Cognitive Impairment in Parkinson’s Disease: What We Know so Far

Abstract: One of the most impactful non-motor manifestations of Parkinson’s disease (PD) is cognitive impairment. Cognitive decline in PD exists as a continuum, with symptoms ranging from normal cognition to mild cognitive impairment (MCI) and finally dementia (PDD). MCI is clinically heterogeneous and its progression varies with cases reverting to normal cognition. On the contrary, when dementia occurs, the decline is usually rapid and stereotyped. The combination of Lewy and Alzheimer’s disease pathology is the most robust pathological correlate of PDD. There are no approved drugs for PD-MCI and the benefit from the only approved symptomatic treatment for PDD is modest. This review aims to present the aspects in which greater evidence exists and summarize the epidemiology, pathogenesis, clinical features, diagnostic approach, and treatment of cognitive dysfunction and dementia in PD.

Keywords: Parkinson, dementia, mild cognitive impairment, review, biomarker, diagnosis, treatment

Introduction

Parkinson’s disease (PD) has been traditionally considered a motor disorder but non-motor symptoms including cognitive impairment and dementia, depression, psychosis, autonomic disturbances, and sleep disorders have increasingly been recognized. Cognitive dysfunction and dementia can have a greater effect than motor symptoms on the quality of life of the patient and caregivers, as well as being a risk factor for nursing home admission and early mortality. Due to all these impactful consequences cognition in PD has been the subject of extensive research, covering multiple perspectives and promoting an enormous amount of literature.

In the text that follows we review the epidemiology, pathogenesis, CSF biomarkers, clinical features, diagnostic approach, and treatment of cognitive dysfunction and dementia in PD aiming to present the aspects in which greater evidence exists. Box 1 highlights the key points of this review.

Epidemiology

Cognitive deficits are common in PD even in early stages and over 75% of PD patients may eventually develop dementia (PDD) over time. Cognitive decline in PD exists as a continuum, with symptoms ranging from normal cognition to subjective cognitive changes with normal neuropsychological assessment, mild cognitive impairment (PD-MCI), and finally dementia. The classification into those groups among different studies vary depending on the design of the study and the criteria applied.7,8
In the last decade, the International Parkinson and Movement Disorder Society (MDS) has proposed formal diagnostic criteria for both PD-MCI and PDD.\textsuperscript{9,10} For PD-MCI cognitive deficits should be present on neuropsychological testing and should not interfere with functional autonomy. Estimates of the prevalence of PD-MCI vary widely with a recent estimate of around 26%.\textsuperscript{11} Two cross-sectional studies have estimated MCI prevalence in 33% and 64% respectively.\textsuperscript{12,13} A pooled analysis of data from eight different cohorts comprising 1346 non-demented PD patients showed that 25.8% of patients had MCI.\textsuperscript{14}

Specific diagnostic clinical criteria have also been established for possible and probable PD-associated dementia.\textsuperscript{10} Diagnosis of dementia must be based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuospatial functions) documented by clinical and cognitive examination, and be severe enough to affect normal functioning. A systematic review of the prevalence of PDD including 12 selected studies found a point prevalence of 24 to 35%.\textsuperscript{15} Different studies have indicated an association between the prevalence of dementia and disease duration. In the CamPaIGN study, a dementia prevalence rate of 15 to 20% after 5 years and 46% at 10 years was reported.\textsuperscript{6,16} Although progression to dementia seems not to be inevitable, it develops in about 80% of PD patients with disease duration, especially longer than 20 years.\textsuperscript{17} Older age, postural instability-gait disorder phenotype, psychiatric symptoms as psychosis, hallucinations, and depression, REM sleep behavior disorder, and diurnal sleepiness have been associated with PD cognitive worsening.\textsuperscript{10,18-21}

As for genetic causes of PD, \(\alpha\)-synuclein duplication and triplication, DJ1, GBA, and MAPT mutations have been linked to prominent cognitive dysfunction and dementia while LRRK2 and Parkin mutations have not.\textsuperscript{22-24}

**Pathogenesis of PDD**

Although the exact neurobiological basis of PDD is not known, dementia in PD probably occurs as a result of progressive involvement of subcortical and cortical structures by Lewy-type pathology and associated Alzheimer histological changes. Other factors such as vascular pathology, among others, may contribute to the development of PDD in some cases.

