Review Article

Often overlooked neuropsychiatric syndromes in Parkinson's disease

Javed Latoo, Minal Mistry, and Francis J Dunne

Abstract

Parkinson's disease (PD) is a subcortical disorder that eventually spreads to the cortex. There is a wide variation in the global incidence and prevalence of PD. The disease usually presents in patients over the age of 65, although 5% of cases are under the age of 40 at the time of diagnosis. PD has a high prevalence of psychiatric co-morbidity. In this article, written with general neurologists and psychiatrists in mind, the main features and pathology of PD will be briefly outlined followed by a review of the epidemiology, aetiology, clinical features, and treatment of other often overlooked neuropsychiatric syndromes associated with PD. Close liaison between neurologists and psychiatrists is recommended in order to optimize treatment.

Introduction

The global epidemiology of PD varies widely which could be partly accounted for by differences in survival rates.[1] One review paper examined the epidemiology of PD in Austria, the Czech Republic, France, Germany, Italy, The Netherlands, Portugal, Spain, Sweden and United Kingdom. It revealed that the prevalence rates range from 65.6 per 100,000 to 12,500 per 100,000 and annual incidence estimates ranged from 5 per 100,000 to 346 per 100,000.[2] The wide variation in incidence and prevalence rates of PD across Europe could be due to environmental and genetic factors. Differences in methodologies for case ascertainment, diagnostic criteria, or age distributions of the study populations, could also account for the wide variations.[2]

Described by James Parkinson in 1817, PD is the second most common neurodegenerative disorder next to Alzheimer's dementia. Depletion of dopaminergic neurones in the substantia nigra is the main pathology found in PD. Symptoms usually appear when dopamine levels are reduced by 50-80%.[3] Noradrenergic, cholinergic and serotonergic pathways are also affected. Clinically PD is characterised by rigidity, tremor (cogwheel, lead pipe, and resting), akinesia, bradykinesia (poverty and slowness of movement), and postural instability (leading to frequent falls).[4] These symptoms may also be accompanied by a range of non-motor symptoms other than well-known neuropsychiatric syndromes of depression, psychosis, and cognitive impairment.

In essence, a syndrome is a combination of signs and symptoms related to an underlying pathological process. PD may present with neuropsychiatric syndromes of depression, psychosis (usually affective in origin) and cognitive impairment.[5] These syndromes are not under discussion here as readers are likely to be familiar with them. However, PD may also present with other neuropsychiatric syndromes and for the purpose of this article we have classified them into: 1) Anxiety disorders, 2) Apathy, 3) Involuntary emotional expression disorder, 4) Sleep disorders, and 5) Impulse control disorders.

Drugs used to treat PD themselves are associated with neuropsychiatric side effects. For example, dopamine agonists are well-known to cause sleep disturbance, dizziness (usually due to postural hypotension), hallucinations, hypersexuality, and compulsive gambling. Anticholinergics may cause confusion, hallucinations and impaired memory. Surgery also may cause adverse effects including depression, confusion and cognitive impairment.[6] Table 1 illustrates the groups of drugs used in PD.

Table 1. Drugs used in Parkinson's Disease	
Group	Drug
Dopamine receptor agonists	Apomorphine, pramipexole, ropinirole, rotigotine
N-Methyl-D-aspartate (NMDA) receptor antagonist	Amantadine hydrochloride
Levodopa	Co-benedopa (levodopa/benzeraside), co-careldopa (levodopa/carbidopa)
Monoamine oxidase B inhibitors (MAO-B)	Rasagiline, selegiline hydrochloride
Catechol-O-methyltransferase (COMT) inhibitors	Entacapone, tolcapone
Antimuscarinic drugs	Benztropine mesylate, orphenadrine, procyclidine, trihexyphenidyl

Overlooked neuropsychiatric syndromes in Parkinson's disease

The prevalence of overlooked neuropsychiatric syndromes found in PD, summarised in Table 2, is generally less common than PD syndromes of depression (up to 50%), psychosis (up to 60%) and dementia (ultimately develops in 80%).[7, 8, 9]

Table 2. Overlooked neuropsychiatric syndromes found in Parkinson's Disease.

