



Review Article

A Review Article in Cognitive Deficits in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a common, progressive, disabling, neurodegenerative disorder, that apart from well-known motor symptoms, reveals a wide spectrum of non-motor features, that are now widely accepted as part of the clinical aspect, and cognitive decline is a very important part of these non-motor presentations. The diagnosis of cognitive decline in PD can be extremely challenging, remaining largely based on clinical and cognitive assessments. Expert work groups have issued diagnostic criteria and methods for PD dementia and cognitive impairment. This manuscript has gathered relevant data in order to obtain an updated review regarding cognitive deficit in PD, from mild stages to dementia. This article has summarized clinical features, diagnostic methods, and therapeutic issues of cognitive decline in PD.

Keywords: Dementia, Diagnostic criteria, Mild cognitive impairment, Non-motor symptoms, Parkinson's disease

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Introduction

Parkinson's disease (PD) is the most common neurodegenerative disease with motor presentation and the second most common neurodegenerative disorder, following Alzheimer's disease. Nearly 200 years ago, James Parkinson described this process for the first time in his manuscript entitled *An Essay on the Shaking Palsy* [1]. He had focused mainly on the motor features of PD, overlooking non-motor symptoms, but cognitive impairment was at that time completely disregarded. Nowadays, we know that the spectrum of non-motor features in PD is broad [2, 3], but may often be missed in clinical practice. Nonetheless, whenever PD is suspected, the routine approach should include a set of questions for exploring their presence, since they may be helpful hints for the diagnosis, although they are non-specific. On the other hand, it is useful to quantify their severity and impact, as they carry an important additional burden on the patients, leading to significantly deteriorated quality of life (QOL), and warranting specific therapeutic interventions, despite the fact that evidence-based data on treatment are unsatisfactory in many instances [4, 5]. Braak et al. have greatly contributed to the awareness of the association between symptoms and the neuropathological lesions in the nervous system [6, 7]. Indeed, due to long term progression and the pattern of pathological spreading, some of the non-motor features of PD may be

present before any of the classical motor signs are noticeable, which may lend them potential utility as supportive diagnostic features in early disease stages; like hyposmia, sleep problems specially rapid eye movement (REM) sleep behavior disorder, constipation, and mood disorders [4, 7-9]. Patients may have these and other symptoms before prominent motor signs. On the other hand, features like dementia and hallucinations tend to occur later in the course of disease, which might be useful for distinguishing PD from other disorders. Cognitive impairment is an important non-motor feature of PD, but the diagnosis is often complex, remaining based on clinical skills and methods, because no reliable diagnostic biomarkers have been described yet (Table 1). Mild cognitive dysfunction is apparent in many cases from early stages [10-12], but recent studies have shown that dominant dementia occur in more than 80% of patients after 20 years of disease [13]. Accurate cognitive assessment and classification is also important in making decision for deep brain stimulation for PD.

Method

We looked for PubMed literatures for published papers, using the keywords "Parkinson's disease," "Parkinson's disease dementia," "mild cognitive impairment." From all the references

Table 1. Clinical features of Lewy Body Dementia, PD dementia and Alzheimer's disease

Manifestation	Lewy-body dementia	PD dementia	Alzheimer's disease
Clinical features			
Common presentation	Psychotic symptoms and/or Parkinsonian features	Parkinsonian features	Memory decline
Psychotic symptoms	Early visual hallucinations with or without delusions	Associated with exposure to PD pharmacotherapy	Usually later in disease process
Memory decline			
Speech impairment	As disease progresses particularly in accessing memories Usually late	Difficulty accessing memories Hypophonia, dysarthria	Early global and progressive difficulty in forming memories Aphasia, Paraphasia
Parkinsonian features			
Tremor at rest	Present in 20-50%	Present in 75%	Only in late disease
Rigidity	Common	Common	Only in late disease
Gait abnormality	Early in disease	Early or late in disease	Late in disease
Response to levodopa	Variable	Common	NA
Antipsychotic sensitivity	Can be extreme	Variable, increased parkinsonism at higher dosages	Development of Parkinsonism at higher dosages

found, the most relevant ones have been chosen. Basically, this review has a specific attention on Parkinson's disease Dementia (PDD), which was described first time by prof. Murat Emre. (*Movement Disorders* Vol. 22, No. 12, 2007, pp. 1689-1707 © 2007 Movement Disorder Society).