**Neuropathological Correlates**

Neuropathological studies using \(\alpha\)-synuclein immunohistochemistry have demonstrated that cortical and limbic involvement by Lewy bodies (LB) and Lewy neurites are the dominant and primary substrate of PDD.\textsuperscript{17} In a recent systematic review including 41 autopsy studies of pathologically-verified PD cases with dementia, \(\alpha\)-synuclein pathology almost invariably extended to the limbic system or neocortex and neocortical involvement was more frequent than in non-demented PD patients.\textsuperscript{25} The severity of cognitive impairment correlated with Lewy body densities in the frontal, straight, angular, cingulate, and middle temporal gyri. In PDD brains, Alzheimer’s disease (AD) -type and LB-type pathologies frequently coexist, suggesting there are interactions between \(\alpha\)-synuclein, tau, and amyloid-\(\beta\) (A\(\beta\)) proteins aggregates. In fact, in combined Lewy-Alzheimer transgenic mice models, both enhancement of \(\alpha\)-synuclein aggregation by A\(\beta\) peptides\textsuperscript{26} and exacerbation of tau and A\(\beta\) accumulation by \(\alpha\)-synuclein, lead to the acceleration of neuropathology and cognitive
In the above mentioned systematic review, tau and Aβ pathologies in demented PD cases were typically moderate to severe only in the entorhinal cortex and mild in the hippocampus. The neocortex was variably affected by amyloid-β. In contrast, what is happening in AD, tau pathology was more prevalent in prefrontal than in the temporal cortex. As for the relative contribution of AD pathology to dementia in PD, tau lesions have been independently associated in one study but Aβ, in contrast, was not independently related to dementia in any study but moderate to severe deposition has been associated with a more rapid cognitive decline and earlier mortality. In another pathological study coexistence of LB-type and tau and Aβ pathologies was found to be a better predictor of dementia than the severity of a single pathology. Neurochemical Deficits in PDD

Degeneration of subcortical nuclei in PD leads to dopaminergic, cholinergic, noradrenergic, and serotonergic deficits. Of them, cholinergic deficits due to degeneration of the nucleus basalis of Meynert (NBM) have been the most involved in PDD. In early neuropathological studies, PDD patients showed more NMB cholinergic neuronal depletion when compared with AD and non-demented PD. A greater reduction of choline acetyltransferase activity (indicative of cholinergic innervation) in frontal and temporal cortex was found in PDD than in PD without dementia. Mattila et al reported reduced choline acetyltransferase activity in the hippocampus, prefrontal cortex, and temporal cortex in PD. Reduction in the frontal cortex correlated significantly with the degree of cognitive impairment. Not only pathological studies but also neuroimaging studies have pointed out a role for a cholinergic deficit in cognition in PD. Both PD and PDD have cholinergic neuron deficits with vesicular acetylcholine transporter (VAcTi) and acetylcholinesterase (AChE) imaging being the decreased VAcTi more important and extensive in the cerebral cortex of PDD subjects. As for the dopaminergic system, evidence indicates that it may contribute to some of the cognitive problems in PDD. Executive dysfunction has been associated with denervation of striatal dopamine and D2 receptor deficiency in the insula lobe region in PD-MCI and with degeneration of nigrostriatal dopaminergic neurons in early PD, but not with memory and visual-spatial functions. Another study, however, using DTBZ and FLB 457 PET imaging, demonstrated that memory-impaired PD patients had more significant reductions in D2 receptor binding in the insular cortex, anterior cingulate cortex, and the right parahippocampal gyrus compared to healthy controls and patients cognitively normal. There are not consistent findings supporting an association between dementia and other monoaminergic systems.

