REVIEW

Neuropsychiatric non-motor aspects of Parkinson's disease

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Parkinson's disease is often recognised as a motor disease characterised by rest tremor, rigidity, bradykinesia, and postural disturbances. However, there are several non-motor aspects of the disease that are of at least equal importance in the management of patients with Parkinson's disease. They include depression, cognitive impairment, anxiety, and psychosis among others. It is important to recognise them, as they are common and they contribute significantly to patients' morbidity, quality of life, and institutionalisation to long term care homes. In addition to the disease duration and severity, other factors including drugs may contribute to their occurrence. Pathogenesis of these aspects is not fully understood, though there has been a significant increase in the knowledge in recent years. Management of these aspects involves a multidisciplinary approach.

Motor symptoms and signs of Parkinson's disease including rest tremors, bradykinesia, rigidity, and postural disturbances are well known to the clinician. They account for a great deal of morbidity associated with the disease. However, it is less often appreciated that Parkinson's disease is not a mere motor disease—there are several non-motor aspects of Parkinson's disease that deserve recognition. These aspects are at least equally important as regards to the overall morbidity of the Parkinson's disease and the quality of life of the patient.

WHAT ARE THE NON-MOTOR FEATURES OF PARKINSON'S DISEASE?

Recently, several non-motor features of Parkinson's disease have attracted attention of physicians; some of them are listed in the box 1.

Box 1: Major non-motor aspects of the Parkinson's disease

- Depression.
- Dementia.
- Anxiety.
- Hallucinations, delusions, and psychosis.
- Weight loss.
- Sleep disturbances.
- Autonomic disturbance.
- Sexual dysfunction.
- Apathy.

WHY ARE NON-MOTOR FEATURES IMPORTANT?

Non-motor features are important because:

- They are common. Sleep disturbances can affect more than 70% of patients with Parkinson's disease.
- They can be missed unless looked for, and may require the use of special scales—for example, depression can be difficult to diagnose in a patient with a mask-like face and bradyphrenia. Use of special scales for assessment of depression, cognitive impairment, sleep disturbance, etc is often required.
- Some of these aspects have been strongly correlated with the quality of life of patients and their carers. Depression has been strongly correlated with poor quality of life and cognitive impairment is the most important risk factor for institutionalisation in Parkinson's disease.
- They may precede motor symptoms of Parkinson's disease.
- Treatment of these aspects is often very difficult, but when successful, it can be very rewarding.
- They are often multifactorial in aetiology—that is, disease duration and severity, drugs, and age all can contribute to their causation.

The following account is an outline of the major neuropsychiatric non-motor aspects of Parkinson's disease.

DEPRESSION AND PARKINSON'S DISEASE

Depression is a common problem in patients with Parkinson's disease. Prevalence rates have been reported from 11% to 44% depending upon the presence of minor or major depressive symptoms and the assessment scales used.^{1–4} Prevalence of 31% was reported in a recent meta-analysis.⁵

The manifestations include apathy, psychomotor retardation, memory impairment, pessimism, irrationality, and suicidal ideation without suicidal behaviour. Depression has been strongly related to the patients' quality of life in Parkinson's disease.

The symptoms of depression in Parkinson's disease vary slightly from the typical symptom profile of primary depression. Depressed parkinsonian patients experience less guilt and self

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Abbreviations: SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

reproach and more irritability, sadness, and concern with health.⁶ Depression associated with agitation creates additional functional incapacity to which young onset parkinsonian patients appear particularly prone.⁷

Mood fluctuations can accompany motor fluctuations of “on-off” states. Depression increases in the “off” state and improves in the “on” state.⁸ Completed suicide appears to be rare in the Parkinson population even though verbalised suicidal ideation is not uncommon.¹ Younger onset patients appear to be more at risk for suicide and suicidal gestures than older patients. Severe depression in Parkinson’s disease may anticipate the development of intellectual impairment.⁹ Depression may also present as pseudodementia that resolves with effective treatment of the depression.

