

4 Mental Health Disorders in Parkinson's Disease

Dr G Lennox

Consultant Neurologist, Department of Neurology, Addenbrooke's Hospital, Cambridge

Introduction

Parkinson's disease (PD) is best thought of as a neuropsychiatric condition. Mental health disorders rather than the motor deficits are the main determinants of the patient's quality of life. They often represent the greatest therapeutic challenge. Mental health problems can arise at any point in the course of Parkinson's disease, but tend to follow a pattern. Newly-diagnosed patients with PD may be particularly troubled by anxiety and depression (and indeed these problems often precede the motor symptoms by a few years). Younger patients with established PD may experience the wide range of impulsive behaviours that can complicate dopaminergic therapy; older patients at this stage are often struggling with apathy, hallucinations or early cognitive impairment. Later on the main problem is dementia.

Anxiety and Depression

Both anxiety and depression are common in PD, even in patients whose motor disorder is mild or well-controlled. Recognition is important, because anxiety and depression have a very deleterious effect on quality of life and are generally easy to treat. Regular screening is worthwhile, for example by asking simply patients (and their partners) if they feel cheerful and relaxed. Successful treatment is often accompanied by a reduced requirement for dopaminergic therapy. Patients with motor fluctuations that are accompanied by off-period anxiety are particularly likely to over-medicate with dopaminergic drugs. There is a paucity of clinical trial data but probably all the main classes of antidepressants are effective (for both anxiety and depression) in PD. Pramipexole has antidepressant effects. Cognitive behavioural therapy also seems helpful.

Apathy

Apathy, with a loss of motivation and drive, can also precede the motor symptoms and also aggravate their impact. It may co-exist with depression, in which case antidepressants may help. Otherwise treatment is difficult and trial data even more sparse. Stimulating PD drugs like selegiline, amantadine and modafanil may turn out to have a role.

Impulsive Behaviours

A wide range of impulsive, repetitive and either purposeless or potentially harmful behaviours have been described in response to dopaminergic medication (both levodopa but especially dopamine agonist drugs). These include overmedicating with the drugs themselves (so-called dopamine dysregulation syndrome), a daunting variety of sexual behaviours, gambling, punting, shopping, over-eating and 'hobbyism'. Some form of impulsive behaviour probably affects about 15% of patients, with a higher risk in young-onset patients and patients with a history of depression or previous impulsive disorders such as gambling or alcoholism. The impulsive behaviours improve with a reduction in dopaminergic medication but this is often poorly tolerated from a motor point of view. In suitable patients, deep brain stimulation offers a way out of this impasse.

Psychosis in Non-demented Parkinson's Disease

Psychosis can occur in patients with Parkinson's disease (PD) who have no serious cognitive impairment. It is typically dominated by complex visual hallucinations of people and animals. These are often accompanied by paranoid delusions and sometimes by hallucinations in other modalities (such as hearing the voices or feeling the touch of the visualised figures) and other neuropsychiatric symptoms including delusional misidentification and impulsive behaviours. The psychosis is often precipitated by PD drugs (especially anticholinergics but also amantadine and all of the dopaminergic therapies) and may improve rapidly when these are withdrawn. Intercurrent infection, depression and

visual impairment may also contribute. Unfortunately most of these cases nonetheless go on to develop dementia in time.

Parkinson's Disease with Dementia (PDD) and Dementia with Lewy Bodies (DLB)

Dementia is common in PD with a cross-sectional prevalence of 20 – 40% and a cumulative incidence of up to 80% when community-based populations are followed for several years. Although a few cases have purely Alzheimer pathology, vascular pathology or no identifiable pathology in the cerebral cortex, the great majority of cases have cortical Lewy body pathology which is indistinguishable from that seen in DLB.

The clinical features of PDD and DLB are very similar. It is best to think of Lewy body pathology as a single process, which can start *subcortically* and cause parkinsonism (or depression, sleep disturbance or dysphagia) or *cortically* to cause dementia, and which usually ends up in both locations to cause a mixture of the two. PDD and DLB have prevalences amongst people aged 65 years or more of 0.3% and 0.7% respectively, together accounting for about 20% of all dementia.

