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Parkinsonian Dementia in Advanced Stages of Parkinson's Disease

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ABSTRACT

Cognitive impairments are common in Parkinson's disease, with a significant impact on the morbidity and mortality rates of the disease, they can present as mild cognitive impairment even in the early stages of the disease. The International Movement Disorders Society has proposed diagnostic criteria for Parkinson's dementia and mild cognitive impairment (MCI) in Parkinson's disease, to provide correct diagnosis, and improve sensitivity and specificity of these diagnoses compared to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV). There are certain risk factors for cognitive impairment in Parkinson's disease with cumulative risk. Their recognition is also important for early diagnosis of the disease.

Keywords

Parkinsonian dementia, Parkinson's disease, Subcortical dementia, Cognitive domains, Cognitive assessment tests.

Introduction

Parkinson's disease (PD) by definition affects automatic movement, manifesting as motor disorders such as slowness and paucity of movements (hypokinesia), resting tremor, and rigidity, along with postural control problems. However, non-motor manifestations include cognitive impairments, previously neglected and poorly understood, which are now attracting the attention of clinicians due to their high prevalence and often significant functional repercussions.

Until 2007, there were no specific diagnostic criteria for Parkinson's disease (PD), and the DSM-IV classified it among dementias secondary to other pathologies.

In 2007, the Movement Disorders Society (MDS) established precise diagnostic criteria for PD, facilitating both diagnosis and the development of clinical and therapeutic studies for this disease [1,2].

Epidemiological Data on Parkinsonian Dementia

Its prevalence is high, observed in 24 to 31% of Parkinson's patients [3]. The risk of developing dementia in Parkinson's patients is 10% per year.

The frequency of mild cognitive impairment (MCI) in newly diagnosed Parkinson's patients is 15 to 25%, and 20 to 60% after several years of disease progression. MCI increases the risk of conversion to dementia in Parkinson's disease sixfold [3,4].

Dementia develops in 80% of Parkinson's patients after 20 years of disease progression. The average interval between the onset of the disease and the appearance of dementia is approximately 10 years. Given these figures, Parkinson's disease is associated with an increased risk of dementia [1].

Pathophysiology of Cognitive Impairment in Parkinson's Disease

PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra and other brainstem nuclei [1].

Numerous pathophysiological mechanisms can explain the cognitive impairments in this disease:

1. Severe damage to the basal ganglia (initially dopaminergic) and damage to other systems (cholinergic, serotonergic, noradrenergic, etc.) that send projections to the cerebral cortex, leading to the various cognitive impairments defining subcortical dementia [3,5];
2. The overlap of multiple pathologies (Alzheimer's disease, vascular dementia, etc.) [1].

Abnormal deposition of α-synuclein in the brainstem and olfactory structures is the neuropathological mechanism of PD. However, the extension of these deposits into the limbic, neocortical, and frontotemporal systems is considered a major determinant of PD [6].

According to Aarsland in 2021, all patients with PD exhibit an accumulation of α-synuclein and Lewy bodies, particularly in the medial temporal lobe regions, but over time, there is an increase in the number of Lewy bodies at the neocortical and subcortical levels. Approximately 50% of these patients also have β-amyloid plaques in the cortex. Two-thirds of these patients also have a deposit of hyperphosphorylated tau protein at the cortical level indicating Alzheimer's disease, often with amyloid angiopathy and neuronal inflammation, which explains the heterogeneity of cognitive disorders in PD [6].

3. Association with genetic risk factors and genotypes (alpha-synuclein duplication/triplication mutations, apolipoprotein E, the epsilon 4 allele, etc.) [1].
4. The effect of some anticholinergic drugs often prescribed as symptomatic treatment for Parkinson's disease, such as: antidepressants, anxiolytics, anticholinergics, antiepileptics, certain cough suppressants, diuretics, antihistamines, etc. [7].

Risk Factors for Parkinsonian Dementia

Several risk factors have been identified, most of which can be assessed in a few minutes during a consultation.