The underlying mechanism of depression is poorly understood. It is suggested that depression results from (A) neurochemical changes of Parkinson’s disease (for example, low levels of serotonin and noradrenaline) and/or as a result of (B) a reaction to a chronic progressive neurological disease. However, it is unclear why some patients develop depression and others do not. The detailed discussion of mechanism of depression is beyond the scope of this article and readers are advised to refer to a recent article by Burn.¹⁰

Depression in Parkinson’s disease is associated with advancing disease severity, recent deterioration, female gender, sleep disturbance, cognitive decline, occurrence of falls, and right hemi-Parkinson’s disease. It is suggested that the axial signs of the disease (postural instability, axial rigidity) are more severe in depressed patients with Parkinson’s disease, suggesting a link between depression and the non-dopaminergic lesions of the disease.¹¹

Management of depression requires an interdisciplinary approach involving physician, Parkinson’s disease nurse, liaison psychiatrist, and patient along with the carer. An explanation that depression is a common intrinsic part of the Parkinson’s disease helps patients and the carer to accept appropriate help and treatment. Optimising dopaminergic therapy should be the first step. There is no evidence to suggest that one antidepressant is superior to another in patients with Parkinson’s disease. However, a selective serotonin reuptake inhibitor (SSRI) may be preferred over tricyclic antidepressants because of their safety profile. Although case reports indicate that SSRIs can potentially worsen the motor symptoms of Parkinson’s disease, this effect has not been confirmed in the small number of open-label studies that have been performed to date. The occurrence of the serotonin syndrome resulting from a combination of selegiline and an SSRI appears to be rare.¹²

Venlafaxine, a combined serotonin and noradrenaline reuptake inhibitor (SNRI) has an anxiolytic effect and low side effect profile. A minimum six week trial is required before changing from one to the alternative drug.

Referral to a psychiatrist should be made in cases of drug failure, suicidal ideation, or in difficult clinical situations. Electroconvulsive therapy has been used with effect in these situations. Recently, repetitive transcranial magnetic stimulation has been used experimentally to treat depression.¹³ Avoidance of a general anaesthetic is an obvious advantage of repetitive transcranial magnetic stimulation over electroconvulsive therapy.

COGNITIVE IMPAIRMENT/DEMENTIA IN PARKINSON’S DISEASE

In the original writings of James Parkinson in 1817, “An Essay on the Shaking Palsy”, he concluded that the senses and intellect are uninjured in this disease.¹⁴ We now realise that changes in cognitive function and behaviour occur frequently and form an integral part of the clinical presentation of Parkinson’s disease.

Box 2: Depression in Parkinson’s disease

- Depression is very common in Parkinson’s disease, affecting nearly a third of patients.
- Diagnosis of depression requires a high index of suspicion as some of the features of Parkinson’s disease—for example, masked facies and bradyphrenia, can cause difficulty in diagnosis.
- Depression is significantly associated with the poor quality of life in Parkinson’s disease.

The subtle form of cognitive impairment in the form of slowness in thinking (bradyphrenia) and word finding difficulty occurs in a majority of patients. This is usually not a significant problem for the patient, as it does not hinder day-to-day activities and responsibilities. Dementia refers to cognitive impairment of sufficient magnitude to hinder daily activities or diminish the quality of life. It is a syndrome of global decline of intellect, memory, and personality. Dementia is reported in approximately 20%–44% of patients,¹⁵ but prevalence varies depending on the age of the patient, duration and severity of the disease, presence of depression, and the assessment scale used. A recent survey showed a sixfold increase in the risk of developing dementia in patients with Parkinson’s disease over controls.¹⁶ A prevalence as high as 90% can be found among Parkinson patients in a nursing home, as dementia is the commonest cause of institutionalisation in those with Parkinson’s disease.

