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COGNITIVE DECLINE IN PARKINSON'S DISEASE: FROM "THE SHAKING PALSY" TO A MORE COMPLEX PARADIGM

DECLINO COGNITIVO NELLA MALATTIA DI PARKINSON: DA "LA PARALISI AGITANTE" A UN PARADIGMA PIÙ COMPLESSO

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Abstract

Parkinson's disease (PD) was originally considered a pure motor disorder according to the first description by James Parkinson in "The Shaking Palsy". Nowadays, an increasing awareness of the complexity underlying PD has been acquired among clinicians: dementia is one of the most investigated PD's non-motor features because of its individual and social burden. Recent evidences report that dementia affects up to 80% of PD patients in later stages and it represents a relevant risk for nursing home-admissions and duration of hospitalization. Clinical diagnostic criteria for dementia associated with Parkinson's disease (PDD) have been suggested to develop common lines of diagnosis. Frequently, PD patients present a state of cognitive impairment since the time of diagnosis, defined as Parkinson's disease mild cognitive impairment (PD-MCI). In non-demented PD population, MCI is the major predictor for conversion to dementia and new diagnostic criteria and guidelines for diagnostic procedures in PD-MCI have been proposed by *Movement Disorder Society* to better identify it. The involvement of different circuits including dopamine, norepinephrine and acetylcholine neurotransmission gives reason of the multifaceted cognitive profile described in PD patients with mild cognitive impairment and dementia. Main clinical features include attention deficits, executive dysfunction, as well as visuospatial and memory impairments. Neuroimaging and the assessment of genetics, central and peripheral biochemistry and neuropsychology seem to be useful in detecting an early cognitive decline. In particular, the combination of these single biomarkers might make more sensible and specific the early diagnosis of PD-MCI and PDD. In 2012, Cochrane analysis outlined the therapeutic efficacy of acetylcholinesterase inhibitors (AChEI) in patients with PDD. Among AChEI, rivastigmine is the most recognized treatment that appears to provide a real benefit in cognitive functions, neuropsychiatric disturbances and activities of daily living in patients with PD-MCI and PDD. Some findings suggest possible therapeutic effects in improving cognition of memantine, which is already used in the treatment of Alzheimer's disease. Also atomoxetine, a selective norepinephrine reuptake inhibitor, proved beneficial for PD's non-motor symptoms linked to the loss of norepinephrine neurons such as global cognition (i.e. attentional modulation) and daytime sleepiness. Finally, the treatment of motor-symptoms with levodopa has demonstrated a positive impact on some cognitive impairments such as working memory and planning activities, but it also seems to lead to iatrogenic cognitive deficits through a dopamine overdose in brain regions less dopaminergically depleted (i.e. caudate nucleus and ventral striatum).The pursuit to optimizing the diagnosis of mild cognitive impairment and to conduct a treatment to slow progression to dementia in Parkinson's disease is a key research priority.

Abstract

La malattia di Parkinson era originariamente considerata come una patologia esclusivamente interessante il sistema motorio, in accordo con la prima descrizione di James Parkinson in "La paralisi agitante". Oggi ,invece, nell'attività clinica si è acquisita una crescente consapevolezza della complessità della malattia: la demenza è uno tra i sintomi non motori più studiati nei pazienti parkinsoniani per le sue implicazioni nel contesto personale e sociale. Recenti evidenze suggeriscono che oltre l'80% dei pazienti con la malattia di Parkinson sono affetti da demenza negli ultimi stadi della malattia e che questo rappresenta un rischio rilevante di ammissione in case di cura e di prolungamento nei ricoveri. Criteri diagnostici clinici sono stati suggeriti per la demenza nella malattia di Parkinson al fine di tracciare linee comuni di diagnosi. Frequentemente i pazienti parkinsoniani presentano un stato di deterioramento cognitivo fin dal momento della diagnosi, definito come deterioramento cognitivo lieve (PD-MCI). Nei pazienti con Parkinson non dementi, il deterioramento cognitivo lieve è il maggiore precursore di conversione alla demenza e nuovi criteri diagnostici e linee procedurali diagnostiche sono state proposte dalla *Movement Disorder Society* per meglio identificarlo. Il coinvolgimento di differenti circuiti comprendenti la neurotrasmissione della dopamina, della noradrenalina e dell'acetilcolina dà ragione del multi sfaccettato profilo cognitivo dei pazienti con Parkinson. Le principali caratteristiche cliniche includono i deficit di