1. Age over 72 and a disease duration of more than 10 years are strongly correlated with an accumulated risk of Parkinsonian dementia.
2. Male sex has long been considered a risk factor for PD [8,9]. However, it is difficult to assess the risk of PD in both sexes when considering mortality rates: male patients die before experiencing cognitive decline, and they even have a higher mortality rate given the frequency of cardiovascular risk factors, whereas female patients survive to the ages at which dementia becomes common [9].
   According to the motor phenotype of the disease: the risk of dementia is significantly higher in patients who have an akinetic-rigid form and axial disorders, who are poorly responsive to L-Dopa, with high UPDRS (Unifed Parkinson Disease Rating Scale).
3. According to the overall cognitive phenotype: a slowing of semantic verbal fluency in PD is associated with a 9-fold increased relative risk of dementia, and the inability to reproduce a pentagonal figure on the Mini-Mental State Examination (MMSE) is correlated with a 5-fold increased risk of dementia [1,10].
4. The association with neuropsychiatric disorders, especially visual hallucinations [1].
5. The association with genetic risk factors: the H1 haplotype of the gene encoding microtubule-associated Tau protein (MAPT) may be a risk factor for developing rapid cognitive decline in PD [1,10].
6. Finally, as in other types of dementia, a low level of education may increase the risk of cognitive impairment in PD [8].

Characteristics of Cognitive Impairment in Parkinson's Disease

Cognitive impairment in Parkinson's disease encompasses a wide range of severity, rate of progression, and affected cognitive domains:

Phenotypic severity varies from subtle changes such as bradyphrenia, manifested by a slowing of thought processes and a prolonged memory recall time, to subjective cognitive complaints without objective evidence of cognitive dysfunction. Their frequency is not well-defined in Parkinson's disease because they can be associated with depression and anxiety, but they should be monitored as they may herald cognitive decline and be accompanied by objective changes [4].

One can have MCI with more than just a simple cognitive deficit of normal aging, evident on neuropsychological tests, without interaction with daily living activities. Or one can have a more severe cognitive deficit, belonging to more than one domain and significantly interfering with daily living activities, resulting in subcortical dementia [4].

Cognitive Domains Affected in Parkinsonian Dementia

Five cognitive domains are affected in Parkinson's disease (PD): attention and executive functions, verbal fluency, visuospatial abilities, and memory.

These cognitive functions, their neuroanatomical correlations, and neuropsychological assessment tests are detailed in Table 1 [4,5].

Positive diagnosis of Parkinsonian dementia

The Dubois chart: In 2007, Dubois and his colleagues proposed a simple clinical tool that can be used in consultations in the form of a rating chart [1] (Table 2).

2. The Parkinson's Disease Cognitive Assessment Scale (PD-CRS): a new cognitive scale, validated by the MDS, specifically designed to assess all cognitive functions impaired in PD and to screen for signs of MCI, with a sensitivity and specificity of 94% [11-13].

This scale assesses posterior cortical (three items) and frontal subcortical (six items) functions, including naming and copying a clock drawing, verbal memory, attention, working memory, visuospatial functions, etc. [12] (Table 3).

Table 1: Cognitive domains affected in PD, their neuro-anatomical correlations and neuropsychological assessment tests [4,5].

Domaines	Corrélation neuro-anatomique	Tests d'évaluation
Attention Executive Functions	Midbrain, projection networks at the thalamic level, basal ganglia, and frontal networks	Subtraction of 7 (MMSE); Enumeration of the months of the year backwards; Clock Drawing Test, BREF, Mattis Scale, Wisconsin Card Sorting Test; Trail Making Test, Stroop Test
Language Verbal Fluency)	Left perisylvian language areas, Broca's and Wernicke's areas, anterior temporal lobe, angular gyrus	Isaac's Test Set
Visuospatial abilities	Parietal and occipito-temporal lobe	Pentagons Test (MMSE)
Memory	Limbic system: Hippocampus Entorhinal and parahippocampal cortex Amygdala Thalamic and hypothalamic nuclei	Free recall, delayed recall in the 3-word memorization test (MMSE)

MMSE : Mini-Mental State Examination
BREF: Fast Front-End Battery Efficiency

Table 2: Scoring sheet for establishing a diagnosis of probable parkinsonian dementia [1].