Dementia in Parkinson’s disease is more common in patients with late onset disease—that is, after 65 years of age. Depression, severe disease, and presence of levodopa induced psychosis are other common associations of dementia. The dementia of Parkinson’s disease usually becomes apparent several years after the onset of motor features. It often takes the form of memory difficulties that respond to external cues (subcortical dementia), difficulty with planning (dysexecutive syndrome), distractibility, slowed thinking, and lack of motivation.¹⁷ Deficits in visuospatial skills are among the most frequently reported cognitive changes accompanying idiopathic Parkinson’s disease and are not just the consequence of impaired motor performance.¹⁸

Aetiopathology of dementia in Parkinson’s disease

Deficits in dopaminergic, cholinergic, and noradrenergic mechanisms have been proposed as the basis of cognitive impairment in Parkinson’s disease. However, there is no direct evidence for or against this postulation. In some patients, dopaminergic drugs provide benefit in cognition when treated for off periods. In a recent study, reduced [¹⁸F] fluorodopa uptake in Parkinson’s disease in the caudate nucleus (and frontal cortex) was related to impairment in neuropsychological tests measuring verbal fluency, working memory, and attentional functioning (planning, organising, and innovating). This indicates that dysfunction of the dopamine system has an impact on the cognitive impairment of patients with Parkinson’s disease. Acetylcholinesterase inhibitors may be useful because of their cholinergic effects. Defective noradrenergic transmission is considered to be important for attention deficit.

Dementia in Parkinson’s disease appears to a heterogeneous condition with a spectrum of pathological changes. In Parkinson patients with dementia, in addition to Lewy bodies in the midbrain, there are Lewy bodies in the brain or cortex. These brain or cortical Lewy bodies are smaller and more irregular than midbrain Lewy bodies. However, brain and brainstem Lewy bodies probably have a common origin. In life these patients begin with symptoms of Parkinson’s

disease and, in time, become demented. In necropsy studies, a high density of cortical Lewy bodies is commonly associated with the dementia. In fact, dementia with Lewy bodies may be the most advanced form of this pathology. Patients who have dementia with Lewy bodies show early onset of cognitive decline, great fluctuations in cognition, marked hallucinations, and extreme sensitivity to neuroleptics. Dementia in Parkinson's disease can also be due to concurrent Alzheimer's disease or a cerebrovascular disease as these conditions are common in the older population.

Management

Principles of management of dementia in Parkinson's disease do not differ from managing any other type of dementia. Comprehensive multidisciplinary assessment, support of carers, and liaison with a psychogeriatrician are of paramount importance. There are no specific medical treatments for dementia in Parkinson's disease. Increasing doses of the conventional antiparkinson drugs such as levodopa does not appear to offer benefit in regard to the cognitive symptoms. Some antiparkinson medications can actually worsen cognitive function. This is particularly true of the anticholinergic drugs. As far as possible, sedation, sleep deprivation, unnecessary hospitalisations, and anaesthesia should be avoided. Hallucinations should be appropriately treated. Though not studied specifically in patients with Parkinson's disease and dementia, acetylcholinesterase inhibitors can be considered on the basis of cholinergic deficit. However, motor aspects of Parkinson's disease may worsen with their use. Antidepressant medications are sometimes prescribed to help with the apathy or lack of motivation commonly seen in Parkinson's dementia. There is often an element of depression in Parkinson's disease, which in an older adult can masquerade as confusion or dementia. As dementia is a progressive disease, it is useful for patients and their relatives to complete an enduring power of attorney at an early stage.¹⁷

ANXIETY IN IDIOPATHIC PARKINSON'S DISEASE

Symptoms of anxiety are common in Parkinson's disease. The prevalence of anxiety has been reported to be around 30% in some of the studies.^{4,19} Anxiety can be a part of depression and thus may respond to antidepressants with sedative effects. It can also be a manifestation of the cognitive impairment, a side effect of the dopaminergic medications,²⁰ or a part of the mood swings noted in patients with on-off periods. It is, therefore, important to take a detailed history from the patient or the carer.

Box 3: Dementia in Parkinson's disease

- Patients with Parkinson's disease are six times more likely to develop dementia as compared with the normal population.
- Dementia is the commonest cause of institutionalisation in Parkinson's disease.
- Depression can masquerade as dementia (pseudodementia) and should be excluded.
- Dementia is commoner in late onset and advanced Parkinson's disease.
- Dementia of Lewy body type can be differentiated by early onset, marked hallucinations, and high sensitivity to neuroleptics.
- Management of dementia in Parkinson's disease requires a multidisciplinary approach involving the nurse, psychiatrist, physician, carer, and social worker.

