Dementia in Parkinson's disease

Author: Doctor Richard Dodel[1], MD
Creation date: November 2004

Scientific Editor: Professor Thomas Gasser

[1]Department of Neurology, Friedrich-Wilhelms-University Bonn, Sigmund-Freudstr. 25, 53105 Bonn. Germany. mailto:richard.dodel@ukb.uni-bonn.de

Abstract
Keywords
Disease name/synonyms
Definition /diagnostic criteria
Differential diagnosis
Etiology
Clinical description
Diagnostic methods
Epidemiology
Management
References

Abstract
Parkinson's disease (PD) is one of the most common neurodegenerative movement disorder, which affects about 1% of the population over age 60. Although PD is often recognized as a motor disorder, there are several non-motor signs and symptoms that may cause a considerable burden to the patient. Especially neuropsychiatric symptoms such as depression, anxiety, cognitive impairment and psychosis may contribute to a reduced quality of life in PD patients. Dementia is common and affects approximately 40% of PD patients during the course of the disease. The risk for the development of dementia in PD patients is approximately 6 times higher than compared to non-PD age matched controls. The dementia associated with PD is characterized by a dysexecutive syndrome affecting mainly executive and visuospatial functions while memory is relatively preserved. In patients with Dementia with Lewy bodies (DLB), dementia is the central feature of the disease. The overlap of clinical symptoms between PDD and DLB suggest that they probably represent different points on a spectrum of lewy body diseases sharing similar underlying processes. Currently, only symptomatic treatment of cognitive impairment is available. Recently, several clinical trials using cholinesterase inhibitors have shown its efficacy in PDD and DLB patients.

Keywords
Dementia; Cholinesterase inhibitors; Parkinson's disease; depression; cognition; neuropsychiatry; lewy bodies; lewy body dementia; Alzheimer's disease

Disease name/synonyms
Parkinson's disease and Dementia (PDD)

Definition /diagnostic criteria
Parkinson's disease (PD) is one of the most common neurodegenerative movement disorder, which affects about 1% of the population over age 60. Although PD is often recognized as a motor disorder, there are several non-motor signs and symptoms that may cause a considerable burden to the patient. Dementia is common and affects approximately 40% of PD patients during the course of the disease.

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are two common syndromes with overlapping clinical symptoms suggesting that they probably represent different points on a spectrum of lewy body disease (synucleinopathies) sharing

similar underlying processes. Distinguishing them as separate disorders may be useful in clinical practice, but may be of limited value in terms of investigating and treating the underlying neurobiology (McKeith and Mosimann, 2004). Consensus guidelines for dementia with Lewy bodies (DLB) suggest that PD patients, who develop dementia within 12 months after the initial motor symptoms should be diagnosed as DLB; if dementia occurs later in the course of the disease, patients should be diagnosed as PD with dementia rather than DLB (McKeith *et al*., 1996).

Differential diagnosis

The diagnoses most likely to be confounded with PDD are DLB, Alzheimer's disease, vascular dementia, delirium and Creutzfeld-Jakob disease. Atypical parkinsonian syndromes, including progressive supranuclear palsy and corticobasal ganglionic degeneration, which also lead to cognitive impairment, must be considered in the differential diagnosis of PDD. Currently, there are no clinically applicable genetic or CSF markers to support the diagnosis. There are, however, sufficient studies to conclude that neuroimaging investigations may be helpful in supporting the diagnosis (see below).

Etiology

In his original writings, James Parkinson concluded that "the senses and intellect are uninjured" in PD. It is now known that changes in cognitive function and behaviour occur frequently and form an integral part of the clinical presentation of PD. Although the cognitive deficits of idiopathic Parkinson's disease are now relatively well known, their neuropsychological and neurobiological basis are still discussed. Deficits in dopaminergic, cholinergic and noradrenergic mechanisms have been proposed as the basis of cognitive impairment of PD (Pillon *et al*., 2003). In a recent study, reduced fluorodopa uptake in the caudate nucleus and frontal cortex was related to impairment in neuropsychological tests measuring verbal fluency, working memory, and attentional functioning (Ito *et al*., 2002). The nucleus basalis of Meynert, which degenerates in Alzheimer's disease, is also severely affected in PDD (Whitehouse *et al*., 1983), indicating the contribution of a cholinergic deficit to the cognitive impairment. It is controversial whether Lewy bodies, which may be found in the cortex in advanced PDD and DLB, may correlate with the cognitive impairment (Hurtig *et al*., 2000).