attenzione, il disturbo delle funzioni esecutive oltre all'alterazione delle abilità visuospaziali e di memoria. Le neuroimmagini, la valutazione genetica, la biochimica periferica e centrale e la neuropsicologia sembrano essere utili strumenti nell'individuare un precoce declino cognitivo in questi pazienti. Nel 2012, l'analisi di Cochrane ha sottolineato l'efficacia terapeutica degli inibitori dell'acetilcolinesterasi nei pazienti con demenza nella malattia di Parkinson. Al momento, la rivastigmina è il trattamento più riconosciuto, in quanto ha dimostrato di fornire un reale beneficio nelle funzioni cognitive, nei disturbi psichiatrici e nelle attività del vivere quotidiano nei pazienti con Parkinson associato a MCI e demenza. Alcuni dati suggeriscono anche possibili effetti terapeutici sulla sfera cognitiva della memantina, già utilizzata nel trattamento della malattia di Alzheimer. Anche l'atomoxetina, un inibitore selettivo del reuptake della noradrenalina, ha mostrato beneficio nei disturbi non motori del Parkinson correlati alla perdita dei neuroni noradrenergici, come nelle capacità cognitive (ad es. capacità attentive) e nella sonnolenza diurna. Infine, il trattamento dei disturbi motori con la levodopa ha dimostrato un impatto positivo su alcuni aspetti cognitivi come la memoria di lavoro e le attività di pianificazione, ma esso sembra anche indurre deficit cognitivi per un sovradosaggio di dopamina nelle aree cerebrali meno dopaminergicamente deplete (ad es. nucleo caudato e ventricolare striato). L'obiettivo di ottimizzare la diagnosi di deterioramento cognitivo lieve e di instaurare un trattamento per rallentare la progressione alla demenza nella malattia di Parkinson è una priorità chiave della ricerca scientifica.

Introduction

The traditional description of Parkinson's disease (PD) defines the disease as a progressive movement disorder clinically characterized by the triad of resting tremor, rigidity and bradykinesia. The diagnosis is usually evoked on the basis of asymmetrical onset of motor symptoms and a good response to levodopa treatment (1). Although motor dysfunction is probably the most burdensome symptom in PD patients, it is important to consider that also non-motor features represent an important aspect of the disease . The original concept stated by James Parkinson in "The Shaking Palsy" (2), which reported "the senses and intellects uninjured", appears already outdated.

Among PD non-motor aspects, dementia is one of the most investigated features for its implications in the patient's quality of life, caregiver distress, health-related costs (3), risk for nursing home-admissions and duration of hospitalization (4). Recent evidences suggest that dementia affects up to 80% of PD patients in later stages of the disorder (5) and the presence of mild cognitive impairment at the time of PD diagnosis is an important harbinger of the future development of a severe cognitive decline (6).

Most research has attempted to improve understanding of the putative neurobiological mechanism which underlies cognitive impairment in PD. Diagnostic consensus criteria have been proposed *by Movement Disorder Society* to better characterize Parkinson's disease dementia (PDD) (7) and mild cognitive impairment in Parkinson's disease (PD-MCI) (8).

The possibility to identify predictors of time to dementia and to start a targeted treatment from the early stages of the disease highlights the need to use a multidimensional assessment in patients with a diagnosis of PD.

The present review will highlight recent findings in understanding of mild cognitive impairment and dementia in Parkinson's disease including epidemiology, neurobiological aspects, genetic factors, biomarkers and treatment.

Epidemiology

Nowadays, 4,1-4,6 million people suffer from PD worldwide and the number of patients over age 50 will probably double by the year 2030 (9). Dementia is common in PD, with a relative risk three-to-six fold higher than in the general elderly population (7), corresponding to lifetime risk estimates of 30%-80% (10).

The incidence of dementia in PD is about 100 per 100 000 patients year; the predictive factors are age, severe motor symptoms (with a Hoehn & Yahr score >2) and Mini-Mental State Examination score below 29 at the time of diagnosis (11). Cognitive impairment is frequent even in non-demented PD population and its presence predicts a more rapid cognitive decline and shorter time to dementia (6, 12). Most studies reported that 17% to 30% of non-demented PD patients are affected by a cognitive impairment (13), with a progression between 6% and 15% from MCI stage to dementia every year (14).

Mild cognitive impairment in Parkinson's disease (PD-MCI)

Mild cognitive impairment is frequently reported in non-demented PD patients and it is associated with old age, disease duration and stage of the disease (15). Consistent with MCI entity, PD-MCI is a dynamic stage that represents the major predictor for conversion to dementia in PD patients (6).