The anxiety disorders in Parkinson's disease patients can manifest as panic attacks, phobia, and/or as generalised anxiety disorder. As yet, there is no trial evidence as to the treatment of anxiety in patients with Parkinson's disease. Appropriate antidepressants (SSRI, sedative tricyclics, SNRI) should be used when anxiety is part of the depressive illness. Low dose benzodiazepines and sometimes low dose atypical neuroleptics may have to be used.

PSYCHOSIS IN PARKINSON'S DISEASE

Psychosis affects nearly one third of patients with Parkinson's disease. This usually manifests as vivid dreams, hallucinations, delusions, and in severe cases as confusional psychosis. It drastically reduces the quality of life for those affected. It also results in increased trauma for caregivers, an earlier transfer to a nursing home, and shorter lifespan. Although there were rare reports of hallucinations and delusions in medication-free Parkinson's disease patients before the advent of effective drug therapy, these cases are exceptionally rare.²¹ When hallucinations occur, the usual clinical context involves one of two situations.²² First, a medical illness can be superimposed on Parkinson's disease with resultant hallucinations that are part of the complications of infection, dehydration, or drug toxicity. These patients usually are confused and agitated in the midst of their hallucinations. Alternatively, in chronic Parkinson's disease on dopaminergic therapy, patients can gradually develop hallucinations that are usually visual in content and without marked agitation or confusion.

There may be a bimodal onset of hallucinations, with early onset (<5.5 years) associated with motor fluctuations and large doses of medication, and more commonly a late onset (>5.5 years) associated with cognitive impairment.²³

In a recent study of 214 consecutive patients with Parkinson's disease, Sanchez-Ramos *et al* evaluated various characteristics to determine potential risk factors for the occurrence of psychosis in Parkinson's disease.²⁴ The hallucinating patients were more advanced in age, or had dementia, a history of depression, or sleep disorders. The duration of disease, the total daily dose of levodopa, and the concomitant use of multiple antiparkinsonian medications were not significant risk factors. In Parkinson's disease, hallucinations are almost always visual in character.

Abnormal dreaming and increased sleep disruption may precede the development of psychotic symptoms by weeks to months and provide an important early clue to their potential occurrence.

Often hallucinations occur in low light situations (sun-downing), and when the individual is going from one state of consciousness to another, such as waking from sleep. Someone might "see" a relative in the bedroom upon awakening, but then realise the person is not really present. Something may be seen darting out of the corner of the eye, or crawling bugs will be seen in patterned wall coverings or floor tiles. Seeing small people (lilliputian figures), children, and animals are common hallucinations. As hallucinations become more vivid, insight into the unreality of the

Box 4: Anxiety in Parkinson's disease

- Anxiety can affect nearly third of the Parkinson's disease patients.
- Anxiety can be a part of "off" state.
- Treatment of anxiety in Parkinson's disease is not based on evidence, but antidepressants, benzodiazepines, and low dose neuroleptics have been used.

perception is lost, and the patient may be unable to distinguish real from hallucinatory experiences.

Confusion and paranoid delusions can also occur. The state of confusion and hallucinations is termed psychosis. Unfortunately, a delusional individual often directs his suspicions towards a spouse or other family member.

Pathogenesis of psychosis is not completely understood. Birkmayer and Riedere suggested that the interplay between two brain chemicals, dopamine and serotonin, is of major importance to occurrence of hallucinations.²⁵ In support of this concept, improvement of psychosis in Parkinson's disease occurs not only with blockers of dopamine receptors, but also with the serotonin receptor antagonist, ondansetron.²⁶