Clinical description

In the majority of the patients, cognitive impairment manifests subtly in the form of slowness of thinking (bradyphrenia) and word finding difficulties. This is usually not a significant problem for the patient, as it does not hinder daily activities and responsabilities. Dementia refers to cognitive impairment of sufficient magnitude to hinder daily activities. The dementia associated with PD is characterized by a dysexecutive syndrome. The changes in different cognitive domains have been extensively assessed in several studies and described in detail in a recent review (Pillon *et al*., 2001). Fluctuating attention as seen in DLB patients is also a feature in PDD, but not in patients with PD without dementia. The cognitive impairment in PDD affects the following domains:

- Impairment of executive functions (ability to plan, organize and perform goal-directed behavior) constitutes the core feature of neuropsychological deficits.
- Visuospatial dysfunction has been reported in several studies, and is more severe than that seen in AD patients with similar dementia severity. Visuospatial impairment affects all subcategories of visuospatial functioning without a specific pattern, except for spared visual sensory abilities and visual recognition.
- Instrumental functions, such as language and praxis are mildly impaired in PDD. Impaired verbal fluency is the main feature and is more severe than in AD.
- Memory functions are relatively preserved in PDD. Deficits in new information learning have been reported, although they are less severe than in AD patients and perfomance on recognition tests are better than free recall. This finding suggests that new information is stored but is not readily accessible.

Diagnostic methods

Cerebrospinal fluid (Holmberg *et al*, 2003): cell count, protein content normal; oligoclonal bands negative.

Disease	Aβ1-42	tau	Ptau (181P)
AD	↓	↑	↑
DLB	↓	n	n
PDD	n	n	n

Electroencephalogram
No difference with AD patients (Barber *et al*., 2000). Temporal slow transients (DLB>AD) (Briel *et al*., 1999).

Single Photon Emission Computed Tomography (SPECT) (Firbank *et al.,* 2003)
In 99mcTc-HMPAO-SPECT studies, the precuneus and inferior lateral parietal regions showed a perfusion deficit in Parkinson's disease with dementia, similar to the pattern observed in DLB. In comparison, AD showed a perfusion deficit in the parietal region, in a more anterior and inferior location than in PDD, involving the posterior cingulate as well as the precuneus.

FP-CIT SPECT (O'Brien *et al*., 2004)
Significant reductions in FP-CIT binding occurred in the caudate and anterior and posterior putamens in subjects with DLB compared with subjects with AD and controls. Transporter loss in DLBs was of similar magnitude to that seen in PD, but with a flatter rostrocaudal (caudate-putamen) gradient. Good separation between DLBs and AD but not among subjects with DLB, PD, and PD with dementia.

18F-dopa PET (Ito *et al*., 2002)
Compared with the normal group, the PDD group showed reduced 18F-dopa bilaterally in the striatum, midbrain and anterior cingulate area. A relative difference in 18F-dopa uptake between PD and PDD was the bilateral decline in the anterior cingulate area, ventral striatum and in the right caudate nucleus in the PDD group.

cMRT (volumetry) (Almeida *et al.*, 2003)
No significant difference in whole brain and caudate nucleus volume on MRI between controls, PD and PDD.

Neuropsychological testing
Memory

working	episodic	semantic	recall
AD>PDD	AD>PDD	AD=PDD	AD>PDD

Perception

Visuoperception	Visuospatial	Visuo-construction
PDD>AD	PDD>AD	PDD/DLB>>AD

Attention	*Executive Functions*	*Fluctuating attention*
PDD<=AD	PDD=AD	DLB=PDD>>AD

Epidemiology
Cognitive deficits in PD patients are common, although they may be subtle. Dementia affects a smaller proportion of PD patients, with a frequency variably reported to range from 2% in early-onset cases to 81% in an unselected population. An analysis of 27 studies revealed an average frequency of 40% (Cummings, 1988). In cross-sectional studies prevalence was reported to vary from 37% to 44% (Hobson *et al*., 1999). Prevalence in patients below the age of 50 was 0% and 69% above the age of 80 years (Mayeux *et al*., 1992). The risk for the development of dementia in PD patients is approximately 6 times higher than compared to non-PD age-matched controls.