Epidemiology of Parkinson's Disease Dementia

According to differences in diagnostic criteria, methodology, and study populations, epidemiological numbers regarding PDD tend to vary. The prevalence of dementia in community-based studies has been estimated at 30–40% [14] but figures range from about 10 to 80% of people with PD [14, 15]. Even in young onset PD, which is defined as symptoms emerging from 21 to 40 years [16], dementia affects up to 19% of patients after an average of 18 years of disease duration [9]. In addition, cognitive decline is noted in up to 36% of newly diagnosed cases of PD [17]. From the published literature, it seems clear that the prevalence of dementia increases with age and duration of the disease [14], although some have suggested that patient age could be preponderant [18]. During an exceptional study in this matter, Sydney Multicenter Study; clinicians followed a single cohort of newly diagnosed people with PD over 20 years. At this study, neuropsychological assessments were performed at baseline and at 3, 5, 10, and 20 years. At 20 years, 25 of 30 (83%) surviving patients had become demented [19].

The incidence of dementia is increased by 2.8- to 6-fold in those with PD when compared to those without the disease [7, 14]. The cumulative prevalence is very high; at least 75% of the patients with PD who survive for more than 10 years will develop dementia [14].

Several risk factors have been defined for PDD, like certain predominant motor features such as rigidity and gait instability, Minimal Cognitive Impairment (MCI), and the presence of visual hallucinations [1]. Older age is broadly accepted as a risk factor for dementia in PD. Some authors have found parameters such as disease duration, age of onset, and motor symptom severity to be significant risk factors [14].

Parkinson's Disease Dementia: Clinical Presentation

Parkinson's disease Dementia holds suggestive phenotypic cognitive features that make it a recognizable and individualized entity [20]. The accurate diagnosis and management are very important because Dementia adds several problems to the burden of disease for the patient and the community [21].

Pattern of onset and progression

The onset of PDD is insidious, often making it difficult to evoke when the first signs of cognitive dysfunction released. The course of disease is progressive. In a prospective, 4-year study, the mean annual MMSE decline was 1 point in PD patients without dementia versus 2.3 points in the PDD group, a figure similar to that seen in subjects with Alzheimer Disease (AD) [22]. In the CamPaIGN cohort study, researchers found that MMSE scores declined at a mean rate of -0.3 ± 0.1 points per year over the 5.2 years of average observation [23].

Dementia in the early stages of PD is not a specific feature of the disease [2]. Whenever Parkinsonism and dementia arise in close temporal relationship, the process should be classified as Diffuse Lewy Body disease (DLB); on the other hand, the diagnosis of PDD requires the preceding diagnosis of PD followed by the later development of dementia [24]. Early indicators associated with cognitive decline may include excessive daytime sleepiness. Visual hallucinations are relatively frequent, as are bizarre but ill-defined misperceptions or psychotic phenomena (such as feeling that there is someone else in the room). Apathy, attention and concentration deficits, and forgetfulness are also frequent features [25], although memory complaints as initial presentation are less frequent than in DLB and, specially, AD. The course of cognitive impairment in PDD is relentless and progressive over time. Patients may remain stable for several months, at times with periods of faster worsening with no additional obvious cause [20]. Fluctuations occur from day to day and even in a day, which is a similar pattern to that of DLB [26].

Hobson and et al; found that standardized mortality ratios (SMR) were significantly higher in PDD patients than in PD non-demented subjects. Life expectancy in lower-age onset PDD (55–74 years old) was significantly lower than in non-demented cases (average 7.5 versus 12.4 years), and the estimated age at death was also much lower in the first group (72.4 versus 77.8 years). Differences regarding life expectancy and age at death in older-onset PDD were less obvious [27]. Other researchers have also found an increased mortality risk in PD patients with dementia [28, 29].

Cognitive phenotypes of PDD

Assessment of cognition in PD patients can be a demanding and exhausting mission for both the patient and physician. Disease symptoms such as tremor, bradykinesia, Rigidity, bradyphrenia, sleepiness, and mood disorders, as well as medication effects, can interfere with cognitive performance and testing.

Executive functions have been defined as capacities that “enable a person to engage successfully in independent, purposive, and self-serving behavior,” and encompass cognitive processes such as initiation, planning, purposive action, self-monitoring, self-regulation, volition, inhibition, and flexibility. Executive dysfunction has been widely recognized as a very important feature of the cognitive phenotype of PD, even in non-demented patients, although published data has been marred by inconsistencies in definitions and research methods [30]. The most widely used tests to assess executive functioning in PD have been Verbal fluency, Digit span backward, Wisconsin Card Sorting Test, Stroop Test, and Trail Making Test [30]. Accumulated research data has shown that executive dysfunction is a prominent feature in PDD [31, 32].