Pathology of PDD and DLB

The pathology of PD and PDD/DLB is defined by the presence of Lewy bodies, which are intraneuronal inclusion bodies. Lewy bodies and the closely-related Lewy neurites contain proteins involved in proteolysis (eg ubiquitin and the E3 ubiquitin ligase, parkin) and proteins of unknown function (eg α -synuclein). Areas affected by these inclusions usually also contain coiled bodies within glia, and signs of neuronal loss. In all cases (whether they start with parkinsonism or dementia) there are Lewy bodies in the substantia nigra, but also in other brainstem nuclei such as the noradrenergic locus ceruleus and in the cholinergic nucleus basalis of Meynert. In the cerebral cortex, the pathology is usually most marked around the amygdala, entorhinal and anterior cingulate regions but also affects most of the neocortex. Several studies have now shown a correlation between the density of cortical Lewy body pathology and severity of dementia, although some have not.

Confusingly, there is often (but not always) accompanying β -amyloid pathology in the form of primitive plaques. Plaque pathology tends to be particularly prominent in patients with rapidly-progressive dementia. But the tau pathology of Alzheimer's disease (neurofibrillary tangles and neuritic plaques) is usually scanty or absent, suggesting that there is a biological link between the Lewy body pathological process and β -amyloid formation rather than with Alzheimer's disease and tau. The link is complex, and may be partly genetic (with Lewy bodies found in some cases of Down's syndrome and familial Alzheimer's disease due mutations in the amyloid precursor protein gene, but also in cases due to presenilin-1 and presenilin-2 mutations). It may also be partly environmental, with one recent study reporting that both amyloid plaque and neurofibrillary tangle pathology is twice as dense in PD patients who have received chronic treatment with anticholinergic drugs and another showing less amyloid pathology in patients who have received cholinesterase inhibitors.

The pathology (and clinical features) of PDD/DLB has also been reported in families with mutations or triplication of the α -synuclein gene, supporting the view that there is a spectrum of Lewy body disease that can manifest with PD or PDD/DLB.

Clinical Features of PDD and DLB

Clearly in those cases which start with parkinsonism, the early clinical features are all the familiar ones of PD. There is evidence that PD patients with prominent postural instability and gait disturbance are at higher risk of going on to develop dementia. Depression is also a risk-factor. Presumably all of these features reflect more widespread brainstem pathology.

Of those cases that start with dementia, parkinsonism subsequently develops in the majority and again has a bias towards axial signs, such as hypomimia, postural instability and gait disturbance with less by way of tremor. Limb signs such as bradykinesia and rigidity may be levodopa-responsive early in

the course of the illness, but become less so as it progresses. Treatment with neuroleptics may unmask parkinsonism to a catastrophic degree.

In both groups of patients, the dementia itself tends to begin with brief periods of confusion alternating with periods of lucidity, against a background of gradually worsening cognitive decline. Attention and executive function is often markedly affected in the early stages, and this tends to manifest in fluctuating cognitive performance and vigilance, periods where the patient stares blankly into space, apathy and excessive daytime sleepiness. Visuospatial abilities are also markedly affected in the early stages, whilst memory may be relatively preserved. Screening tests like drawing a clock face or intersecting pentagons are an easy way of revealing these deficits. This neuropsychological picture is characteristic of PDD/DLB and distinguishes it from Alzheimer's disease. As the disease progresses, memory and language do become involved and the dementia becomes global.

Psychiatric manifestations are common, especially visual hallucinations, delusions and anxiety. The visual hallucinations tend to be worse in dim conditions, suggesting that they arise partly from misperception and misinterpretation of environmental stimuli. Some hallucinations may be due to brief intrusions of REM-related dreams into wakefulness. Disrupted sleep, especially REM-sleep behaviour disorder (in which the patient shouts and lashes out during vivid dreams) is very common, and may precede all the other symptoms by years.

Other neurological manifestations include myoclonus (which can be florid and give rise to confusion with CJD), supranuclear vertical gaze palsy, and dysautonomia. The autonomic dysfunction again may be a very early feature, with complaints of dizziness, fainting and unexplained falls and signs of orthostatic hypotension or carotid sinus hypersensitivity.

In most cases the clinical progression is gradual, with survival of several years from onset of dementia. A minority of patients progress very rapidly over the first few months, but then usually enter a plateau. Several studies have shown very high levels of carer burden and financial care cost, together with reduced survival compared with Alzheimer's disease.