Neuropsychiatric syndrome	Prevalence
Anxiety disorders	Up to 40%
Apathy	16-42%
Involuntary emotional expression disorder	Up to 16.8%
Sleep disorders	60-98%
Impulse control disorders	Up to 13.6%

Anxiety Disorders

Epidemiology

There is a wide range in the reporting of the prevalence of anxiety in patients with PD. Anxiety is significantly more prevalent in PD sufferers compared with age and sex matched non-sufferers. Prevalence is quite high with estimates indicating that up to 40% of PD patients suffer significant anxiety.[10] However, clinicians' recognition and awareness of anxiety in PD need to be raised because it is likely to be under-diagnosed and untreated.[11, 12] Consequently the prevalence of anxiety may be even higher. Severity of anxiety is not correlated with severity of parkinsonian symptoms, duration of levodopa use, or current dose of levodopa.

Aetiology and risk factors

Anxiety is an understandable psychological response to the physical symptoms, to the neurochemical changes of the disease itself, or as a side effect of the various medications used to treat the condition.[10] Sleep disturbances and cognitive impairment have been proposed as possible aetiological factors for anxiety in PD.[11, 12] Depression in PD may manifest in two clinical phenotypes, one 'anxious-depressed' and the other 'depressed'. However, a further large proportion of patients can have relatively isolated anxiety.[13]

Anxiety frequently precedes the development of motor symptoms, suggesting specific neurobiological processes are involved, not merely social and psychological reactions in learning to adapt to PD.[14]

Patients with postural instability and gait dysfunction have a higher incidence of anxiety compared with tremor-dominant patients. Younger-onset PD patients are also more likely to experience anxiety. The pathogenesis of anxiety involves noradrenergic, serotonin and dopamine neurotransmitters. GABAergic pathways may also be involved.[14] Right hemisphere disturbances have also been implicated, particularly with panic disorder. Symptom variation in PD may be due to medication, as well as motor fluctuations.[11] One study revealed that although the dose of levodopa was not associated with anxiety, the experience of dyskinesia or on-off fluctuations increased the risk of anxiety.[12, 14, 15]

Presentation and diagnosis

The commonest disorders found in PD are generalised anxiety, panic disorder, and social phobia. Anxiety contributes to the complexity of PD and lowers quality of life.[14, 15] The degree of comorbidity between anxiety and depression in PD patients is in excess of that found in patients without PD. While anxiety is significantly associated with depression, some patients show anxiety without depression.[10]

The main features of anxiety are inappropriate feelings of apprehension as well as mood, cognitive, and somatic changes. Some symptoms may be common to PD, such as autonomic symptoms, fatigue, muscle tension, insomnia and attention problems. Psychologically, anxiety in PD is understandable because being diagnosed with a chronic disease with no known cure and an inexorable course, would be difficult for anyone to contemplate. Motor signs and changes in appearance could explain social anxiety. However, the frequency of anxiety in PD seems to be higher than in other chronic diseases and unrelated to the severity of motor signs. Even in social phobia the phobic symptoms do not correlate with disease severity and are not restricted to performance situations. Furthermore, anxiety can precede motor signs by several years, suggesting that the neurobiological substrate of PD is responsible for anxiety at least in part.

Treatment

Treatment comprises the use of selective serotonin reuptake inhibitors (SSRIs) such as sertraline, fluoxetine and citalopram as well as other newer antidepressants - serotonin and noradrenaline reuptake inhibitor (SNRIs) for example, venlafaxine, cognitive behavioural therapy (CBT), exercise, the occasional use of atypical neuroleptics, and benzodiazepines.[14] However, benzodiazepines have a tendency to cause sedation, unsteadiness of gait, and even confusion. Antidepressants are useful because they treat both anxiety and depression that often overlap: depression coexists with anxiety in 14% of cases.[15] Low dose tricyclic antidepressants with minimal anticholinergic effects may be useful in those patients who do not respond to benzodiazepines.