The Movement Disorder Society (MDS) (8) established a task force to provide diagnostic criteria and guidelines for diagnostic procedures in PD-MCI (see table 1). The diagnosis requires a "gradual decline on day-to-day functioning reported by the patient or an informant, or observed by the clinician in the context of an established PD". The diagnosis is possible when at least two tests of one domain ("single domain mild cognitive impairment") or at least one test of two or more domains ("multiple-domain cognitive impairment") are impaired. Exclusion criteria are represented by a diagnosis of PD dementia based on MDS Task Force criteria and other conditions explaining the cognitive deficits.

The neuronal degeneration of different circuits involving dopamine, norepinephrine and acetylcholine neurotransmission can explain the heterogeneous cognitive profile described in PD patients. The most common subtype of PD-MCI is the nonamnestic single-domain impairment (16) which includes executive deficits (17, 18), verbal fluency impairment (19, 20), visuospatial deficits (19) and memory and language dysfunction (18, 21). Cognitive abilities change over time and different domains' evolutions have yet to be understood in detail. Two types of cognitive impairments have been described: "frontal executive" deficits and "posterior cortically" based deficits (22, 23). The former seems to be associated with a dopaminergic overdose state in the prefrontal cortex, influenced by genetic background (COMT genotype) and environmental factor (dopaminergic therapy); the latter is dependent on MAPT H1-H2 genotype and it is strongly related to the occurrence of dementia in PD patients even though it is not a dopamine dependent event (22). According to these results, subjects with frontal executive deficits such as phonemic fluency and planning impairment seem to remain stable for longer time, while subjects with "posterior cortically" based deficits such as semantic fluency and visuoconstruction dysfunction would convert faster to dementia (22, 23). Some studies reported a predictive association between deficits in verbal fluency, abstract reasoning, picture completion, Stroop performance and PD dementia (17). Evidences suggest, however, that impairment of language and visuospatial domain, due to an incipient Lewy bodies deposition in the occipito-parietal cortex and temporal lobe, is more likely to progress to dementia compared to executive dysfunction. In fact, the impairment on pentagon copying and semantic fluency seem to predict cognitive decline and Parkinson's disease dementia at 3 and 5 years follow-up (6, 22).

Table 1- *Diagnostic criteria and guidelines for diagnostic procedures in PD-MCI proposed by Movement Disorder Society (8)*

I. Inclusion criteria
• Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria (76);
• Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician;
• Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III);
• Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present.

II. Exclusion criteria
• Diagnosis of PD dementia based on MDS Task Force proposed criteria (7);
• Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma);
• Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing.

III. Specific guidelines for PD-MCI level I and level II categories
A. Level I (abbreviated assessment)
• Impairment on a scale of global cognitive abilities validated for use in PD or
• Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed).
B. Level II (comprehensive assessment)
• Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial);
• Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains;
• Impairment on neuropsychological tests may be demonstrated by:
– Performance approximately 1 to 2 SDs below appropriate norms or
– Significant decline demonstrated on serial cognitive testing or
– Significant decline from estimated premorbid levels.

IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)
• PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or
• PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains).

Dementia in Parkinson's disease

The term "Parkinson's disease dementia" refers to dementia that develops at least one year after diagnosis of Parkinson's disease (7). If dementia precedes or coincides within one year with the development of motor symptoms, the disease meets criteria for the diagnosis of dementia with Lewy bodies (DLB) (24). PDD and DLB share several clinical and neuropathological aspects, suggesting that they represent two distinct clinical entities on the same spectrum of Lewy body disease (25).

PD patients seem to inevitability develop dementia, as reported in a longitudinal study on newly diagnosed patients, in which dementia was present in 83% of 20-year survivors (5). Dementia in Parkinson's disease is characterized by insidious onset and slowly progressive decline of cognitive abilities in the course of the disease (23, 26). The rate of global cognitive decline shows a non-linear progression with a stable first period, followed by a more rapid impairment of abilities in later stages. The inflection point occurs 13.3 years after the diagnosis of PD, with an annual decline of 2.8 points on the mini-mental state examination (MMSE) (27). A similar decline is also described in Alzheimer's disease patients in the course of the disorder (28). However, PD patients present more frequently visuospatial, attention and executive deficits and less severe impairment of memory, as well as visual hallucinations compared to Alzheimer's disease patients.

Diagnosis criteria (see table 2) imply that : two or more cognitive domains should be impaired with an impact in social and occupational activity of the subject. Clinical features include attention deficits, executive dysfunction, as well as

visuospatial and memory impairments. Frequently psychiatric symptoms - such as hallucinations, delusions, apathy and mood changes - are also manifest in PDD patients.

