

COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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SUMMARY

Parkinson's disease is the second most frequent neurodegenerative disorder. There is significantly elevated risk of cognitive decline and associated neuropsychiatric symptoms.

Dementia may develop insidiously several years after manifestation of Parkinson motor symptoms (dementia associated with Parkinson's disease; Parkinson's disease dementia) or in close temporal relationship (within one year) after onset of motor symptoms (Dementia with Lewy bodies). There are clinical, pathophysiological and therapeutic similarities between these two conditions. Men are more frequently affected than women. Risk factor or indicators are advanced age at disease onset, disease duration, rigidity, akinesia and posture and gait impairment and falls as opposed to tremor dominance, and associated neuropsychiatric symptoms (depression, apathy, hallucinosis, delirium). Dementia is treatable with cholinesterase inhibitors (rivastigmine, donepezil), memantine, and adjustment of the pharmacological regimen of parkinsonian motor symptoms. Concomitant autonomic nervous system symptoms and neuropsychiatric complications warrant early clinical awareness and are accessible to pharmacological therapy.

Key words: Parkinson – dementia - dementia with Lewy bodies - review

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Epidemiology

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder after Alzheimer dementia (AD). It is clinically characterized by bradykinesia, and one of the following motor features: impairment of stance and gait, tremor (mostly resting tremor) and/or rigidity (Hughes 1992). PD motor symptoms are mostly asymmetrical and respond to levodopa and other dopaminergic substances over years and decades. PD may start in the second or 3rd decade (onset before age of 40 is named young-onset PD), usually later, with a mean age-at-onset of around 60 years and a peak of prevalence in the 8th to 9th decade (1087 to 1903/100,000; Aarsland 2008; Pringsheim 2014). The age-and gender-adjusted incidence rate of PD is around 13 per 100,000 (Van den Eeden 2003). Men are more frequently affected than women (Hughes 2000, Van den Eeden 2003, Pringsheim 2014, Savica 2013), and men seem to be at higher risk of developing dementia in PD than women (Hughes 2000).

Clinical diagnosis

Dementia is a disabling condition. It is therefore important to diagnose cognitive decline in time, to modify pharmacological treatment of motor functions accordingly and start with antidementive pharmacotherapy together with non-pharmacological interventions (Rongve and Aarsland 2006). PD is not only characterized by motor symptoms; a typical spectrum of non-motor symptoms manifests in PD including neuropsychiatric features and cognitive decline leading to dementia in up to 80-90% of patients (Buter 2008). Age at disease onset, age at a given time point in the course of the disease, disease duration, rigidity, akinesia,

posture and gait impairment, and neuropsychiatric symptoms are indicative of elevated risk of dementia in PD (Hughes 2000, Aarsland 2014). Associated neuropsychiatric features of dementia in PD are depression, apathy, or psychotic episodes including delirium, hallucinosis, delusions and paranoid ideation. Development of dementia in PD restricts the therapeutic armamentarium against the motor symptoms; high-dose levodopa therapy, dopamine agonists, anticholinergic substances, amantadine and their combinations become problematic with cognitive decline because of mental and autonomic nervous system complications (psychosis, orthostatic hypotension, sleep disorders etc.). Levodopa, can often not be administered at optimum doses although demented PD patients suffer from more severe akinesia, rigidity and postural and gait disorder than patients without dementia.

Dementia in association with PD (Parkinson's disease dementia; PDD) may develop after several years of „uncomplicated“ PD. With increasing age at disease onset (8th to ninth decade) there is growing probability that parkinsonian motor symptoms and dementia manifest in close temporal relationship, i.e. dementia develops within one year after or concomitantly with the onset of motor symptoms, or, in rare cases, months to years before the manifestation of parkinsonian motor symptoms. For such a condition the term Dementia with Lewy Bodies has been coined (DLB; Table 1, McKeith 2005). „Probable DLB“ is clinically characterized by dementia including attentional deficits, and frontal dysexecutive and visuospatial impairments, in combination with a minimum of 2 of the 3 following core symptoms: spontaneous (primary) parkinsonian motor syndrome, repeated, detailed visual hallucinations, and cognitive fluctuations including reduced

vigilance and attentional span. Often the transition from dementia to delirium is vague (Gore 2015). Indicative of DLB are REM-sleep behavior disorder, severe sensitivity to usual doses of neuroleptics, urinary incontinence and pathological dopamine transporter SPECT or F-DOPA-PET findings (McKeith 2005). Falls and syncope, sudden loss of consciousness, severe autonomic failure, hallucinations of other modalities than visual and delusions are supportive of the diagnosis of DLB.

Table 1. Clinical characteristics of DLB

Dementia including attentional deficits, and frontal dysexecutive and visuospatial impairments

Probable DLB: 2 of 3 of the following features:

- parkinsonian motor syndrome
- repeated, detailed visual hallucinations
- cognitive fluctuations including reduced vigilance and attentional span

Indicative features:

- REM-sleep behavior disorder
- severe sensitivity to usual doses of neuroleptics
- urinary incontinence
- pathological dopamine transporter SPECT or F-DOPA-PET findings

Supportive features:

- Falls and syncope
- sudden loss of consciousness
- severe autonomic failure
- hallucinations of other modalities than visual and delusions

PDD (Dubois 2007, Emre 2007) is clinically similar to DLB, however, onset is generally insidious, and progression may be less rapid than in DLB. Before there is evidence of dementia, patients may develop mild cognitive impairment involving those cognitive functions which are later implicated in dementia (Litvan 2012). Attentional, visuospatial, and executive deficits are likewise found. There may also be short-term memory deficits and associated neuropsychiatric features such as depression, delusions, hallucinosis, delirium and apathy.

