Parkinson Disease (PD) patients and their caregivers. They can be classified into four groups: affective disorder, psychosis, cognitive dysfunction and impulse control disorder. In this mini-review, we will offer an overview of neuropsychiatric symptoms in PD patients and discuss if there is a genetic predisposition to these psychiatric symptoms.

Parkinson's Disease (PD) is the second commonest neurodegenerative disease in the world affecting both the motor and non-motor domains (Figure 1). In general, it affects 1% of the population above 60 years of age [1]. Even though motor symptoms remain the cardinal features of the disease, it is known that PD patients have a wide spectrum of non-motor symptoms.

Barone have reported that almost all the PD patients have at least one non-motor symptoms, with psychiatric symptoms as the most frequent non-motor symptom (67%) [2]. Similar findings were described in the Australian group. [3,4] According to the 15-year Sydney multicentre Study of PD, cognitive decline was observed in 84% of PD patients whereas depression and hallucination were seen in half of the cohort [3]. In the 20-year follow-up study of the same cohort, visual hallucination and dementia were present in 74% and 83%, respectively [4]. Eventually, these neuropsychiatric symptoms lead to a reduction in the dopaminergic medication dosage, as well as, an addition of psychiatric medications (such as anti-psychotics and cholinesterase inhibitors), and hence attribute to a decline in motor function, loss of independence, institutionalization and mortality.

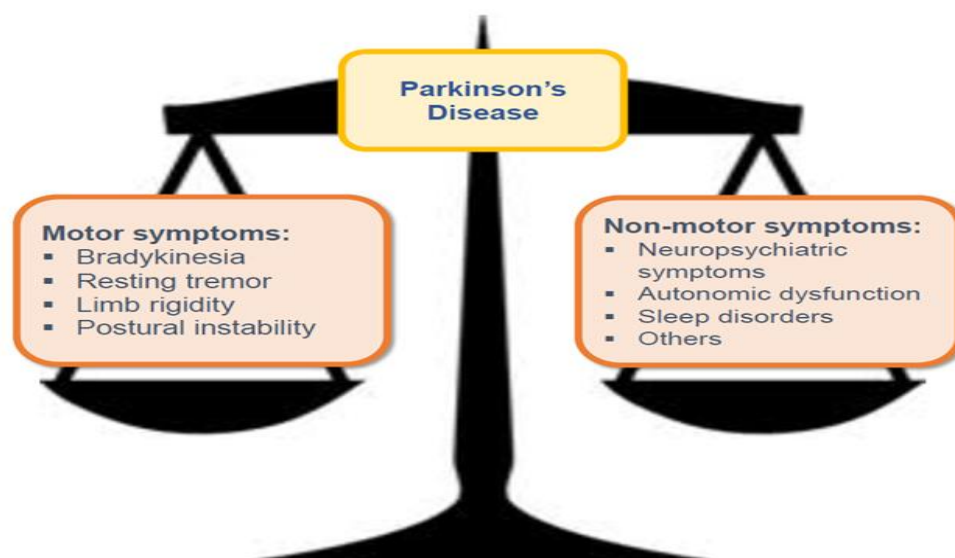


Figure 1: Motor and non-motor symptoms of Parkinson's Disease (PD).

As discussed earlier, neuropsychiatric symptoms are common and bothersome to PD patients. Moreover, they can be seen in all stages of the disease. At the prodromal stage, some patients may experience mood disorders such as apathy.

On the contrary, advanced PD patients can develop psychosis and dementia. In general, neuropsychiatric symptoms in PD can be classified into 4 groups and will be discussed in detail.

1. Affective disorder
2. Psychosis
3. Cognitive dysfunction
4. Impulse control disorder

Affective disorder

Affective disorder is frequently encountered in PD patients, though it is often neglected by both the patients and health care professionals. It includes apathy, depression, and anxiety. In some cases, PD patients with mood disorders may develop suicidal ideas, or even commit suicide.