There is clinical evidence of slowed cognition in PDD, although this may be apparent even in non-dementia stages [32]. Attention deficits have been consistently shown in PDD. In tests such as the letter cancellation test, PDD patients are slower, tend to fluctuate more, and incur on a higher number of errors than AD subjects, whereas the profile of PDD seems to be similar to that seen in DLB [26].

Visuospatial function is a term used to describe a wide range of functions that should be assessed by different tests, the unifying feature being that all of them rely on visual function and processing [33]. Findings from studies pertaining to this matter have found greater deficits in PDD than AD patients [34]. It has been shown that visual perception, space-motion, and object-form perception are globally more impaired in PDD patients than in control subjects, including normal controls and non-demented PD patients, and AD [34].

Short-term memory in PDD is impaired, for both initial learning and immediate recall. Traditionally, amnesic deficits in PD have been considered to be basically of retrieval, rather than encoding and storage [35]. In PDD, however, patients may also be impaired on cued recall [35]. A meta-analysis has shown that verbal fluency impairment is more pronounced than that seen in non-demented PD patients; also, semantic fluency seems to be more compromised than phonemic fluency [36]. Concept formation is also impaired in PDD [37, 38]. The Clock-Drawing Test displays marked changes in PDD, although it is similar to

that found in DLB, and AD. PDD and DLB patients demonstrate more planning errors, as compared to AD [38].

Significant dysphasia is not basically seen in PDD, and language deficits occur much less frequently in PDD than in AD [39].

Special phenotypic characteristics pertaining to cognitive decline have been used to differentiate “cortical” from “subcortical” dementia syndromes [28, 40]. Cortical dementia syndromes display impairments of cognitive domains such as episodic memory, praxis, language, and calculation, whereas subcortical dementias tend to show slowed mental processing speed and frontal lobe changes such as apathy, irritability, and executive functions impairment. The “cortical” profile is typical of AD, whereas PDD and DLB typify the “subcortical” dementia type, but many cases fit the opposite prototype [41]. Characteristically, early impairment of episodic memory is seen in AD [42].

Neuropsychiatric symptoms

Mood and anxiety

Aarsland et al. have shown major depression in 13% of PDD patients, compared with 9% of non-demented PD subjects. This rate is lower than DLB, but higher than AD [21]. Dysphoric mood with depressive symptoms occurs approximately with the same frequency in PDD and AD (40–58%) [15]. Anxiety occurs at same frequency (30–49%) as depressed mood, and these symptoms may frequently co-exist in the same patient [43]. Irritable mood, anger, and aggression are common in AD, but uncommon in PDD [44]. Manic or hypomanic mood is infrequently seen in PDD [45].

Psychotic symptoms

Hallucinations occur in 45–65% of PDD cases, which is more common than non-demented PD [15, 21, 22]. In PD patients without dementia, hallucinations are an important predictor for the development of dementia [46]. Hallucinations tend to be more common in DLB than in PDD and in these more frequent than in AD [15, 21].

Hallucinations in PDD and DLB tend to present similar characteristics, as they are usually complex and well formed, colorful moving images, with people and animals being a frequent motif [23]. Brief, ill-defined peripheral images (*de passage*) may also occur and be less appreciated by the patient [47]. Delusions seem to be less frequent than hallucinations in PDD, and are estimated to occur in about 30% of patients; this rate is greater than in AD but lower than in DLB [22]. Delusional activity in PDD includes “feeling of presence,” phantom boarder (the delusional belief that there are foreign people in the house, who may even interfere with the patient’s daily life), paranoid, or grandiose delusions; delusional activity may be broad or isolated to a single subject.

Apathy

It has been reported in 54% of PDD cases [15]. Prominent apathy is very common in other forms of dementia, including frontotemporal dementia [48], progressive supranuclear

palsy [22], AD [49], and DLB [44]; thus, this feature is not specific enough to show diagnosis.

Non-cognitive featured of PDD

Non-motor presentations of PDD are common, and those features are now assumed to be an intrinsic part of the pathological processes involved. Therefore, it seems legitimate to assume that motor and non-motor features must be interrelated.