Diagnosis of DLB

Consensus criteria have been developed for probable DLB (arbitrarily excluding PDD), based on:

- Dementia with prominent attentional and visuospatial deficit
- Plus 2 of:
 - Fluctuating cognition
 - Visual hallucinations
 - Spontaneous parkinsonism
 - Supporting features including symptoms of dysautonomia (falls, syncope), REM-sleep behavioural disorder, neuroleptic sensitivity, depression and other hallucinations.

These clinical criteria seem to be reasonably specific but relatively insensitive. Using dopamine transporter SPECT scans (presumably as a surrogate for the clinical detection of parkinsonism) improves both specificity and sensitivity. In routine practice, PDD/DLB is still under-recognised, with many cases being erroneously attributed to vascular dementia or Alzheimer's disease.

Routine CT brain scanning is helpful in excluding the remote possibility of structural pathology (e.g. frontal meningioma) and vascular disease, but in early cases is usually strikingly normal. MR imaging may reveal relative preservation of the hippocampus and subtle regional atrophy in the basal ganglia.

Management

PDD/DLB is difficult to manage because treatments for parkinsonism aggravate psychosis and traditional treatments for psychosis aggravate parkinsonism. Non-drug strategies, education and practical support for the patient and carers are vital.

There is now clear evidence that cholinesterase inhibitors are useful in treating PDD/DLB. Fluctuations in cognition and alertness, visual hallucinations and sleep disturbance may all respond to drugs like rivastigmine, donepezil and galantamine. This neuropsychiatric improvement is not generally associated with any motor deterioration, although some patients cannot tolerate treatment because of worsening tremor, orthostatic hypotension, drooling, agitation or diarrhoea. As one would expect of a symptomatic therapy, the benefits tend to wane with time. Some patients then benefit from an increase in their cholinesterase inhibitor beyond the licensed dose or to the addition of memantine, but neither strategy has been tested with a controlled trial. Cholinesterase inhibitors should be withdrawn with care, because some patients deteriorate markedly when this is done.

An alternative way of treating psychosis is with an atypical neuroleptic, although again care is required because of the risk of causing motor deterioration. Quetiapine is currently popular because it is relatively safe, but two studies have now shown no significant benefit over and above the (large) placebo response. Clozapine may be more effective, but is burdensome to use because of the need for haematological monitoring.

Finally, where relevant, there is the traditional strategy of withdrawing PD drugs which may be aggravating the psychosis, starting with anticholinergics. It is generally accepted that levodopa and apomorphine are the drugs which are least likely to aggravate psychosis, which in practice usually means simplifying treatment to levodopa alone if cholinesterase inhibitors and quetiapine have failed.

In patients who develop parkinsonism after their dementia, it may or may not be desirable to attempt to treat this but again levodopa is the least risky option.

There is remarkably little trial data on which to base decisions about treating depression in PDD/DLB. In clinical practice, SSRIs and SNRIs appear effective and reasonably well-tolerated but tricyclics (which have anticholinergic side-effects) are best avoided.

If REM-sleep behaviour disturbance has not responded to a cholinesterase inhibitor, then clonazepam is usually effective in suppressing night-time disruption, but may exacerbate nocturnal incontinence, daytime drowsiness or falls.

Conclusions

Mental health problems are common and important in PD. Anxiety and depression are easy to identify and gratifying to treat. Apathy and impulsive behaviours are more challenging, but management strategies are emerging. Dementia remains the largest problem and the greatest therapeutic challenge, although temporary palliation can usually be achieved.

Further reading

Burn DJ. Cortical Lewy body disease and Parkinson's disease dementia. *Curr Opin Neurol* 2006 Dec; 19(6):572-9.

Lippa CF et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology* 2007 Mar 13;68(11):812-9.

McKeith I. Dementia with Lewy bodies and Parkinson's disease with dementia: where two worlds collide. *Practical Neurology* 2007 Nov;7(6):374-82.

Schrag A. Quality of life and depression in Parkinson's disease. *J Neurol Sci* 2006 Oct 25;248(1-2):151-7.

Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch Neurol* 2007 Aug;64(8):1089-96.

Williams-Gray CH et al. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain* 2007 Jul;130(Pt 7):1787-98.