TREATMENT

General strategies

- Vivid dreams alone usually do not warrant medical therapy. Similarly, occasional visual hallucinations with insight retained may not require any action beyond reassurance.
- When hallucinations begin, a thorough search should be undertaken for an intercurrent physical illness, overdosage of medication, or infection. If hallucinations occur early after the introduction of dopaminergic treatment for Parkinson's disease, alternative diagnoses should be sought, especially Alzheimer's disease with extrapyramidal features and Lewy body dementia.²⁷
- General treatment measures for hallucinations in a patient with a clear sensorium include encouraging good sleep habits, avoiding excessive patterned furniture, and reducing sensory deprivation and sensory overload.
- If these measures do not abate the hallucinations, mild decreases in medication or elimination of one or more antiparkinsonian agents should be considered. Agents with the lowest antiparkinsonian efficacy (anticholinergics, amantadine, selegiline) should be reduced and/or eliminated first. This intervention may alleviate the psychotic symptoms and often allows for the use of adequate doses of levodopa and dopaminergic agonists to alleviate any worsening of the parkinsonian symptoms. Dopamine agonists are also commonly associated with psychosis and stopping them may reverse it. Whereas a drug holiday was once used in the treatment of psychosis in Parkinson's disease, its major potential complications (lengthy hospitalisations, pressure sores, compressive neuropathies, contractures, aspiration, deep venous thromboses,

pulmonary emboli, neuroleptic-like malignant syndrome) have limited its utility.²⁸

Drug treatment

Patients, who fail to improve despite above measures, will require specific pharmacological treatment.

Typical and atypical neuroleptics

In the past, typical low potency neuroleptics (for example, thioridazine) were used in small doses in an effort to improve psychosis. Unfortunately, these medications frequently cause intolerable worsening of motor function and should be avoided.

As a consequence of a non-selective antagonism at both serotonergic and dopaminergic receptors, atypical antipsychotic drugs are associated with fewer extrapyramidal side effects. They should be started at very low doses that are increased gradually.

New "atypical" antipsychotics, including clozapine,²⁸ risperidone,²⁹ remoxipride,³⁰ zotepine,³¹ olanzapine,³² and quetiapine have been used in open-label studies with mixed success. Clozapine is a drug that belongs to the dibenzodiazepine class of chemicals and has a regional selectivity for action at dopamine receptors in the mesolimbic behavioural system, rather than the nigrostriatal motor system. Clozapine was first used to treat psychosis in Parkinson's disease in 1985, and numerous subsequent reports corroborate its usefulness in this population.²⁸ In general, over 80% of patients respond with complete or partial resolution of psychosis. However, despite clozapine's efficacy at very low doses, side effects like sedation, orthostatic hypotension, and agranulocytosis can occur. Because of the latter clozapine has a restricted license in UK. Quetiapine appears to be favoured because of its low side effect profile. It is important to know that all neuroleptics can cause QT prolongation and therefore an electrocardiogram should be obtained before their use and thereafter on a regular basis.

Cholinomimetic therapy

Acetylcholinesterase inhibitors may prove to be helpful in the prevention and treatment of psychosis in patients with Parkinson's disease, given the effects observed in patients suffering from dementia with Lewy bodies.

Ondansetron (a 5-HT₃ antagonist)

In an open-label, short term (4–8 week) trial, ondansetron was used to treat psychosis in Parkinson's disease at a daily dose of 12–24 mg.²⁶ There was marked to moderate improvement in measures of visual hallucinations, paranoid delusions, confusion, and the associated global functional impairment; but the Mini Mental State Examination scores remained unaltered. Ondansetron did not cause any worsening in basic Parkinson's disease symptoms or levodopa efficacy and was well tolerated with no major side effects.

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Box 5: Psychosis in Parkinson's disease

- Psychosis affects nearly third of patients with Parkinson's disease.
- It is usually a result of an intercurrent infection, electrolyte imbalance, or drug use (often an antiparkinsonian drug).
- Psychosis results into poor quality of life for patient and caregivers, early institutionalisation, and increased mortality.
- Hallucinations (usually visual) are common manifestation of psychosis.
- Typical neuroleptics tend to worsen Parkinson's disease and therefore should be avoided. Newer atypical neuroleptics have been shown to be effective in the management of psychosis of Parkinson's disease.

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