Motor phenotypes

It has been shown that certain motor features, such as postural instability and gait disorder (PIGD) are associated with a faster progression rate of cognitive decline in PD, being a risk factor for dementia [50]. They have shown that older persons with more severe parkinsonian signs had a relatively increased risk for dementia than younger and mildly affected subjects. Tremor dominant type of PD has been associated with a lower risk for cognitive decline in some studies. Several studies have shown that dementia is more common in Rigid-Akinetic type PD than tremor dominant [16]. Papapetropoulos et al. showed that poorer cognitive performance is also associated with poorer outcomes in motor and non-motor domains [51]. Other predictors of cognitive decline include previous falls, longer time from disease onset, and decreased arm swing [52]. Data are inconsistent about levodopa responsiveness in showing any pattern that differentiates PDD patients from PD patients without dementia [28]. However, Caparros-lefebvre et al. (1995), had documented more cognitive decline in PD patients with less than a 50% levodopa-induced improvement at baseline [53]. Furthermore, an autopsy study has suggested that loss of levodopa responsiveness is correlated with dementia due to greater loss of striatal Dopamine Receptor 3 (D3) receptors [54]. Although fewer dyskinesias were reported in PDD patients in a cross-sectional study, a longitudinal study found greater mental deterioration in those PD patients with baseline levodopa-induced dyskinesias [55].

Sleep disorders

Rapid Eye Movement (REM) sleep behavior disorder (RBD) is characterized by dream passing behavior, like jumping out of bed, talking, or kicking. In patients with PD, abnormal electromyographic activity is detectable over the REM sleep, demonstrating the anomalous absence of muscle atonia may occur in this stage of sleep [56]. The pathophysiology is thought to be related to lesions inflicted on the brainstem REM sleep centers that inhibit the spinal cord motor neurons and their connections, as these structures are usually damaged in PD [57].

RBD may be idiopathic or linked to several neurodegenerative diseases like PD, DLB, and Multiple System Atrophy (MSA). Iranzo have reported that 45% of the idiopathic RBD patients studied developed a neurological disorder after a mean of 11.5 years from the onset of RBD [58].

Patients with idiopathic RBD usually do not experience cognitive problems, but Terzaghi et al. Demonstrated that a visuospatial construction deficit was present in 44% of the cases that suffered from idiopathic RBD [59]. The cognitive profile in patients with idiopathic RBD usually comprises visuospatial

factor, verbal memory, attention, and executive function impairment. Usually these subjects show no impairment in semantic memory and language, which commonly seen in AD [42] (66,67). Similarities have also been found between EEG patterns of idiopathic RBD and PD patients, like cortical EEG slowing (abundant delta and theta waves) in frontal, temporal, and occipital regions [60]. Some authors have tried to show relation between RBD and MCI. Gagnon and et al. found that most PD patients (73%) with RBD display MCI, while many patients with idiopathic RBD (50%) also show MCI. It is basically accepted that RBD occurs in PD cases with associated MCI and dementia, however RBD may also occur in PD patients with no associated cognitive deficits [61].

Autonomic involvements

Dementia and significant autonomic features may develop in PD, especially in advanced disease stages [7]. The data about the relative frequency of autonomic problems in demented compared to non-demented PD cases is scarce. It has been shown a high incidence of cardiovascular dysfunction in demented PD cases versus non-demented subjects [62]. The presence of autonomic dysfunction has also been reported in the Sydney multicenter study, after 15 years follow-up, like orthostatic hypotension and urinary hypotension [7].

The pathophysiology of autonomic involvement seems to be depended on typical Synuclein deposits throughout the central and peripheral autonomic nervous systems. The extension of these deposits to the limbic and cortical areas may be the cause for the dementia. Comorbidities are also important, as the presence of symptoms, such as orthostatic hypotension, constipation, and urinary incontinence may be due to other causes other than autonomic dysfunction; like dopaminergic drugs side effects [63].

In summary, PDD patients typically present with executive dysfunctions, fluctuating attention deficits, visuospatial impairment, and memory dysfunction, associated with behavioral symptoms [20], like depression, anxiety, apathy, delusions, and recurrent prominent complex visual hallucinations that may seem disproportionate to the severity of dementia. PDD is most frequently associated with the postural imbalance gait disability motor phenotype of PD. The evolution is progressive. These clinical features are in many aspects similar to those seen in DLB, and distinguishing both disorders from each other can be challenging [64].