	OUI	NON
1. Parkinson disease		
2. Parkinson's disease begins before dementia.		
3. MMSE score < 26		
4. Dementia has an impact on quality of life		
5. Cognitive impairment; the patient's performance is impaired in at least 2 of the 4 cognitive domains: - Attention: subtraction of "7" task on the MMSE or reciting the months of the year backwards. - Executive functions: phonemic verbal fluency or clock drawing test. - Visuospatial abilities: pentagon task on the MMSE. - Memory: delayed free recall on the MMSE 3-word memorization task.		
6. No major depression		
7. No delusional symptoms		
8. No other abnormalities that would complicate the diagnosis (infection, etc.)		
Diagnosis of Parkinsonian dementia if a "yes" answer is given to each of the 8 items.		

Furthermore, translations are available in various languages (English, Italian, Spanish, Dutch, and Chinese). It takes approximately 20 minutes to administer. The variance in results is influenced by age and education level [12,13].

Table 3: Parkinson's Disease Cognitive Assessment Scale (PD-CRS).

Item	Score
1. Immediate verbal memory	
2. Visual naming	
3. Sustained attention	
4. Working memory	
5. Drawing of a clock	
6. Copying a clock	
7. Delayed verbal memory with spontaneous recall	
8. Alternating verbal fluency	
9. Categorical verbal fluency	
FRONTAL SUBCORTICAL SCORE	
POSTERIOR CORTICAL SCORE	
TOTAL SCORE	

3. The Montreal Cognitive Assessment (MoCA) can also be used to screen for signs of MCI in PD, as it explores the five domains affected in PD [3,4].

4. Diagnostic criteria for Parkinsonian dementia:

We have the diagnostic criteria for PD established by the MDS in 2007 [2,6] (see Table 4) and the diagnostic criteria for MCI in PD [2,6] (see Table 5).

Table 4: Diagnostic criteria for Parkinsonian dementia (PD) from the MDS [2].

Levels	
Brief Level	• Confirmed diagnosis of Parkinson's disease; • Parkinsonian signs precede the onset of dementia; • Parkinson's disease associated with global cognitive impairment. • Cognitive impairment interferes with activities of daily living; • Involvement of more than one cognitive domain (attention, executive functions, visuospatial skills, or memory).
Detailed Level	• All criteria for the brief level. • Assess four domains of cognition (global cognition, subcortical frontal function, instrumental and neuropsychiatric functions).

Imaging

No neuroimaging technique has been able to identify a functional or anatomical brain abnormality that is predictive of early

Table 5: Diagnostic criteria for MCI in Parkinson's disease [2].

Inclusion Criteria	PD diagnosis confirmed. • Progressive cognitive decline, observed by the patient or physician. • Cognitive impairment documented by neuropsychological tests or a global cognitive scale. • Cognitive impairment is not sufficient to interfere with functional independence, but patients may have mild difficulty with complex tasks.
Exclusion Criteria	Dementia diagnosis based on MDS criteria. • Other changes that may explain cognitive deficits (delirium, stroke, severe depression, metabolic disorders, adverse drug reactions, etc.); • Other comorbidities related to Parkinson's disease (major motor impairment, severe anxiety, depression, daytime sleepiness, or psychosis) that may interfere with the treating physician's opinion and cognitive assessment.
Level 1 (Abbreviated)	Impairment on a validated global cognitive scale for PD or impairment on at least two brief neuropsychological assessment tests (fewer than 5 tests are assessed)
Level 2 (Full)	Two neuropsychological tests in each of the five cognitive domains. Deficit in at least two tests, represented by two changes in a cognitive domain (one or two changes in different cognitive domains).
Classification of MCI Subtypes in PD	MCI-MP with impairment in a single domain: assessment of two tests in a single cognitive domain. MCI-DP with impairment in multiple domains: change in at least one test across two or more impaired cognitive domains.

Table 6: Difference between subcortical dementia such as Parkinsonian dementia (PD) and cortical dementia such as Alzheimer's disease (AD).