Management
The dementia in PD poses a significant therapeutic challenge since these patients are quite sensitive to dopaminergic drugs, which can precipitate confusion and hallucinations. (Friedman *et al*., 2000). In PD patients who have become acutely confused and psychotic, intercurrent infection and subdural hematoma should be excluded. Non-essential medications capable of causing confusion should be discontinued. Antiparkinsonian medication should be reviewed and a gradual, graded withdrawal undertaken in the order of anticholinergics, amantadine, selegiline, and dopamine agonists. If there is no improvement in psychotic features, a cautious trial of an antipsychotic agent must be undertaken (*e.g.* Clozapine, Quetiapine) (Friedman *et al*., 2000).
Currently, only symptomatic treatments are available for the treatment of cognitive impairment by acetylcholine esterase inhibitors (ChEI). ChEIs prevent the inactivation of acetylcholine after its release by blocking acetylcholine esterase. Three ChEIs are currently available, including rivastigmine, donepezil and galantamine, and several studies have been performed in PDD (Aarsland *et al*., 2002; Aarsland *et al*., 2004; Kurita *et al*., 2003; Leroi *et al*., 2004; Marder, 2002).
Several open-label studies using ChEIs were performed in PDD (Kurita *et al.*, 2003; Minet *et al.*, 2003; Bergman *et al*., 2002; Bourke and Druckenbrod, 1998; Bullock and Cameron, 2002; Fabbrini *et al.*, 2002). Placebo-controlled trials were reported, however, with a limited number of patients (Marder, 2002; Werber *et al*., 2001). One study included 14 PD patients with cognitive impairment, who were randomly assigned to receive either donepezil or placebo in a crossover design of two following 10 weeks periods (Aarsland *et al*., 2002). The primary outcome measures were the mini

mental state examination score (MMSE), the clinician's interview-based impression of change plus caregiver input (CIBIC+) score, and the motor subscale of the unified Parkinson's disease rating scale (UPDRS). Two patients on donepezil (14%) dropped out after one and four weeks of the first treatment period because of peripheral cholinergic side effects, otherwise the adverse effects were few and not severe. Parkinsonism did not increase during donepezil treatment. After 10 weeks of treatment, the mean MMSE score was increased by 2.1 (SD 2.7) points on donepezil and 0.3 (SD 3.2) points on placebo, and the CIBIC+ score was 3.3 (SD 0.9) on donepezil and 4.1 (SD 0.8) on placebo. Five (42%) patients on donepezil and two (17%) on placebo were rated as improved on the basis of the CIBIC+ score. The authors concluded that donepezil improves cognition, seems to be well tolerated and does not worsen parkinsonism in patients with cognitive impairment.

Another study used a randomized, double-blind, placebo-controlled design with nine patients receiving placebo and seven patients receiving donepezil (2.5-10 mg/day) for a mean duration of 15.2 weeks (Leroi *et al*., 2004). The primary efficacy outcomes were derived from a neuropsychological battery that assessed global cognitive status as well as memory, attention, psychomotor speed, and visuospatial and executive functions. Patients on donepezil showed selective and significant ($p<0.05$) improvement on the memory subscale of the Dementia Rating Scale. There was also a trend toward improvement on a measure of psychomotor speed and attention. There were no group differences in psychiatric status, motor function, or activities of daily living as measured at baseline or end-point. Adverse effects resulted in premature withdrawal of four patients on donepezil, two for peripheral cholinergic effects and one for increased parkinsonism. Side effects were associated with dosage increases. The authors concluded that donepezil has a beneficial effect on memory and may improve other cognitive deficits in patients with PD and cognitive impairment. However, variable tolerability underscores the need for careful monitoring when prescribing donepezil to patients with PD, especially with dosage increases.

International, multicenter, double-blind, placebo-controlled studies are currently underway to assess the effects of ChEIs in PDD more thoroughly.

Recently memantine has been shown to be effective patients with moderate to severe Alzheimer's disease (Koch *et al*., 2004). No studies have been yet performed in PDD patients concerning its effect on cognition.

References

Aarsland D, Mosimann UP, McKeith IG. Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. J Geriatr Psychiatry Neurol. 2004 Sep;17(3):164-71.