Diagnostic criteria of PDD

Specific diagnostic criteria did not exist for PDD for a long time. Eventually, in 2007, Emre and et al. published diagnostic criteria for PDD, proposed by a Movement Disorder Society task force. Two levels of clinical diagnostic certainty have been defined: possible and probable PDD [20]. According to this study, the essential defining feature of PDD is the emergence of dementia in the setting of established PD, as diagnosed according to the Queen Square Brain Bank criteria. Dementia is defined as a syndrome with insidious onset and progressive decline of cognition and functional activity, which is not related to motor or autonomic involvements.

Impairment in at least two of the four typically involved cognitive domains (impaired and often fluctuating attention; executive dysfunctions; visuospatial impairment; and free recall abnormalities that improves with cueing) must be documented without prominent language dysfunction, as demonstrated by clinical and cognitive assessment [20]. Emre reported that the main behavioral or neuropsychiatric symptoms seen in PDD include visual hallucinations, delusions, apathy, depressed mood, anxiety, and excessive daytime sleepiness. The presence of at least one symptom from this set supports, but is not required for, the diagnosis of PDD [20].

Dujardin and coworkers have evaluated 188 PD patients, using the two-step cognitive assessment, recommended by the MDS task force (shorter battery and then longer comprehensive cognitive assessment battery), recording also the presence or absence of dementia after each step had been taken [65]. After the short battery had been applied 18.62% of PD patients were suspected of having dementia, whereas 21.81% fulfilled criteria for probable PDD following the longer study. The authors have found that the short battery's sensitivity and specificity were 65.85 and 94.56%, respectively – but using specific cutoff scores the sensitivity would increase considerably without significant loss of specificity, thus suggesting that PDD can be diagnosed accurately with the shorter battery as well as the longer assessment method. Specifically, an MMSE score less than 27, the inability to recall five words immediately after learning, being unable to generate more than 7 words beginning with “S” within 60 s, the lack of full personal independence in managing antiparkinsonian medications, and age >69 years seem to be associated with a high probability of PDD [65].

Martinez and et al. (2011) compared the Movement Disorders Society (MDS) criteria for PDD with dementia criteria established by the DSM-IV and suggested that the MDS criteria are more sensitive than DSM-IV for PDD, and that it could be more difficult to diagnose PDD in older patients, as well as those with less psychotic symptoms or severe motor impairment [66].

Ideally, it seems that clinicopathological studies should also be carried out in the future using the MDS criteria for the diagnosis of PDD, in order to promote in-depth understanding of their diagnostic acuity [66].

Mild Cognitive Impairment in PD

Like AD, a pre-dementia period exists in PD. MCI may be defined as a cognitive decline from a previous baseline, that is considered abnormal for the patient's age, but with retention of normal daily functioning. Such a condition appears frequently in PD, even in early stages and prior to the initiation of dopaminergic therapy [12, 67-69]. In clinical and research settings, the term “MCI” is applied to PD patients who present cognitive complaints and whose neuropsychological examinations confirm the deficits, but PDD criteria cannot be fulfilled due to the lack of prominent functional decline related to cognitive impairment [68].

Deterioration can occur in a range of cognitive domains. Non-amnestic single domain MCI seems to be more common than amnestic MCI [67, 69].

Due to published data, most PD patients will develop dementia, provided that enough time elapses since disease

onset. Since PD-MCI precedes PDD, one could postulate that the lifelong cumulative prevalence of PD-MCI must be at least as high as that of PDD. Approximately 27% of PD patients will meet criteria for PD-MCI at any given time [70] have reported that PD-MCI affects 25.8% of PD patients (ranging between 23.5 and 28.8%).

Several studies have shown that increasing age, late disease onset, severity of PD, and lower educational level are risk factors associated with PD-MCI [17, 69, 71].

The complexity of defining MCI in early stages of PD is high, for significant confusion with early DLB should be anticipated. On the other hand, there is a concern that the definitions used to determine MCI may lack sensitivity to detect early cognitive decline in high functioning people, as these have to suffer added decline before they reach the defined cutoff below normative means. Hence they may potentially be classified cognitively unimpaired when in fact a decline from baseline performance has already occurred. It is commonly argued that high functioning people may have additional protection from dementia – but their work and social settings also tend to be more demanding, and subtle cognitive decline may thus become more apparent. Importantly, the clinical definition of MCI requires that the person has experienced a change in cognition, compared to baseline [12].