	Cortical dementia (AD)	**Subcortical dementia (PD)**
Memory	Encoding deficit Deficits in free recall, cued recall, and recognition	Déficit des stratégies du rappel
Executive functions and attention skills	Less severe impairment Primarily affecting attentional functions and inhibitory processes	Altération majeure ayant des répercussions sur les autres fonctions cognitives
Langage	Word-finding difficulties with paraphasias Comprehension difficulties Primarily affecting lexico-semantic abilities Reading difficulties with dyslexia Writing difficulties with agraphia Aphasia	Troubles de la fluence phonémique Pas de troubles de la compréhension Pas d'aphasie
Visuospatial abilities	Altered	Altered

Table 7: Difference between DP and DCL.

	DCL	**DP**
Time between extrapyramidal motor symptoms and cognitive impairment	Usually within 1 year. Cognitive impairment may precede motor impairment.	10 to 15 years after the onset of motor symptoms
xtrapyramidal motor symptoms	Parkinsonian syndrome, poorly responsive to Dopa. Rare tremor. Axial rigidity with early gait instability. Symmetrical signs. Early and frequent falls. Frequent and severe autonomic disturbances, which may cause repeated syncope.	Dopa sensitivity. Dementia primarily affects akinetic-rigid forms. Asymmetry of motor signs. Gait instability and falls are later and less frequent. Late and moderate autonomic dysfunction.
Cognitive impairment	Fluctuation of cognitive impairment and episodes of confusion. Memory problems secondary to disturbances of vigilance and attention rather than to actual memory impairment. Visual-constructive abilities more affected than other cognitive domains	No fluctuation in cognitive impairment. Visuoconstructive abilities are less affected than in Lewy body dementia.
Psychiatric disorders: **- Delirium** **- Hallucinations** **- Sleep disturbances**	Early and severe symptoms: Visual hallucinations: frequent, threatening, sometimes auditory, olfactory, and tactile. Complex, bizarre delusions. REM sleep disturbances, parasomnia, intense dreams potentially accompanied by actions; the patient may sometimes be aggressive towards their partner in bed.	Less frequent and less severe: Benign hallucinations A simple feeling of persecution
Sensitivity to neuroleptics	Sensitive to neuroleptics.	No worsening of cognitive impairment under neuroleptics.

progression to PD, especially in the absence of longitudinal studies and the limitation to only a few cross-sectional studies [1,6].

A greater decrease in glucose metabolism in the medial parietal cortex and the inferior tempro-parieto-occipital regions in Parkinson's disease may be a risk factor for PD. This abnormality can even be observed in Alzheimer's disease and is thought to be present in up to 30% of non-demented Parkinson's patients [1].

Differential Diagnosis of Parkinsonian Dementia

This is much more relevant with cortical dementias such as Alzheimer's disease (AD) and Lewy body dementia (LBD).

Unlike dementia associated with Alzheimer's disease (AD), the main cognitive domains affected in PD are executive, attentional, and visuospatial [3]. Tables 6 and 7 summarize the differences between these types of dementia [14-17].

Treatment of cognitive impairment during PD

This is based on three main approaches [1]:

Reducing the doses, or even stopping, anticholinergic drugs, limiting intercurrent factors, and treating any depressive syndrome associated with PD [1,7].

The general order for discontinuing anti-Parkinsonian medications is as follows:

a. Anticholinergics
b. Monoamine oxidase (MAO-B) inhibitors
c. Amantadine
d. Dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors
e. Levodopa reduction if necessary [6,7].

Address modifiable risk factors where possible and other associated comorbidities such as cerebrovascular disease, diabetes, obesity, heart disease, and lifestyle factors (alcohol consumption and smoking) [4].

Pharmacological Treatment

The 2018 update of the MDS on treatments for non-motor symptoms of PD concluded that there is currently insufficient evidence to support any pharmacological or non-pharmacological (transcranial stimulation) treatment for MCI in PD [3,19].

In the dementia stage of Parkinson's disease, two drug classes are used either alone or in combination: anticholinesterases and atypical antipsychotics [1].

