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Review

Features of dementia as non-motor symptom of Parkinson's disease

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Abstract. Parkinson's disease, the third frequent between neurological disorders and the second between neurodegenerative disorders shows in addition to motor symptoms many non-motor symptoms. From the non-motor symptoms in Parkinson's disease, dementia has a special impact on patient and patient's family, being associated with increased mortality, greater probability of hospitalisation or home care. This review reveals epidemiological, pathophysiological, clinical, paraclinical, diagnostics and terapeutic features of dementia and of cognitive impairment associated to Parkinson's disease, which could help in diagnosis, evaluation and treatment one of the most debilitated non-motor symptoms of Parkinson's disease.

Key Words: dementia, cognitive impairment, non-motor symptoms, Parkinson disease

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Introduction

Already in 1817, as Parkinson's disease (PD) was first described, James Parkinson refers besides motor symptoms (rest tremor, bradykinesia, rigidity with cogwheel phenomen, postural instability) to some non-motor symptoms such as sleep disorders, constipation, dysarthria, dysphonia, sialorrhoea, urinary incontinence and delirium (Parkinson 1817).

In the recent years non-motor symptoms were increasingly in the spotlight, these having a critical role in quality of life in patients with PD (Naismith et al 2010; Martinez-Martin et al 2011; Lageman et al 2014).

Studies show that the non-motor symptoms are a major cause of morbidity, hospitalization and mortality (Weintraub et al 2008; Thippeswamy et al 2014).

The non-motor symptoms associated to Parkinson's disease

Chaudhuri et al (2009) divided the non-motor symptoms into the following domains with its specific symptoms:

1. neuropsychiatric symptoms: depression, apathy, anxiety, panic attacks, anhedonia, attention deficit, hallucinations, illusions, delusions, dementia, confusion, delirium, obsessional and impulsive behaviour, repetitive behavior;
2. sleep disorders: restless legs, periodic limb movements, REM behavior disorders, excessive daytime somnolence, non REM sleep-related movement disorders, vivid dreaming, insomnia;
3. autonomic symptoms: bladder disturbances such as urgency, nocturia, frequency; hyperhidrosis, orthostatic hypotension, sexual dysfunction, xerophthalmia or lacrymation, xerostomia, sialorrhoea;
4. gastrointestinal symptoms: delayed gastric emptying, aguesia, dysphagia and choking, reflux, vomiting, constipation, faecal incontinence, etc;
5. sensory simptoms: pain, paraesthesia, hyposmia;
6. others: fatigue, diplopia, blurred vision, seborrhoea, weight loss.

Some of them appear before the motor symptoms, and some appear already in the early stages of disease (Chaudhuri et al 2011; Khoo et al 2013). In a retrospective study of 433 pathologically proven PD cases has been found that 21% of the patients had just non-motor symptoms at presentation to general practitioner such as pain, urinary dysfunction, affective disorders, cognitive impairment without functional limitation and fatigue (O'Sullivan et al 2008). Dementia appears usually in later stages, and when it appears early, in the first year of disease, it is likely dementia with Lewy body (DLB) (Emre et al 2007; Massano 2012). However, cognitive impairment, in particular memory impairment appear already in the early stages especially in patients with late onset of disease (Williams-Gray et al 2007; Pfeiffer et al 2014).

Risk factors and predictors for the development of Parkinson's disease dementia

According to a study from 2007, increased life expectancy and not the age at onset is the most important factor for the incidence of Parkinson's disease dementia (PDD) (Aarsland & Kvaloy et al 2007). Contrary, besides fewer years of education, higher daily levodopa dose and excessive daytime sleepiness, higher age was independent risk factor in a study on 406 PD patients (Zhu et al 2014). Other factors that have been associated with increased risk of developing dementia in PD are progressive

motor disability, symmetric motor symptoms, axial motor disorder with reduced tremor, akinetic-rigid form, the long duration of disease, male gender, older age, depression, psychosis, and some genetics factors such as the presence of APOE4 and MAPT alleles (Williams-Gray & Goris et al 2009; Aarsland et al 2010; Setó-Salvia et al 2011). Using of anticholinergics, poor response to L-dopa, and hallucinations as side effect of treatment with dopaminergics may also be risk factors for PDD. L-dopa-induced hyperhomocysteinemia may contribute to cognitive impairment, while amantadine and simvastatin may delay or reduce dementia, fact supported also through neuropsychological tests (Bar-On et al 2008; Iablonskaia et al 2010; Inzelberg et al 2006; Zoccolella et al 2010).

The patients with postural instability gait difficulty (PIGD) subtype developed more rapid cognitive decline, compared with non-PIGD subtypes (Burn et al 2012).

Another important point to discuss is whether and to what extent is mild cognitive impairment (MCI) a predictor for developing of dementia in PD. Foltynie et al (2004) found that 36% of those with PD had cognitive impairment at presentation and 3.5 years after diagnosis, in the same cohort 10% of them had developed dementia (Williams-Gray et al 2007). Patients with PD are 5-6 times more likely than the control group of the same age to develop dementia.

In a study conducted by Janvin et al (2006) of 72 nondemented patients over 4 years resulted that 62% of those with MCI at baseline developed dementia, while of those cognitive intact only 20% developed PDD. In order to detect predictors for PDD were followed 205 subjects (89 newly PD patients, 52 established PD and 64 control subjects) over 3 years. In both groups of PD patients about 50% showed cognitive decline and 9% of them developed dementia. In this study age at disease onset and axial impairment were related with cognitive decline in established patients (Muslimović et al 2009).