Reijnders, et al. reported that the prevalence rate of clinically significant depressive symptoms in PD was 35%, with a wide variation across studies, ranging from 2.7% to more than 90% [5]. A recent review conducted by a Chinese group showed similar findings and revealed that the prevalence of depression in PD was 38% [6]. Also, anxiety disorder was found in 25%-50% of PD patients [7-9].

Moreover, depression and anxiety often overlaps, making the diagnosis difficult. In addition, mood symptoms can coexist with other motor symptoms in PD. The PROMS-PD Study Group from the UK suggested an increased risk of anxiety in patients with motor fluctuations, especially with a young age of onset [10]. On the other hand, depression was strongly associated with freezing of gait and axial motor symptoms [10].

The degeneration of the extranigral pathways, which results in a loss of noradrenergic, serotonergic and cholinergic neurons, may account for the co-occurrence of levodopa refractory gait dysfunction and mood disorders. Furthermore, mood disorders

such as depression and anxiety were found to be associated with poorer quality of life in PD patients [11]. In particular, patients with depression were reported to have longer disease duration and a poorer motor function, which may account for a decline in quality of life [11].

Psychosis

PD psychosis is defined as the presence of at least one of the characteristic symptoms, namely illusions, false sense of presence, hallucinations or delusions, which occurred after disease onset. These symptoms must be recurrent or continuous for one month. Besides, there are no alternative diagnoses that can reasonably account for the symptom.

Furthermore, these symptoms may be associated with loss of insight, dementia, or use of anti-parkinsonian treatment [12]. Psychosis is prevalent and bothersome in PD patients and so it can cause poorer quality of life, increased caregivers' stress, institutionalization, and mortality.

In a 12-year prospective longitudinal study, 60% of PD patients were found to develop either delusions or hallucinations by the end of the study [13]. Moreover, the presence of delusions or hallucinations was reported to be significantly associated with nursing home placement [14].

Likewise, PD patients with psychosis were found to have a 70% increased risk of mortality, as compared with those without psychosis [15]. In general, PD psychosis can be divided into two groups: early PD psychosis symptoms and late PD psychosis symptoms.

In early PD, patients may experience passage hallucinations (i.e. seeing a non-existing person or object passing in the peripheral visual field), presence hallucinations (i.e. feeling that somebody is in the proximity), and illusions.

With disease progression, patients develop formed visual hallucinations of people, animals, or objects with preservation of insight. At a late stage of PD, delusions and multimodality hallucinations will occur with loss of insight and cognitive decline [16].

Cognitive dysfunction

Dementia associated with PD is defined as an insidious, slowly progressive dementia syndrome, which develops in an established PD patient [17]. He usually has both cognitive and behavioural symptoms. Classically, executive dysfunction and visuospatial impairment are the cardinal features of cognitive profile in PD dementia.

For instance, the patient may find it difficult to follow the instructions of taking medications. Also, a patient with PD dementia often suffers from impaired attention, poor recall, and short-term memory. His long-term memory, however, is usually preserved. In contrast, behavioural problems are prevalent in these patients, particularly apathy, visual hallucination, and psychosis [18].

PD dementia is common, with a point prevalence rate ranging from 22%-48% [19,20]. With increasing age and longer disease duration, the prevalence rate of PD dementia further increases. It has been reported that 15 years after disease onset, almost half of PD patients have dementia [3].

It is crucial to identify cognitive impairment and dementia in PD patients because this can affect the choice of treatment. For example, we may need to cut down the dosage of anti-cholinergic agents in the PD patients with cognitive impairment.

On the contrary, the presence of severe dementia can preclude a patient from implantation of deep brain stimulation. Furthermore, with the executive dysfunction and visuo-spatial impairment in patients with PD dementia, driving can be dangerous to both the patients and pedestrians [21].

Impulse control disorder

Impulse Control Disorders (ICDs) are known as a group of disorders which is characterised by a failure to resist an impulse, drive, or temptation to perform an act that is harmful to the individual or to others. It is frequently seen in PD patients treated with dopaminergic agents, especially levodopa and dopamine agonists [22]. According to the

DOMINION study, ICDs are found in 13.6% of PD patients [23].

