Dementia in Parkinson’s disease

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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
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 responsibilities. 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 performance 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.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Aβ1-42</th>
<th>tau</th>
<th>Ptau (181P)</th>
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<tbody>
<tr>
<td>AD</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>DLB</td>
<td>↓</td>
<td>n</td>
<td>↑</td>
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<tr>
<td>PDD</td>
<td>n</td>
<td>n</td>
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**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 99mTc-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**

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<tr>
<th>working</th>
<th>episodic recall</th>
<th>semantic recall</th>
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<tbody>
<tr>
<td>AD&gt;PDD</td>
<td>AD&gt;PDD</td>
<td>AD=PDD</td>
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**Perception**

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<tr>
<th>Visuoperception</th>
<th>Visuospatial</th>
<th>Visuo-construction</th>
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<tbody>
<tr>
<td>PDD&gt;AD</td>
<td>PDD&gt;AD</td>
<td>PDD/DLB&gt;&gt;AD</td>
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**Attention**

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<th>Executive Functions</th>
<th>Fluctuating attention</th>
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<tr>
<td>PDD&lt;=AD</td>
<td>PDD=AD</td>
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**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, intermittent 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; Fabbbrini 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+), 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