Underlying pathologies

Both in PDD and DLB, the characteristic pathology of PD, intraneuronal Lewy bodies and Lewy neurites staining positive with antibodies to α -synuclein are found both in extrapyramidal motor (substantia nigra) and autonomic nuclei, in the basal ganglia, the limbic system and the cortex and their projection areas. Moreover, in a variable proportion of DLB and PDD patients, Alzheimer-type pathology is found. There is also substantial neuronal loss in specific cholinergic brain stem (pedunculopontine nucleus) and basal forebrain nuclei and to a lesser degree, in limbic and cortical areas (Irwin 2012).

Neurochemical data

Similar to PD and AD, there is marked decrease of nigrostriatal and mesocorticolimbic dopamine in PDD and DLB due to loss of substantia nigra neurons, serotonergic (raphe nuclei), noradrenergic (locus coeruleus) projections and acetylcholine in hippocampal and cortical projection areas of cholinergic basal forebrain nuclei (Nucleus basalis of Meynert, longitudinal band of Broca, septal nuclei; Halliday 2014, Vermeiren 2015). The cortical and hippocampal cholinergic deficits are related to memory problems and may be more severe in PDD and DLB than in AD. On the other hand, aminergic and cholinergic receptor function is often spared rendering substitutive therapies effective (Francis 2009).

In the CSF, reduction of α -synuclein is found, which contrasts to AD (Lim 2013, Gao 2014). A β 1-42, the characteristic protein of AD, is mildly and moderately reduced in PD and in DLB compared to normal controls, but still higher than in AD (Tang 2014).

Neuropsychological assessments

Dementia is characterized by a combination of several neuropsychological deficits including memory decline causing impairment in routine activities. Minimal State Examination (Folstein 1975; usual scores below 26 of 30) and combinations of tests assessing various cognitive categories are needed, such as the Mattis Dementia Rating Scale or CERAD-plus (www.memoryclinic.ch/content/view/55/54/; Dubois 2007, Emre 2007). Frontal executive dysfunction is under-represented in these batteries. Therefore, complementary test, such as the Wisconsin Card Sorting Test, the Stroop Word-Color Test and verbal fluency tests are suggested. Attention can be tested using the 100 minus seven in series calculation paradigm or digit span forward and backward, verbal short-term memory and visuospatial tests are parts of CERAD-plus or Mattis Dementia Rating Scale. The clock drawing test (Shulman) assesses visual conceptualisation and is particularly sensitive for diagnosing PDD or DLB. For assessment of depression the Beck Depression Inventory and for apathy the Apathy Scale are suggested (Dubois 2007)

Neuroimaging

In DLB and PDD, similar to AD, there is atrophy of the frontal lobes, to a lesser degree of the temporoparietal cortex and the mesial temporal lobe including the hippocampal region (Barber 2000, Lee 2013, Borroni 2015). MRI is useful in detecting these changes and may contribute to the diagnosis. However, these findings are not specific for the diagnosis. Molecular neuroimaging reveals dopamine transporter deficits in the putamen and, to a lesser degree, in the caudate nucleus, sometimes more symmetrical than in PD without dementia (Ransmayr 2001). Similar findings are

obtained using fluoro-DOPA PET. Moreover, in addition to temporoparietal hypoperfusion or hypometabolism in the temporoparietal cortex, occipital hypometabolism/hypoperfusion is found (Donnemiller 1997, Minoshima 2001).

Therapy

A recent Cochrane database systematic review supports the use of cholinesterase inhibitors (rivastigmine, donepezil) in PDD and found uncertainty with regard DLB (Emre 2004; Rolinski 2012). Significant effects were found on cognitive functions, and behavioral impairments and activities of daily living. However, side effects, mainly loss of appetite, nausea, vomiting, and tremor may occur. No significant increase of falls was observed. There is no study comparing directly rivastigmine and donepezil. Memantin may also show some benefits in PDD and DLB (Aarsland 2009, Wesnes 2015). Cholinesterase inhibitors seem to be particularly effective in patients with visual hallucinosis (Burn 2006). In case of hallucinations, dopaminergic therapy has to be reduced, in particular dopamine agonists. Clozapine is the only substance showing evidence of efficacy for the treatment of hallucinations. However, regular white blood cell counts are warranted because of the albeith small risk of agranulocytosis. Moreover, clozapine may cause orthostatic hypotension and sedation. Therefore, quetiapine is often used an alternative treatment of hallucinations. Serotonin reuptake inhibitors may improve depression and anxiety in PDD and DLB. Fluid intake and midodrine or fluoro-cortisone are suggested to treat orthostatic hypotension (Sonnesyn 2009, Seppi 2011).

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