Apathy

Epidemiology

Apathy, a state of lethargic indifference and loss of motivation, and fatigue are prominent non-motor symptom in PD with a prevalence of between 16-42%.[16, 17] Fatigue is a sense of tiredness or exhaustion, due to mental or physical causes. Apathy and fatigue are important because they have significant repercussions for the quality of life in PD.[18, 19] Apathy can exist without depression but, by definition, patients themselves do not complain of apathy, though are found to be unmotivated to engage in activities. Apathy and fatigue are often difficult to

distinguish from low mood and daytime sleepiness, both of which are common to depression.

A four-year prospective longitudinal study of 79 patients found that 13.9% of those with PD had persistent apathy and 49.4% had developed apathy at follow up. The study showed apathy to be a frequent and persistent behavioural feature in PD with a high incidence and prevalence over time, and associated with neurotransmitter deficits.[20]

Aetiology and risk factors

The dorsolateral, medial and orbital frontal cortices, as well as subcortical structures such as the basal ganglia, thalamus and internal capsule are implicated in the pathogenesis of apathy. The independent risk factors for apathy are dementia at baseline, a more rapid decline in speech, and axial impairment (e.g. poor ability to turn in bed) during follow up.[20, 21] A more recent study showed that male gender, higher depressive scores, and severe motor symptoms, were significantly associated with apathy, but not with greater cognitive impairment.[22] It has been observed that deep brain stimulation (DBS) may contribute to the development of apathy[23] but other studies show conflicting results.[24]

Presentation and diagnosis

There is a higher incidence of depression and dementia in PD patients with apathy. Therefore differential diagnosis between apathy and cognitive deficits and depression is essential because the therapeutic approaches are different.[19, 20] It is equally important to differentiate between apathy and depression that are different clinical entities although both may coexist. The crucial difference is that people with apathy lack serious self-reproach or feelings of guilt.[21, 25] The Lille Apathy Rating Scale (LARS), administered as a structured interview, can be a useful tool to distinguish them both[26] though further research is needed to differentiate the neurological and neurochemical basis for depression and apathy.

Treatment

Treatment options for apathy are limited. The use of methylphenidate, a stimulant drug related to amphetamine, has been suggested but evidence is scarce and side effects may outweigh its clinical benefit.[27] Methylphenidate has been described as effective for both apathy and fatigue[28] but more studies are necessary. Antidepressants are not effective, can cause unnecessary side effects and can even aggravate apathy, demonstrating that these syndromes are really independent.[29] The association between cognition and apathy, along with the potential benefit of cholinesterase inhibitors on both cognition and apathy, suggests that cholinergic mechanisms take part in the pathophysiology of apathy.[30, 31] 'Off-time' refers to periods of the day when the medication is not working well, causing worsening symptoms of fatigue and apathy. 'Wearing-off' episodes may occur predictably and gradually, or they may emerge suddenly and unexpectedly. Wearing-off periods may be improved with appropriate changes in the medication regimen. This would mean optimizing dopaminergic agents or using a long-acting levodopa or a catechol-*O*-methyltransferase (COMT) inhibitor. Wearing off may be also better controlled by shortening the time between medication doses. In a study of 23 PD patients in both the 'on' and 'off' states compared to 28 controls, L-dopa had a positive effect on motivation suggesting striatofrontal loops are involved.[32]

Involuntary emotional expression disorder

Epidemiology

Involuntary emotional expression disorder (IEED) has been found to occur in 16.8% of PD patients, and in 15.3% if comorbid depressive disorder was excluded.[33] However, other studies suggest that the *symptoms* of IEED are present in up 15% of PD patients but the actual IEED disorder occurs in half of these cases.[34] This implies that IEED symptoms occur in PD but the condition of IEED is not present although this may depend on the criteria used for the diagnosis. If IEED does develop in PD it is particularly common in the later stages of PD and is likely to be distinct from depressive disorder which remains an important differential diagnosis.[33, 35]