Cerebro-Vascular Pathology

The contribution of cerebral vascular lesions in PDD is controversial. In an 18 months prospective study we found that progression to dementia was more frequent in PD patients with moderate to severe parieto-occipital white matter hyperintensities (WMH) and low CSF Aβ levels. Others have reported increased burden of WMH in PD subjects later progressing to dementia and the WMH volume has been found to predict longitudinal cognitive decline among PD patients with MCI and early PD. However, in a multicenter study, no differences were observed in early PD and normal controls and more recently a pathological study found no correlation between the severity of subcortical small vessel disease and dementia. A possible explanation of these apparent discrepancies is that the presence of cerebrovascular lesions might be modest cross-sectionally but it might have a role in cognitive worsening with the progression of the disease.

CSF Biomarkers in PDD

Many studies on CSF aimed to identify biomarkers reflecting the abnormal protein aggregates associated with PDD. In the majority of them, the level of Aβ was found reduced whereas the levels of total (t-tau) and phosphorylated tau (p-tau) were increased or unchanged in PDD. The use of more or less strict definition for dementia and the inclusion of more or fewer patients with “AD-memory problems” can partially account for the discrepancies in the tau level reported. Based on the data from cross-sectional and longitudinal studies there is the strongest evidence that low levels of Aβ and increased levels of tau in the CSF at baseline might predict future cognitive decline in patients with PD. We performed a longitudinal study in non-demented PD patients including CSF, neuropsychological and MRI at baseline and 18 months follow-up. We found that a combination of lower CSF Aβ, reduced verbal learning, semantic fluency, and visuoperceptual scores, as well as cortical thinning in superior-frontal/anterior cingulate and precentral regions, were predictive for PDD.
Several studies of CSF levels of total α-synuclein have been published, most of them reporting low values in PD, which has been confirmed by a recent meta-analysis performed by Eusebi et al. However, the relationship between α-synuclein levels and cognitive decline remains uncertain. Both high and low CSF levels have been observed as significant predictors of cognitive impairment in PD. In general, the association between high levels and cognitive impairment was found in more advanced disease stages. In other studies, no prognostic effect was observed. In addition to total α-synuclein, post-translationally modified forms such as oligomeric α-synuclein, have been analyzed concerning PD cognition. Hansson et al found levels of CSF α-synuclein oligomers significantly higher in patients with PDD and DLB compared with patients with AD and controls. Compta et al determined CSF oligomeric- and total-α-synuclein in patients with idiopathic REM-sleep behavior disorder (iRBD) and non-demented PD and PDD intended to reflect the premotor-motor-dementia PD continuum. CSF oligomeric-α-synuclein was higher in non-demented than iRBD and PDD than iRBD and controls and correlated with UPDRS-III, MMSE, semantic fluency and visuoperceptive scores. Although promising further research is needed to confirm the diagnostic and prognostic utility as markers of oligomeric and other forms of α-synuclein for cognitive impairment in PD.

**Clinical Characteristics**

The difference between MCI and PDD is based on the extent to which cognitive impairment interferes with daily life activities. PD-MCI is clinically heterogeneous with a range of cognitive domains affected. PD-MCI can be classified into single or multiple domains, being the domains attention, executive, language, memory, and visuospatial functions. If neuropsychological assessment includes one test for each of the five domains it is considered as level 1 assessment for detecting MCI-PD, whereas a level 2 assessment includes at least two tests for each domain and allow for MCI subtyping. Using level II criteria, multi-domain MCI is more frequent than a single domain. Non-amnestic is the most frequent subtype in PD-MCI single domain according to several studies. In PD-MCI multi-domain, the most affected domains are executive, visuospatial, memory, and attention tasks. Although less frequently, language impairment has also been observed in some studies. The “dual syndrome hypothesis” has been proposed to distinguish between MCI: 1) in some, there is a predominant frontal-striatal impairment (disturbances in planning, working memory, and response inhibition), modulated by dopamine, that may be present even in very early phases of PD and frequently with little progression over time; 2) patients with predominant temporal and posterior cortical dysfunction (attentional, semantic verbal fluency, and visual-spatial difficulties) which are more likely to progress to dementia. PD-MCI usually precedes PDD and patients with PD-MCI present a higher risk (19%–62%) of developing dementia when they are followed from 2 to 5 years after diagnosis. However, some patients with PD-MCI will revert to normal cognition during follow-up. In a community-based cohort study that assessed 115 newly diagnosed patients with PD found that having MCI at baseline (n: 49, 42.6%) increased the risk of developing PDD (n: 25, 51%) within 5 years 6.5 times (Hazard ratio: 6.5, 95% CI 2.60–16.13, p < 0.001). Besides, six patients (12.40%) that were initially classified as MCI reversed back to normal cognition and ten patients fluctuated between MCI and normal cognition at different assessments. Another prospective cohort study with 178 PD patients at baseline evidenced that 39.1% of patients with PD-MCI progressed to dementia. Those who had persistent PD-MCI (OR: 16.6, 95% CI: 5.1–54.7) and those who converted from normal cognition to PD-MCI (OR: 6.4, 95% CI: 1.7–23.8) at the 1-year follow-up presented an increased risk to develop dementia compared to those with normal cognition. Finally, a recent meta-analysis showed that 20% (95% CI 13–30%) PD-MCI patients converted to dementia while 28% (95% CI 20–37%) reverted to a state of normal cognitive function. When the study follow-up was equal or greater than 3 years, rates to MCI and dementia were higher, and reversion rates lower.