Anticholinesterases: Rivastigmine (Exelon®) is the only anticholinergic currently approved by the FDA and EMA. Its main side effects include nausea and gastrointestinal problems (reduced with the transdermal formulation of rivastigmine), tremor, as well as bradycardia and syncope [1,3,4]. Other anticholinergics (donepezil and galantamine) can be used [1,3,19]. Studies on memantine in PD have yielded mixed results [4].

Atypical antipsychotics: Clozapine and pimavanserin are the only atypical antipsychotics that have proven effective in treating behavioral disturbances in Parkinson's disease [19]. This also includes the symptomatic treatment of associated signs such as fatigue, depression, anxiety, apathy, psychosis, REM sleep behavior disorder, insomnia, and impulse control disorders [3].

Other medications have been tested for the treatment of MCI during PD: in small randomized studies, such as rasagiline, the results were negative. Creatine (n = 75, one-month trial) showed significant effects (5 g twice daily), and the combination of coenzyme Q10 (100 mg three times daily) showed statistically significant differences in MoCA scores after 12 to 18 months of treatment. Atomoxetine, an SNRI (selective norepinephrine reuptake inhibitor) (n = 55, five-week trial), also had overall positive cognitive effects [3,4,7].

Other pharmacological treatments currently being tested and evaluated include:

SYN120, a dual serotonin 5-HT6/5-HT2A antagonist.
ANAVEX2-73 (Blarcamesin), an agonist of the intracellular chaperone protein sigma-1.
Mevidalen, a dopamine D1 receptor activator.
Prasinezumab, an anti-α-synuclein monoclonal antibody.
The modulators NYX-458 and the D-amino acid oxidase (DAAO) inhibitor (DAAOI-P) [3].

Non-pharmacological treatment: Non-pharmacological options are essential and are similar to those used for other types of dementia.

These include explaining the different facets of dementia to patients and their families, and avoiding situations that divide attention while walking, as Parkinson's patients with dementia have an increased risk of falls compared to those without, and attentional difficulties are a predictor of falls. Patients can even be offered colored visual cues to address perceptual and attentional deficits while walking [1].

Regular physical activity may decrease the risk of worsening cognitive impairment, particularly in executive functions [1,4,7].

Different types of physical exercise have been evaluated for their effects on cognition, including treadmill training, dance, stationary cycling, Wii Fit, Tai Chi, and aerobics, especially in MCI [3].

Cognitive interventions in the treatment of MCI in PD are divided into three types: cognitive stimulation, which consists of non-specific cognitive and social actions; cognitive training, which uses standardized cognitive tasks on a computer or on paper; and cognitive rehabilitation, which targets specific areas of difficulty in activities of daily living to improve function [3].

Non-invasive brain stimulation techniques (such as transcranial magnetic stimulation) represent potential treatment avenues,

currently under evaluation, for improving angiogenesis, synaptic plasticity, and neurogenesis [3,4,7].

Deep brain stimulation (DBS) and cognitive impairment in Parkinson's disease

DBS is an evolving field that responds to the consensus of the CAPSIT program (Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease) which specifies the criteria for selecting patients for surgery, among these criteria, the cognitive profile of the patient is distinguished, which must be preserved, because according to several studies DBS can induce or worsen behavioral and/or cognitive impairments in the medium or long term, hence the importance of a neuropsychological assessment before any DBS procedure [7].

In a previous study by Alberto Romagnolo and colleagues, comparing the long-term outcomes of DBS in Parkinson's patients with MCI versus Parkinson's patients without cognitive impairment, they found good results in terms of motor signs and observed cognitive status, measured with a comprehensive neuropsychological battery, after one year in both groups. However, longer follow-up revealed a significantly faster conversion to dementia in patients with MCI [19].

After more than two decades of using DBS in the treatment of Parkinson's disease, the correct identification of the patients best suited for surgery remains a subject of debate [19].

Conclusion

Cognitive impairment is common in Parkinson's disease, with varying degrees of severity. Understanding the risk factors for cognitive impairment is important for early diagnosis, which remains purely clinical according to the 2007 and 2012 MDS diagnostic criteria.

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