Aetiology and risk factors

IEED can occur in neurological conditions such as stroke, traumatic brain injury, amyotrophic lateral sclerosis, multiple sclerosis, seizure disorders, multiple system atrophy, corticobasal degeneration, and Alzheimer's disease.[35] Injury to the neurological pathways that control the expression of emotion have been implicated in its pathogenesis. Emotional expression involves various pathways within the frontal lobe, limbic system, brainstem and cerebellum, with disruption of regulatory and inhibitory mechanisms in this network implicated.[36, 37]

Presentation and diagnosis

IEED is described as sudden episodes of laughing or crying that may be spontaneous or disproportionate to the triggering stimuli. The emotional outbursts of IEED may involve laughter, crying or anger. The episodes all share common features in that they are involuntary, uncontrollable, and excessive, not sustained, and usually last from seconds to minutes. Outbursts are often stereotyped though single individuals may have episodes of both laughing and crying. IEED is also known as pseudobulbar affect, pathological laughter and crying, emotional lability, emotionalism, and emotional dysregulation. Despite the various terms used to describe the disorder, IEED is often missed and even sometimes mistaken for depression.[33, 35] Symptoms of IEED are important because they are associated with an impairment of social and occupational functioning.[38] It is hypothesized that neurological disease and injuries affect the excitatory action of glutamate,

leading to excessive glutaminergic signalling and increased electrical activity in neurons. As glutamate is the primary excitatory neurotransmitter of the central nervous system, stabilizing or reducing glutaminergic activity could prove useful in the treatment of IEED.[39]

Treatment

Medication options include the use of SSRIs, tricyclic antidepressants (TCAs) for example, amitriptyline, and less frequently dopaminergic agents.A combination of dextromethorphan and quinidine has also been suggested. [35][38]

Sleep disorders

Epidemiology

Sleep disorders have been known to affect 60-98% of patients with PD.[40]

Aetiology and risk factors

The aetiology of sleep disorders includes PD itself or other comorbid conditions such as depression, and cognitive impairment.[41] Nocturnal pain from rigidity or dystonia, restless legs syndrome, and autonomic disturbance leading to nocturnal frequency and urgency, also contribute to insomnia. Degeneration of sleep regulatory centres in the brainstem and thalamocortical pathways, side effects of drugs, motor impairment, and incontinence may affect sleep. Sleep disorders may precede the onset of motor symptoms. Rapid Eye Movement (REM) sleep behaviour disorder (RBD), which occurs in almost a third of PD patients, is often associated with cognitive impairment and hallucinations. This disorder is directly related to the degenerative process of the pedunculopontine nucleus, the locus subceruleus and the retrorubral nucleus. A sudden onset of the disorder is almost always due to the introduction or the withdrawal of drugs, especially antidepressants. Curiously, parkinsonism can disappear during the RBD.[42]

Sleep fragmentation is the earliest and most common sleep disorder in PD, and gradually worsens as the disease progresses. Vivid dreaming, nightmares and night terrors are common and occur in up to 30% of patients using levodopa for long periods. Dream content is probably altered in PD and many patients vocalize during sleep. Vocalization may vary from incomprehensible sounds to detailed conversations, laughing, cursing or screaming. Excessive daytime sleepiness and 'sleep attacks' affect half of patients with PD and may precede disease onset. The causes are a combination of the disease process, the consequence of other sleep disorders and medication. A sudden onset of sleep during the day is a phenomenon in PD which resembles narcolepsy, and it is commonly associated with dopaminergic drugs. PD patients may be more prone to restless legs syndrome, periodic limb movements and obstructive sleep apnoea.