Aarsland, D. *et al*. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry, 2002. 72(6): p. 708-12.

Almeida, O.P. *et al*. MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord, 2003. 16(2): p. 57-63.

Barber, P.A. *et al*. The electroencephalogram in dementia with Lewy bodies. Acta Neurol Scand, 2000. 101(1): p. 53-6.

Barber, R. *et al*. Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. J Neurol Neurosurg Psychiatry, 2002. 72(3): p. 406-7.

Bergman, J. and Lerner V. Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. Clin Neuropharmacol, 2002. 25(2): p. 107-10.

Bourke, D. and Druckenbrod R.W. Possible association between donepezil and worsening Parkinson's disease. Ann Pharmacother, 1998. 32(5): p. 610-1.

Briel, R.C. *et al*. EEG findings in dementia with Lewy bodies and Alzheimer's disease. J Neurol Neurosurg Psychiatry, 1999. 66(3): p. 401-3.

Bullock, R. and Cameron A. Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: a case series. Curr Med Res Opin, 2002. 18(5): p. 258-64.

Cummings, J.L. Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol, 1988. 1(1): p. 24-36.

Fabbrini, G. *et al*. Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurol Sci, 2002. 23(1): p. 41-3.

Firbank, M.J. *et al*. Regional cerebral blood flow in Parkinson's disease with and without dementia. Neuroimage, 2003. 20(2): p. 1309-19.

Friedman, J.H. and Factor S.A. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord, 2000. 15(2): p. 201-11.

Hobson, P. and Meara J. The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. Age Ageing, 1999. 28(1): p. 39-43.
Holmberg, B. *et al*. Cerebrospinal fluid Abeta42 is reduced in multiple system atrophy but normal in Parkinson's disease and progressive supranuclear palsy. Mov Disord, 2003. 18(2): p. 186-90.
Hurtig, H.I. *et al*. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology, 2000. 54(10): p. 1916-21.
Ito, K. *et al*. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[18F]fluoro-L-dopa PET study. Brain, 2002. 125(Pt 6): p. 1358-65.
Koch, H.J., Szecsey A., Haen E. NMDA-antagonism (memantine): an alternative pharmacological therapeutic principle in Alzheimer's and vascular dementia. Curr Pharm Des, 2004. 10(3): p. 253-9
Kurita, A. *et al*. The beneficial effect of donepezil on visual hallucinations in three patients with Parkinson's disease. J Geriatr Psychiatry Neurol, 2003. 16(3): p. 184-8.
Leroi, I. *et al*. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry, 2004. 19(1): p. 1-8.
Marder, K. Donepezil for cognitive impairment in Parkinson's disease: a randomized controlled trial. Curr Neurol Neurosci Rep, 2002. 2(5): p. 390-1.
Mayeux, R. *et al*. A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. Arch Neurol, 1992. 49(5): p. 492-7.
McKeith IG, Mosimann UP. Dementia with Lewy bodies and Parkinson's disease. Parkinsonism Relat Disord. 2004 May;10 Suppl 1:S15-8.
McKeith, I.G. *et al*. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies. Neurology, 1996. 47: p. 1113-1124.
Minett, T.S. *et al*. What happens when donepezil is suddenly withdrawn? An open label trial in dementia with Lewy bodies and Parkinson's disease with dementia. Int J Geriatr Psychiatry, 2003. 18(11): p. 988-93.
O'Brien, J.T. *et al*. Dopamine transporter loss visualized with FP-CIT SPECT in the differential diagnosis of dementia with lewy bodies. Arch Neurol, 2004. 61(6): p. 919-25.
Pillon, B. *et al*. Cognitive deficits and dementia in Parkinson's disease, in Handbook of neuropsychology, F. Boller and S. Cappa, Editors. 2001, Elsevier: Amsterdam. p. 311-371.
Pillon, B., V. Czernecki, and B. Dubois. Dopamine and cognitive function. Curr Opin Neurol, 2003. 16 Suppl 2: p. S17-22.
Werber, E.A. and Rabey J.M. The beneficial effect of cholinesterase inhibitors on patients suffering from Parkinson's disease and dementia. J Neural Transm, 2001. 108(11): p. 1319-25.
Whitehouse, P.J. *et al*. Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol, 1983. 13(3): p. 243-8.