PDD is characterized by a more devastating cognitive impairment and is a common late manifestation in PD. Unlike MCI, when dementia occurs the decline is usually more rapid and stereotyped. Dementia involves executive, attention, visuospatial, and memory impairment, with the language being usually preserved. Executive dysfunction is at the root of most cognitive changes in PD and is characterized by impairment in planning, abstract thinking, mental flexibility, verbal fluency, and apathy. Patients with impaired attention may present difficulties to follow a conversation and present drowsiness and reduced arousal. The attentional deficit has been shown to interfere significantly in the patient’s quality of life. Regarding memory, PDD patients typically present poor performance in free recall with benefit from cueing, but some patients may also present impaired recognition similar to what is seen in.
Alzheimer’s disease. Visuospatial problems include both visuospatial and visuoperceptive deficits and present high sensitivity to detect the conversion to PDD. PDD is often accompanied by neuropsychiatric symptoms such as mood disorders, psychosis, and hallucinations. Visual hallucinations are typically complex, with well-formed figures such as people, animals or objects and often with preserved insight.

Sleep problems like excessive daytime sleepiness or insomnia and autonomic disturbances including urinary incontinence and orthostatic and postprandial hypotension are also frequent in PDD.

**Diagnostic Approach**

Differential diagnosis between DLB and PDD has been based on an arbitrary distinction between the time of onset of motor and cognitive symptoms. Thus, the Movement Disorders Society does not consider any more the presence of dementia in an early phase as an exclusion criterion for PD. A diagnosis of PDD is based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuospatial functions) and those have to be severe enough to impair activities of daily living. For the differential diagnosis with other kinds of dementia, the neuropsychological battery is the gold standard. It is recommended, at least, to cover cognitive domains most frequently affected and to use more than 1 test per domain to increase sensitivity.

The assessment of cognition with cognitive rating scales is frequent and can be useful for screening and monitoring in clinical practice. A recent systematic review by the Movement Disorders Society classified the Montreal Cognitive Assessment (MoCa), the Mattis Dementia Rating Scale Second Edition (DRS-2), and the Parkinson’s Disease-Cognitive Rating Scale (PD-CRS) as recommended scales. The MoCa is a brief (10–30 minutes), 30-point, cognitive test which was developed as a screening measure for MCI. It covers visuospatial and executive functions, attention and memory, language, and orientation. Cutoff points have been established in 25/26 for PD-MCI and 20/21 for PDD. The DRS-2 is a global cognitive function test, administered in 20–30 minutes, for patients with neurodegenerative diseases. It assesses different cognitive areas like attention, initiation-perseveration, construction, conceptualization, and memory. Cutoff scores have been established at 132/144 for PDD and 139/144 for PD-MCI. The PD-CRS is a brief scale, specifically designed to capture the whole spectrum of cognitive functions impaired throughout Parkinson’s disease. It is composed of frontal and subcortical tasks (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate and delayed free recall verbal memory) and posterior cortical tasks (confrontation naming and clock copying). Administration time is about 20 minutes. Overall, these three scales have been validated and show good test-retest and interrater reliability. The Mini-Mental State Examination (MMSE) has been traditionally used as a standard bedside clinical test for cognitive dysfunction. However, it is not recommended as the first option of neuropsychological evaluation because it evaluates cortical cognitive aspects, which are usually preserved in PDD, but its sensitivity to detect executive dysfunction is low.