Sleep disorders in PD are seldom diagnosed and treated. Although an accurate diagnosis of a particular sleep disorder depends on polysomnography, sometimes the diagnosis can be based on clinical observation. Treatment is based on the correct diagnosis and underlying cause of the sleep disorder. Often it is difficult to decide whether excessive daytime sleepiness is cause or consequence of insomnia.[43]

Presentation and diagnosis

Sleep disorders may manifest as insomnia, excessive daytime sleepiness and sleepwalking.[44],[45] Sudden attacks of sleepiness are known to occur during stimulating activities such as walking, eating, and even driving a car. These sudden sleep episodes can be associated with medication such as dopamine agonists and levodopa.[46]

RBD is characterised by the loss of the normal atonia during dreaming. In other words, patients act out their dreams as manifested by crying out, kicking or thrashing about during their sleep. RBD can predate the development of motor symptoms by several years and a longitudinal study of a cohort of 26 patients found an association between RBD and the later development of PD. [47]

Treatment

Management involves the review of medication that may be contributing to the sleep disorder. Treatment of comorbid conditions such as depression and cognitive impairment is essential.

Sleep hygiene is the initial and basic measure applied to all patients. For instance, stimulating patients during the day can decrease the excessive naps and improve sleep at night, thus improving daytime sleepiness. Additional techniques include going to bed only when sleepy, exposure to natural and bright light during day, reduction of light and noise exposure at night as much as possible, and maintenance of a regular schedule.

Long-acting dopaminergic drugs might improve insomnia caused by worsening of motor symptoms at night. Clonazepam, a benzodiazepine, is efficacious and well tolerated by the majority of patients afflicted by RBD and should be considered as initial treatment.[48] Antidepressants with a sedative effect might be helpful in cases of insomnia with comorbid depression or anxiety. Quetiapine, an antipsychotic which has sedative properties as a side effect, may be a safe and effective treatment for insomnia in PD because it has no untoward effects on motor function.[49] Small clinical trials with Modafinil for excessive daytime sleepiness had controversial results. An additional remark concerning treatment of sleep disorder in PD is that sleep may provide a short-term benefit on motor symptoms.[28],[43]

Impulse control disorders

Epidemiology

A large multi-centre investigation (the DOMINION study) of 3,090 patients with PD revealed that impulse control disorder (ICD) was identified in 13.6% of PD patients; specifically, pathological gambling in 5%, compulsive sexual behaviour in 3.5%, compulsive buying in 5.7% and binge-eating disorder in 4.3%.[50] The prevalence of ICD rises to 14% for patients taking dopamine agonists, compared with 0.7% for patients taking levodopa alone.[51] It is not clear whether these ICD symptoms reflect a primary pathology of PD or whether dopaminergic medication is interacting with an underlying predisposition or vulnerability.[52] Possible neurobiological explanation centres around dopamine-receptor binding profiles. Dopamine D2 and D1 receptors, abundant in the dorsal striatum, may mediate the motor effects of dopamine replacement therapies, whereas D3 receptors are abundant in the ventral striatum, a brain region associated with addictive behaviour and substance misuse disorders. Second generation non-ergot dopamine agonists (e.g. pramipexole and ropinirole) demonstrate relative selectivity for D3 receptors compared with D2 and D1 receptors.[50]

Aetiology and risk factors

Addiction to dopaminergic medication used in the treatment of PD may explain behaviours such as drug-seeking, gambling, and hypersexuality. The risk of pathological gambling increases if dopamine agonists are used in those with younger age of onset, higher novelty seeking traits, and a personal and family history of alcohol misuse.[53]

Presentation and diagnosis

In addition to the above PD patients with ICD may present with compulsive shopping, compulsive eating, and compulsive medication use, all of which can have potentially devastating psychosocial consequences because they are often hidden. Complex stereotyped repetitive behaviours (punding) may also be present.[54] Punding behaviour is stereotyped and purposeless and includes hoarding, shuffling papers, sorting labels, assembling and disassembling objects, to name a few.

Treatment

Stopping dopaminergic medication should be considered in the first instance. Further treatment options are limited but one double-blind crossover study demonstrated the use of amantadine in abolishing or reducing pathological gambling.[55] In addition, one case report suggested the antipsychotic quetiapine to be effective in treating pathological gambling.[56] Whether other treatments, such as DBS, are effective for these compulsive repetitive behaviours, remains to be seen.