Profile of cognitive impairment in PD

Cognitive impairments in PD are basically seen as subcortical in nature, and there is a significant impairment in executive functions such as poor planning, sequencing, cognitive flexibility, and problem solving capacities [11, 60]. Memory, including encoding, recall, and procedural memory are also affected [17]. Recognition is thought to remain relatively well preserved [17]. Language dysfunction is rarely reported, with an exception of deficits in phonemic and semantic tasks, which exist and tend to decline over time and with disease severity, predicting also a future diagnosis of dementia [11].

Identifying PD-MCI is clinically relevant, given that these patients may be at increased risk for developing PDD [12]. On the other hand, one wonders if drug therapy known to be effective in PDD could be also of benefit at the stage of MCI, although this has not been formally studied in large trials [12].

Diagnostic criteria for MCI in PD

PD-MCI has been accepted and used for many years, but only recently, the first set of criteria for the formal diagnosis of PD-MCI has been proposed [70]. A great contributor to a stagnant state regarding concrete definitions and criteria has been the scarcity of long term in-depth prospective studies that would allow better characterization of the phenotype of PD-MCI, to establish biomarker correlates, and to clearly define the progression and risk of dementia for PD-MCI patients. The MDS task force on PD-MCI has built this concept on the previous classic definitions of MCI and made the necessary adjustments regarding the specificities of PD. The diagnosis of this condition requires a few key points. First of all, the diagnosis of PD should be well established. Then, cognitive decline must be reported by the patient or family, or documented by the clinician. These

are subsequently documented by means of formal cognitive assessment. Lastly, cognitive impairment must not cause significant functional decline. Exclusion criteria have also been described and two levels of assessment and diagnostic certainty have been proposed [70]. However, no biomarkers could be recommended at this stage to incorporate the diagnostic criteria, as evidence is still scarce concerning this matter in the field of PDD [70].

Genetic and cognitive impairment in PD

Hereditary forms of PD with cognitive impairment

Near 15% of PD patients reveal a family history suggesting Mendelian inheritance. These tend to be younger than the typical PD patients [16, 72]. A number of levodopa responsive parkinsonian syndromes have been described and linked to a specific gene, and 18 of these have been classified as PARK syndromes [73]. Some of these represent true PD but others denote more complex phenotypes and different diseases [73].

Several autosomal dominant forms of PD have been described, the most important being PARK1/PARK4 (gene *SNCA*, α -synuclein) and PARK8 (gene *LRRK2*, leucine-rich repeat kinase 2). In PARK1/PARK4, which are infrequent forms of PD, symptoms usually emerge in the fourth or fifth decades, and patients display typical PD features, except that early prominent cognitive decline and dementia is a common event. Hence, the clinical aspect may resemble DLB, although age at onset is much lower than in the classical cases. PARK1 and PARK4 are due to *SNCA* mutations and duplications/triplications, respectively [39, 74]. PARK8 is probably the most common type of inherited PD. The clinical picture resembles the classical sporadic PD [75], and cognitive singularities have not been reported in this form of the disease, with a dementia prevalence of about 11% [76].

Three forms of autosomal recessive PD have been described: PARK2 (gene *Parkin*), PARK6 (gene *PINK1*, PTEN-induced putative kinase 1), and PARK7 (gene *DJ-1*), listed by decreasing order of frequency. The clinical pattern of PARK2 includes, in addition to typical PD features, a variety of symptoms such as hyper-reflexia, prominent dystonia, sensory axonal neuropathy, increased sensitivity to levodopa induced dyskinesias, and psychosis [77, 78]. Interestingly, non-motor symptoms seem to be less prevalent than in sporadic PD, except anxiety [39]. It means that, cognitive decline is apparently less frequent. Lewy bodies were absent in most patients that came to autopsy [77]. Age at onset of symptoms ranges from childhood to mid-fifties. It is responsible for most PD cases under the age of 30 years. PARK6 and PARK7 cases are clinically similar to PARK2, including early onset, excellent response to levodopa, and frequent levodopa induced dyskinesias, but psychiatric features may be more prominent in PARK6 [76].