**Neuroimaging**

Structural and functional imaging is not recommended in the differential diagnosis between PDD and other types of dementia. However, studies have reported some differences between PD with cognitive problems and control groups. Cross-sectional studies have indicated higher regional brain atrophy in PDD and PD-MCI when comparing with control groups (healthy subjects, PD patients without cognitive impairment or subjects with other dementias), specifically in the frontal, temporal, parietal and basal forebrain areas. Subcortical volume loss has also been observed, mostly in hippocampus, parahippocampus, amygdala, and insula, even in MCI patients. MRI analysis of cortical thickness has also shown a prognostic value with greater thinning showing an increased risk of developing dementia. A longitudinal study revealed that patients with PD-MCI showed more extensive atrophy and a greater percentage of cortical thinning compared to PD with no cognitive impairment. Regarding resting-state functional MRI a 3 years follow-up period study demonstrated a progressive loss of resting-state functional connectivity for multiple brain regions, but mostly posterior regions, and a strong correlation with decreasing cognitive performance. A recent meta-analysis showed that PD patients with cognitive impairment presented reduced connectivity in specific brain regions that are part of the default mode network.

**Treatment**

**Symptomatic Drugs**

According to several meta-analyses, there is robust evidence to support the use of acetylcholinesterase inhibitors in patients with Parkinson’s disease and dementia.
Acetylcholinesterase inhibitors, specifically rivastigmine and in a minor degree donepezil, have been shown to improve cognitive function.\textsuperscript{108–111} In a large randomized placebo-controlled study, with 541 PDD patients, the rivastigmine treated group presented a moderate but significant improvement in cognition. Patients receiving rivastigmine had a mean improvement of 2.1 points in the Alzheimer’s Disease Assessment Scale (ADAS-cog), whereas those receiving placebo had a mean decline of 0.7 points over 6 months. Rivastigmine treated group also presented a better score in the Alzheimer’s Disease Cooperative Study–Clinician’s Global Impression of Change.\textsuperscript{111} Regarding donepezil, its efficacy was tested in another large randomized placebo-controlled study.\textsuperscript{108} Although the primary endpoint was not achieved, the treated group presented a significant improvement in cognition and global status. Because of the failure to achieve the primary end-point, donepezil has been considered only as “possibly useful” in a recent systematic review.\textsuperscript{112} Galantamine is another acetylcholinesterase inhibitor, but its efficacy has not been proved consistently.\textsuperscript{106} There is insufficient evidence for the use of acetylcholinesterase inhibitors drugs in MCI-PD.\textsuperscript{112}

Results in memantine, a glutamatergic modulator, have been inconsistent\textsuperscript{113,114} and it is not considered as a good candidate for the treatment of PDD.

Overall, these drugs are safe and higher frequency of adverse events between the treatment group and the placebo group have only been reported with rivastigmine.\textsuperscript{111}