In brief, ICDs are addictive behaviours and include pathological gambling, hypersexuality, compulsive shopping, binge eating, punding and compulsive medication use [22]. In addition, PD patients with ICDs experience more neuropsychiatric problems, such as depressive and anxiety issues, obsessive-compulsive symptoms, novelty seeking and impulsivity behaviours.

They are also found to be more disabled. Those with multiple ICDs are reported to have more dyskinesia [24]. Studies showed that young age, male sex and history of smoking, together with use of levodopa and dopamine agonists (especially with a high dosage), are risk factors of ICDs in PD patients [25].

Therefore, it may be worthwhile to watch out for these impulse control behaviours in young, male PD patients taking dopamine agonists because these behavioural problems can significantly affect their economy, social and family relationship.

Genetic predisposition of neuropsychiatric problems in PD: A fact or a myth

To date, there is no literature comparing the overall prevalence of neuropsychiatric symptoms in idiopathic PD and in monogenic parkinsonism. Nevertheless, for some types of monogenic parkinsonism, the patients are reported to be predisposed to neuropsychiatric problems, especially cognitive impairment.

For example, patients with SNCA and GBA mutations were at a higher risk of dementia while those with PRKN mutation seldom developed cognitive impairment. Neuropsychiatric symptoms are associated with poor quality of life and institutionalization in PD patients. They can also increase caregivers' burden.

The genetic risk factors of each neuropsychiatric disorder in PD are shown in Table 1.

Therefore, it is crucial to watch out for these symptoms and offer timely treatment, especially in the PD patients who are known to have risk factors.

Table 1: Genetic risk factors of neuropsychiatric disorders in PD.

Author	Study design	Number of subjects	Results
Affective disorder			
Cong, et al. [6]	Systematic review	38304	PD patients with depression were more likely to have the GBA1 L444P mutation.
			An association between PD patients with depression and LRRK2 G2019S mutation was not reported.
			An association between PD patients with depression and SNCA rs356219 polymorphism was not observed.
Beavan, et al.[26]	Prospective cohort study	90	PD patients with GBA mutation were found to have higher depression scores.
Psychosis			
Radojević, Branislava, et al. [27]	Cross-sectional study	234	GG homozygotes of rs2734849 ANKK1 mutation were found to be an independent predictor of PD psychosis.
Oeda, et al. [28]	Multi-centre retrospective cohort study	224	PD patients with GBA mutation were found to develop psychosis significantly earlier than those without mutation.
Fuente-Fernández, et al. [29]	Cross-sectional study	17	The APOE 4 allele was significantly associated with the development of visual hallucination in non-demented PD patients.
Cognitive dysfunction			
Campelo, et al. [30]	Case control study	PD patients: 105	SNCA G-rs356219 single nucleotide polymorphism was associated with an increased risk of cognitive impairment in PD patients.
		Control: 101	
Tan, et al. [31]	Prospective cohort study	3364	APOE 4 variant, rs429358, was significantly associated with cognitive progression in PD.
Liu, et al. [32]	Longitudinal study	3821	GBA and APOE mutations were reported to be associated with cognitive progression in PD.
Alcalay, et al. [33]	Case control study	93	Early onset PD patients with GBA mutation were found to have poorer performance on the Mini-Mental State Examination, especially on the memory and visuospatial domains.
		GBA mutation: 33	
		No GBA mutation: 60	
Cilia, et al. [34]	Prospective longitudinal study	2843	PD patients with GBA mutation were found to have a greater risk of dementia.
Impulse control disorder			
Jesús, et al. [35]	Cross-sectional study	353	DOPA decarboxylase gene (DDC), rs1451375, may modulate the risk of ICDs in PD patients.
Lee, et al. [36]	Cross-sectional study	404	The T allele of HTR2A gene was associated with impulse control behaviours in PD.
Lee, et al. [37]	Cross-sectional study	404	Carriers of either AA genotype of DRD3 or CC genotype of GRIN2B were associated with the occurrence of impulse control behaviours in PD.

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