Glucocerebrosidase mutation: more than a risk factor for PD

Interesting observations have been made in the last few years in families with Gaucher's disease, an autosomal recessive disorder caused by homozygous mutations in the *GBA* gene encoding the lysosomal enzyme glucocerebrosidase. Some years ago,

heterozygous *GBA* mutations have been associated with a higher risk of PD [79], and data even suggested that these patients could have an increased risk for cognitive impairment. Two pathogenic mutations (L444P and N470S) seem to be particularly prevalent, but others have been described [79, 80]. Interestingly, *GBA* heterozygosity has also been associated with DLB, another synucleinopathy that shares clinical and pathological features with PDD [81]. Further clarifying these issues, SetóSalvia and coworkers have recently investigated *GBA* mutations in DLB and PDD [82]. Mutations were significantly more frequent in PD and DLB as compared to controls, and PD patients carrying *GBA* mutations were at higher risk of dementia, with an estimated adjusted odds ratio of 5.8, $p = 0.001$ [83]. In fact, this study has shown that *GBA* mutations are associated with more diffuse Lewy body neuropathology and greater cortical involvement, which might explain the higher risk of cognitive decline in these PD patients [80, 84].

A word of caution should be given regarding *GBA* testing in clinical practice. Current evidence clearly shows that heterozygous pathogenic mutations are a risk factor for PD and DLB. Thus, it has not been demonstrated that *GBA* mutations cause a monogenic form of PD or DLB. Therefore, like to what has been suggested for ApoE genotyping in AD [85], testing for *GBA* mutations is not currently recommended with clinical diagnostic purposes.

Microtubule associated protein tau and PD with cognitive impairment

Classically, microtubule associated protein tau (*MAPT*) gene mutations have been linked to autosomal dominant frontotemporal dementia, usually the behavioral variant, in particular the clinical forms also displaying parkinsonism [86]. In addition, *MAPT* haplotype H1 has been associated with increased susceptibility for the development of PD [87]. In recent years, an interesting relationship has been acknowledged between *MAPT* haplotype H1 and clinical progression in PD, specifically with regard to cognitive decline [23].

A Spanish case-control study has shown that the haplotype H1 is significantly over-represented in PD patients compared with controls and that the association was significantly stronger in PDD than in non-demented PD patients, suggesting that *MAPT* H1 haplotype seems to be a strong risk factor for PD and for dementia in PD patients. In addition, no association could be found between any of *MAPT* sub-haplotypes and DLB or AD [82].

Andrew Siderowf has studied genotypic variants of apolipoprotein E (*APOE*), catechol-O-methyltransferase (*COMT*), and *MAPT*, whether these could be correlated with cognitive decline in PD patients followed up prospectively. *APOE* allele E4 was associated with faster decline, and *MAPT* and *COMT* could be correlated with performance in memory and attention, respectively, but not with the rate of general cognitive decline.

Management of PDD

Patients with PD suffer decline in their Quality Of Life (QOL), due to motor symptoms, motor complications, and non-

motor symptoms [3, 8, 9]. Among these, dementia is a very important aspect, because it brings an additional loss of QOL. The achievements in the last few decades regarding cognitive and behavioral issues in PD have been important scientific progresses [50]. There are no established disease modifying strategies in PDD and every therapy here mentioned is currently seen as purely symptomatic.

Physicians should make an open dialog with the patient and family regarding the issue of cognitive decline in PD. Subjective cognitive complaints should be noted and delved in detail. Screening scales like the Montreal Cognitive Assessment [88] can be used to quickly probe the severity of cognitive decline, although comprehensive neuropsychological assessment is the best way of defining the profile of impairment in detail.

Common sense advises that, as in other circumstances when cognitive decline is apparent, with or without concomitant functional impairment (i.e., dementia), treatable causes should be ruled out through suitable laboratory testing, such as hypothyroidism, vitamin B12 or Folate deficiencies, renal, or liver failure, anemia, and exceptionally even Venereal Disease Research Laboratory test (VDRL) or Human Immunodeficiency Virus (HIV) antibodies in the appropriate setting (i.e., classical risk factors). Structural brain imaging specially MRI should be considered in the context of new onset cognitive decline, including when brain vascular disease or atypical degenerative parkinsonian disorders are suspected [89]. Exceptionally, genetic testing can be considered, in carefully selected cases.