Frequently, patients with PDD can associate psychosis and hallucinations. In front of these symptoms, the first step, especially when the onset is acute, is to rule out secondary causes as infections or toxic-metabolic etiologies. The next step should be discontinuing any non-essential non-antiparkinsonian drug, for example, anticholinergics, benzodiazepines, or opioids. If this is not enough, reducing and simplifying parkinsonian treatment should be considered.\textsuperscript{115} If there is still no optimal improvement of psychotic symptoms, adding an atypical antipsychotic should be considered. There is robust evidence to recommend clozapine for psychosis in PD. Randomized controlled trials\textsuperscript{116–118} have proven its efficacy. However, it is associated with agranulocytosis, a rare but severe life-threatening adverse event, so proper close monitoring is required. Quetiapine, an atypical dibenzothiazepine, despite having less supportive evidence, it is very used in the clinical practice. Two randomized controlled trials, rater-blinded, compared quetiapine with clozapine without finding significant differences.\textsuperscript{118,119} However, there have been numerous placebo-controlled trials showing inconsistent results.\textsuperscript{120–122} Despite this, physicians have generally positive clinical experiences with quetiapine\textsuperscript{123} because it is generally well-tolerated, does not require monitoring, and is equally effective as clozapine in some studies. In a recent systematic review, it has been considered as “possibly useful” for psychosis in PD patients.\textsuperscript{112} Finally, pimavanserin, is a novel antipsychotic with selective serotonin 5-HT2A inverse agonist activity, which is effective for psychosis treatment and does not worsen motor function.\textsuperscript{124,125}

Acetylcholinesterase inhibitors drugs have been proposed for psychosis and hallucinations management, as a prior step to antipsychotics, by some authors.

**Non-Pharmacological Interventions**

Non-pharmacological interventions for PDD and PD-MCI include cognitive training, physical exercise, music, and art therapy, and non-invasive brain stimulation techniques. Overall, there is little evidence about the efficacy of these therapies.

Although the number of studies is relatively small, cognitive training could be useful according to a meta-analysis.\textsuperscript{126} In this work, seven randomized controlled trial studies, with relatively small sample sizes, were analyzed. They found an overall improvement in global cognition with the largest effect size in working memory, executive function, and processing speed. Regarding exercise, a systematic review of nine randomized clinical trials, performed within the last decade, found significant effects of physical exercises on cognitive function in PD patients. Trials included in this review studied a different kind of therapies such as tango, cognitive training associated with motor training, and treadmill training. Programs promoted a positive effect on global cognitive function, processing speed, sustained attention, and mental flexibility.\textsuperscript{127} Literature relating to the impact of non-invasive brain stimulation techniques is limited, with very few studies with a control group. More well-designed studies and powered populations are needed to elucidate the efficacy of these therapies.\textsuperscript{128,129}

**Conclusions**

Cognitive symptoms represent an important aspect of the clinical spectrum of PD even in early stages and can lead to a significant reduction in the quality of life of patients and caregivers. Lewy pathology is generally considered to be an important etiopathogenic factor in the development of cognitive impairment in PD, however, the combination of Lewy pathology and AD pathologies is the most robust...
pathological correlate of PDD. Studies highlight the clinical heterogeneity and progression variability of cognitive impairment in PD patients. Currently, we have formal diagnostic criteria for both mild cognitive impairment and dementia associated with PD. Although neuropsychological battery covering the four core cognitive domains (attention, memory, executive and visuospatial functions) is the gold standard, the assessment of cognition with cognitive rating scales like MoCa, DRS-2, and PD-CRS, can be useful in the clinical practice. Finally, patients with PDD should be considered for acetylcholinesterase inhibitors drugs which have been shown to present modest effects. Finding successful disease-modifying therapies and clarifying the underlying pathophysiology are still unmet needs of paramount importance.

**Abbreviations**

ACHe, acetylcholinesterase; AD, Alzheimer disease; ADAS-cog, Alzheimer’s Disease Assessment Scale; Aβ, Amyloid-β; iRBD, idiopathic REM-sleep behavior disorder; LB, Lewy bodies; DRS-2, Mattis Dementia Rating Scale Second Edition; MCI, mild cognitive impairment; MCI-PD, mild cognitive impairment in the context of Parkinson’s disease; MMSE, Mini-Mental State Examination; MoCa, Montreal Cognitive Assessment; NBM, nucleus basalis of Meynert; PD, Parkinson’s disease; PD-CRS, Parkinson’s Disease-Cognitive Rating Scale; PDD, Parkinson’s disease dementia; ptau, phosphorylated tau; t-tau, total tau; V AChT, vesicular acetylcholine transporter; WMH, white matter hyperintensities.

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