Table 2 - *Clinical diagnostic criteria for dementia associated with Parkinson's disease proposed by Movement Disorder (7)*

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria;
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
• Impairment in more than one cognitive domain;
• Representing a decline from premorbid level;
• Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.

II. Associated clinical features

1. Cognitive features:
• Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day;
• Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia);
• Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction;
• Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall;
• Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present.
2. Behavioral features:
• Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior;
• Changes in personality and mood including depressive features and anxiety;
• Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects;
• Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions;
• Excessive daytime sleepiness.

III. Features which do not exclude PD-D, but make the diagnosis uncertain

• Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging;
• Time interval between the development of motor and cognitive symptoms not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

• Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
Acute confusion due to:
a. Systemic diseases or abnormalities;
b. Drug intoxication.
Major Depression according to DSM IV;
• Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits).

Neurobiological aspects

Neuropathologically PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and deposition of Lewy bodies in the nigrostriatal system (29). These findings can explain the emergence of motor symptoms and non-motor manifestations such as deficits in cognitive flexibility, planning, working memory, and learning which belong to a fronto-striatal dysexecutive syndrome linked to the damage of dopaminergic pathways. In these cases, a dopamine replacement therapy can produce beneficial effects both for motor symptoms and neuropsychological tasks related to frontal lobe impairment (30).

On the other hand, a dopaminergic enhancement can lead to iatrogenic cognitive deficits through dopamine overdose in caudate nucleus and ventral striatum (regions less dopaminergically depleted particularly in the first phase of the disease). The cognitive functions more frequently impaired seem to be concurrent and probabilistic reversal learning, gambling and decision making, delayed responding with distraction and visual hallucinations (30).

Besides nigrostriatal system deterioration, an early involvement of cortical cholinergic circuits, leading to degeneration of basal forebrain nuclei and ascending cholinergic pathways, has been described (31, 32).

Cortical cholinergic function can also be affected even more severely in patients with Parkinson's disease dementia than in patients with Alzheimer's disease or Parkinson's disease, involving the frontal, parietal, and temporal cortices and the amygdala (30, 33, 34, 35).

The appearance of visual hallucinations and the relative relief by cholinesterase inhibitors treatment in early PD stages have been related to a functional involvement of central cholinergic circuits (36). Moreover, the cholinergic denervation of the limbic archicortex seems to be the putative mechanism in olfactory dysfunction, a common feature in subjects with moderately severe Parkinson's disease (37).

Finally, loss of the noradrenergic neurons in locus coeruleus has been associated with PD dementia. Involvement of higher mental activities such as attentional set-shifting, a type of higher-order of cognitive flexibility and learning in extra dimensional shifting, seem to be the areas of cognitive dysfunction (30).

Genetic factors

Dementia is more common in PD patients with a strong familiarity for the disease (38), suggesting an interplay of genetic factors in occurrence of cognitive impairment in PD.

Mutations of the H1 haplotype of the microtubule associated protein (MAP) gene and α-synuclein gene (SNCA) seem to exert a relevant susceptibility not only to PD (39), but also in the emergence of cognitive decline in these patients. Given these findings, a shared pathway of the tau and α-synuclein may be hypothesized in neurodegenerative disease (39).

The ε4 allele of the Apolipoprotein E (APOE) gene, which increases susceptibility to Alzheimer's disease and cholinergic dysfunction (40), has been also correlated with impairment functioning of PD patients (41, 42) , although more studies are needed to confirm its role.

A possible overlap between Alzheimer's disease (amyloid-β and tau) and Lewy body (α-synuclein) type pathologies in patients with PD and cognitive impairment (43, 44) has been supposed: preliminary findings showed as the combination of these pathologies (Lewy body, amyloid-β and tau) is the strongest pathological correlate of dementia in patients with PD (45).

In addition, cognitive decline and dementia have been observed in PD patients carrying glucocerebrosidase gene (GBA) mutations (46), indicating a likely link between GBA and synucleinopathies.

Finally, an over-representation of the BDNF (Met/Met) homozygote genotype is related with more frequently and severe cognitive decline in PD patients (47)