Management of overlooked neuropsychiatric syndromes in PD

Because of the significant disability and impact on quality of life caused by overlooked neuropsychiatric symptoms in PD, it is important for neurologists and psychiatrists to recognise them and develop their clinical skills in order to be aware of their significance. Early detection is crucial. We have shown there is a limited range of treatment strategies available to guide the clinician in treatment choices. Because neuropsychiatric diagnoses in PD are different in phenomenology it is important to remember that treatment with 'psychiatric' drugs will often be insufficient and therefore more consideration should be given to 'antiparkinsonian' medications because the underlying pathology of PD is causing the various syndromes mentioned.

Table 3 provides an overview of the medical treatment of overlooked neuropsychiatric syndromes in PD, although it should be noted that overall very few studies document the effectiveness of the solutions proposed and more controlled studies are needed. Nonetheless, the reader should find the following useful.

Table 3. Summary of the medical treatment of overlooked neuropsychiatric syndromes in Parkinson's Disease.	
Psychiatric syndrome	Treatment
Anxiety	- Antidepressants - sertraline, citalopram, fluoxetine, venlafaxine- Others - antipsychotics, benzodiazepines - Cognitive Behavioural Therapy - Exercise
Apathy (diminished motivation)	- Cholinesterase inhibitors - Dopamine agonists - Possible use of methylphenidate
Involuntary emotional expressive disorder	- Antidepressants - Dopaminergic agents. - Possible combination of dextromethorphan and quinidine
Sleep disorders	- Benzodiazepine - clonazepam - Antipsychotic (sedating) – quetiapine - Sleep hygiene
Impulse control disorders	- Possible use of amantadine or quetiapine in pathological gambling - Further research required

Conclusion and implications

The management of PD is often complicated because of the diverse factors underlying its aetiology. Dopaminergic, serotonergic, noradrenergic and cholinergic pathways are involved.[57] Clinicians are generally competent in recognising the more common disorders such as depression, psychosis and cognitive impairment associated with PD though there is a tendency to focus too much on these at the expense of other nonmotor symptoms. Anxiety, apathy, involuntary emotional expression disorder, sleep disorders, and impulse control

disorders cause significant disability and impact heavily on patients and carers.

Before introducing treatment for psychiatric complications it is essential to exclude causes such as antiparkinson's medication, DBS (implicated in apathy), and underlying medical conditions. Once excluded or treated, subsequent management includes psychotropic pharmacotherapy but there are limited options. With no specific drug designed to treat the overlooked conditions, a wide range of medications (e.g. antidepressants, antipsychotics, benzodiazepines, dopaminergic agents, and psychostimulants) are available to manage the symptoms.

Neurologists and psychiatrists need to work together to manage these syndromes and they must be innovative in setting up joint research ventures into developing treatment options. Simple questionnaires may alert physicians when presenting symptoms are abstruse because many of the nonmotor symptoms predate the motor symptoms[58] (the presymptomatic phase of stages 1-2 of Braak's classification system).[59] [60] For example, anosmia, constipation and other autonomic symptoms are not considered neuropsychiatric syndromes per se, but are some of the nonmotor problems associated with PD and may give clues that PD is developing.

Despite research highlighting the presence of these disorders in PD, they generally go unrecognised by clinicians, being less common, and therefore psychiatrists in old age and adult psychiatry as well as general neurologists may lack skills to recognise them. Besides, there are no clear treatment guidelines on how to manage the conditions.

Competing Interests
None declared
Author Details
JAVED LATOO, Consultant Psychiatrist, 5 Boroughs Partnership NHS Foundation Trust, Hollins Lane, Warrington WA2 8WA, UK. MINAL MISTRY, Consultant Psychiatrist, Southern Health NHS Foundation Trust, Hampshire, UK. FRANCIS J DUNNE, Consultant Psychiatrist and Honorary Senior Lecturer, North East London Foundation Trust (NELFT) United Kingdom, & University College London.
CORRESSPONDENCE: JAVED LATOO, Consultant Psychiatrist, 5 Boroughs Partnership NHS Foundation Trust, Hollins Lane, Warrington WA2 8WA, UK. Email: javedlatoo@gmail.com

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