Marked cholinergic deficits can be found in the brain of PDD patients [31], thus providing the rational basis for cholinesterase inhibitor therapy in this condition. Only one large randomized placebo-controlled trial has been published so far regarding the use of cholinesterase inhibitors in PDD [52]. Emre and collaborators have demonstrated that Rivastigmine, a dual inhibitor of acetylcholinesterase and butyryl- cholinesterase, brings modest but significant improvements in mild to moderate PDD [52]. Gastrointestinal side effects such as nausea and vomiting were more common in the group treated with Rivastigmine [52]. One wonders whether newer formulations (i.e., transdermal patch) would reduce gastrointestinal adverse events as compared to capsules, which has already been demonstrated for AD in the large randomized, controlled, double- blind, double-dummy IDEAL trial [90]. Interestingly, visual hallucinations seem to predict better clinical outcomes under Rivastigmine, as a mean statistically significant difference of 2.3 points on the Progressive Deterioration Scale has been documented in rivastigmine- versus placebo-treated patients without hallucinations at baseline, compared with a mean statistically significant difference of 5.3 points in patients with hallucinations at baseline [20]. Memantine has also been studied in PDD. One trial demonstrated marginal efficacy of Memantine over placebo, regarding global clinical impression, and attention, whereas it failed to establish significant improvements in other secondary outcome measures [10]. The second trial has shown clinical benefits of Memantine on global clinical status and behavioral symptoms, but activities of daily living and did not improve [91].

Behavioral or neuropsychiatric symptoms are common in PDD and often exceedingly disturbing for the patient and family.

They must be properly explored and managed. For instance, visual hallucinations are commonly uncovered in clinic during patient interview, which were previously not suspected at all by the family.

Tricyclic antidepressants have been found superior to placebo in PD [92], but their anticholinergic effects advises against their use in PDD, since the risk of additional cognitive deterioration and new onset confusion would be significantly increased [92, 93]. Thus, depression in PDD is usually treated with serotonin selective reuptake inhibitors (SSRIs), such as sertraline and citalopram, although evidence in favor of this practice is scarce [42, 92]. Noradrenaline and serotonin reuptake inhibitors like venlafaxine could be an alternative. Bupropion, that inhibits the reuptake of dopamine and noradrenaline, has been suggested by some to have a role in the treatment of depression in PD [94]. Recent research has found that Pramipexole, a dopamine agonist widely used in the treatment of PD motor symptoms, improves depressive symptoms in PD [95], but the prescription should be carefully considered in PDD due to the risk of visual hallucinations and confusion with this drug class.

Psychotic symptoms can be a challenging clinical problem in PDD. Patients should be questioned about the content of their visual hallucinations and whether these are disturbing or not. They can be a source of significant anxiety and agitation or, on the other hand, be felt by the patient as friendly or at least non-threatening. At times the diagnosis of delirium is considered in PDD, as patients may appear confuse and attention may become more volatile than usual. In this case, comorbid medical conditions should be searched for and treated, such as urinary tract infections, pneumonia, gastroenteritis, dehydration, or aggravated pre-existent disorders (e.g., renal or cardiac failure). Certain drugs seem prone to cause psychosis and confusional states, thus pharmacological therapy should be thoroughly reviewed and optimized. Antiparkinsonian drugs are often implicated – anticholinergic, selegiline, amantadine, dopamine agonists, and catechol-*O*-methyltransferase inhibitors should be discontinued, and lastly, a reduction in levodopa dosage should be considered. Antipsychotics should be used only as a last resort in PDD. Atypical agents such as quetiapine can be used [94, 96]. Clozapine has been studied with a few positive results in PD patients [97], but the hematological safety profile and significant muscarinic receptor affinity [98, 99] advise against its use in PDD. Ondansetron, a 5-HT₃ receptor antagonist used for the treatment of severe vomiting, has also been tried as an antipsychotic agent, based on the rational that psychotic symptoms could be due to central serotonergic over- stimulation.

Conclusion

PD is much more than a motor disorder and a wide range of non-motor symptoms have been recognized along the years. Among them, cognitive decline, in a wide range of severity, is particularly important to recognize, due to the meaningful impact on the life of patients and family, as well as the social and economic burden brought about by this condition. Expert consensus guidelines have been recently issued specifically for the diagnosis of MCI in PD and PD dementia. An array of

cognitive and behavioral symptoms has been associated with PDD, which should be properly characterized and managed, as patients benefit from specific interventions. Nevertheless, many clinical decisions and practices do not find solid support on evidence-based data, and rely on the older and less objective “experience-based medicine” practices. This is an important point to be addressed in the future, as multicenter randomized trials using recent consensus definitions should be considered in relevant clinical areas.

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