Biomarkers

Magnetic resonance imaging (MRI) can represent an useful biomarker in detecting structural and functional changes in PDD. MRI studies have reported a higher rate of brain atrophy in parietal-temporal lobe, entorhinal cortex, hippocampus, prefrontal cortex and posterior cingulated in PDD patients compared to those non-demented with PD, (48, 49). In PD-MCI, the atrophy pattern appears less extended and a relationship between affected regions and specific cognitive impairments has been demonstrated: prefrontal atrophy with increased reaction times (50), hippocampal

atrophy with verbal memory deficits (50), and volume reductions of orbitofrontal cortex with decline decision-making performance (51).
The use of diffusion tensor imaging (DTI) and fractional anisotropy (FA) allowed to explore the relationship between white matter pathology and cognitive decline in PD, suggesting the role of white matter hyperintensity (WMH) as an independent risk factor for MCI in PD (52, 53). The association between vascular risk factors and WMH could represent a target for diagnostic and therapeutic intervention in PD-MCI (52).
Preliminary findings from functional imaging studies with fluorodeoxyglucose-positron emission tomography support that in drug-naïve PD patients cortical metabolic changes in prefrontal and posterior cortical circuits are strongly associated with cognitive decline since the very early stage of the disease (53, 54, 55).

Molecular biology can also provide biomarkers for an early identification of PDD: low cerebrospinal fluid (CSF) levels of amyloid-β $(A\beta)_{1-42}$ are linked to semantic deficits, memory impairment (56, 57) and to a more rapid decline in neuropsychological performance (58). At the early stages of PDD, amyloid-β species such as 42,40 and 38 are reduced and in particular there is a relevant linear association between CSF Ab42, Ab40 and Ab38 levels and memory performance, but not visuospatial or executive-attentional dysfunction in PD (59). These findings suggest that alterations in Aβ protein metabolism can be detected and related to patterns of cognitive performance in PD, since the first stages of the disease (45). In contrast with Alzheimer's disease, there have not been findings of an increase in total and phosphorylated tau in PDD patients compared to controls (45).
Quantitative EEG (qEEG) abnormalities in background rhythm frequency and relative power in the theta band can provide data of cortical dysfunction in these findings and together with neuropsychological testing can be useful for detecting cognitive impairment in PD patients (60-64).
A combined assessment of these single biomarkers might make more sensible and specific the early diagnosis of PD-MCI and PDD. In particular, the combination of CSF amyloid-β, neuropsychological and cortical thickness biomarkers might provide a basis for dementia-risk stratification and progression monitoring in PD (65).

Treatment

In 2012, a Cochrane analysis highlighted the therapeutic efficacy of acetylcholinesterase inhibitors (AChEI) in patients with PDD (66). In particular, rivastigmine (an inhibitor of acetylcholinesterase and butyrylcholinesterase) showed a positive impact on global assessment, cognitive functions, behavioral disturbance and activities of daily living in PD patients compared with placebo (67). Moreover, rivastigmine seems to reduce visual hallucination and other neuropsychiatric disturbances occurring in the course of the disease. Other cholinesterase inhibitors have been less investigated, however, donepezil showed no significant benefits for cognition and other symptoms in PDD (68, 69).
A few studies have been conducted on efficacy of memantine, a partial N-methyl D-aspartate (NMDA) receptor antagonist, showing some beneficial results (70): improvement in the quality of life (71) and amelioration of rapid-eye-movement sleep behavioral disturbances (72). However, larger size studies are needed to confirm these conclusions.
Atomoxetine, a selective norepinephrine reuptake inhibitor, has been associated with a relief in global cognition and daytime sleepiness in PD patients, underlining the possible role of SNRIs for disorders of mood, cognition, and wakefulness in PD (73).This approach may be beneficial for PD's non-motor symptoms linked to the loss of norepinephrine neurons (i.e. attentional modulation), increasing noradrenergic tone (74).
Finally, the treatment of motor-symptoms with levodopa has demonstrated a positive impact on some cognitive impairments such as working memory and planning activities, but also negative or controversial results on other aspects (30). Among the common drugs utilized in PD, the monoamine oxidase type B inhibitor rasagiline has shown beneficial effects on attention and executive function in non-demented PD patients (75).

Conclusion

In this review, we have highlighted recent findings in Parkinson's disease mild cognitive impairment and Parkinson's disease dementia, in order to identify risk-factors of cognitive decline and dementia in these patients. PD-MCI appears the major predictor for conversion to dementia in PD patients and new diagnostic criteria and guidelines for diagnostic procedures in PD-MCI have been proposed to better characterize it. In particular, among the two recognized sub-types of MCI, the "posterior cortically" based deficits seem to progress to dementia faster than the "frontal executive" deficits.

The study of risk includes the assessment of genetics, central and peripheral biochemistry and neuroimaging, neuropsychology that can support an early diagnosis. Cochrane analysis has outlined the therapeutic efficacy of rivastigmine, in patients with PDD. Preliminary findings suggest possible therapeutic effects of memantine and atomoxetine in improving cognition. The development of diagnostic and therapeutic strategies to detect and manage cognitive impairment in these patients is a key research priority.

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