Aarsland, Brønnick & Fladby (2011) sustain that MCI in PD predicts a shorter time to dementia, particularly in posterior cognitive deficits. In an incident PD cohort was examined over 3 years the course of MCI and its progression to dementia and it has been found that almost half (45,5%) of the patients with persistent MCI at baseline and at the 1-year visit developed dementia (Pedersen et al 2013).

The early presence of mild cognitive impairment in patients with PD is associated with a faster rate of grey matter thinning in various cortical regions and a significant diminishment of limbic subcortical structures, what may lead to development of dementia (Hanganu et al 2014).

Epidemiological features

Hely et al (2005) found in a prospective cohort study conducted over 15 years on 52 patients that dementia occurs at a rate of 48%, and patients with a 20 years evolution of disease were affected in 83% of dementia (Hely et al 2008).

The prevalence of dementia in community-based studies has been estimated at 30-40%, but figures range from 10% to 80% and the incidence of dementia is increased by 2.8- to 6- fold in PD patients compared to those without PD. At least 75% of the PD patients that survived more than 10 years develop dementia (Aarsland & Kurz 2010). The incidence of PDD among parkinsonism is 2.5 per 100,000 and increase with age (Savica et al 2013).

Regardless of the time of PD onset, evolution of PDD occurs around 70 years of age (Reid et al 2011).

One study shows that about one third of the patients with newly diagnosed PD met the diagnostic criteria for mild cognitive impairment, and after five years, the percentage was 50% (Broeders et al 2013). Aarsland, Muniz and Matthews (2011) conducted a study of 238 PD patients over 15 years and observed that the rate of global cognitive decline measured with Mini-Mental Status Examination (MMSE) was nonlinear. After a stable period, the annual decline was 2.8 points. Similar data were found also in older studies.

Pathophysiological features

The variability of clinical features and fluctuation of cognition suggest a functional substrate rather than a structural one and the probability of more underlying processes (Chaudhuri 2009). The pathologic substrat is heterogeneous, it includes synuclein pathology, Alzheimer-type pathology, vascular changes, neuronal loss and neurochemical deficits. Some of these interact synergistically, so that the presence of one process facilitates the accumulation of another (Adler et al 2010; Chaudhuri 2009; Choi et al 2010; Sabbagh et al 2009). Cortical Lewy bodies pathologie has been found as the most significant correlate of PDD (Irwin et al 2012). PDD is associated with increasing neocortical Lewy body staging and more than 50% of PDD met neuropathological criteria for AD (Adler et al 2010; Sabbagh et al 2009). More and more evident becomes the aggregation of proteins as process in dementias, and using more sensitive techniques has been proven massive presynaptic aggregation of α-synuclein and postsynaptic loss of dendrites, leading to the conclusion that synaptic dysfunction plays a fundamental role in the pathology of dementias with Lewy bodies (Kramer & Schulz-Schaeffer 2007). A recent study supports the role of clusterin (apolipoprotein J, a protein involved in ß-amyloid deposit and neurotoxicity) in the pathogenesis of PD and PDD (Vranová et al 2014).

The genetic theory is also discussed as a susceptible process to develop dementia. The ε4 allele of APOE was associated with more rapid cognitive decline, MAPT haplotype and COMT genotype were associated with measures of memory and attention, respectively, over the entire follow-up period, but not with the overall rate of cognitive decline (Morley et al 2012).

A high frequency of TAR-DANN-binding protein-43 in frototemporal lobar degeneration compared with patients with PD but nondemented and healthy control group may have a co-morbid effect in PDD (Nakashima-Yusuda et al 2007; Rayaprolu et al 2013).

The polymorphism in the gene encoding mitochondrial transcription factor A (TFAM) that has been until now associated with AD, has been studied also in patients with PDD and in patients with DLB. The results support the probability of TFAM SNP rs2306604 A allele as a risk factor for PDD, particularly in males, but not for DLB. The genetic factors may differ therefore in PDD and DLB (Gatt et al 2013).

Clinical features

The onset of cognitive impairment and dementia is usualy insidious but dementia may develop also over a short period of

time and even in patients without cognitive impairment according to Janvin (2006). PDD belongs to subcortical dementias with important dysfunction of nonamnestic domains such as executive function (e.g. planning, set shifting, set maintenance, problem solving), attention, visuospatial function and less important of memory, language and praxis (Litvan et al 2011; Ferrer et al 2011).

Already in stage of MCI differs DLB from PD. It seems that patients with DLB-MCI have more severe cognitive impairment in frontal executive, memory, and visuospatial functions than those with PD-MCI (Yoon et al 2014).

PD patients demonstrate relatively preserved recognition and language. It has been suggested two distinct mild cognitive syndromes, one affects mainly the frontostriatal executive deficits that are modulated by dopaminergic medications and by a genetically determined level of prefrontal cortex dopamine release. The other affects the more-posterior cortical abilities, such as visuospatial and memory functions, and is suggested to be associated with an increased risk for conversion to dementia (Tachibana 2013).

The pattern of cognitive dysfunction, in terms of attention, episodic memory, and executive functions, is different in patients with PDD compaired with patients with DLB or AD. PDD patients achieved better scores on verbal memory function, delayed recall, verbal learning, task of three-word recall, phonemic word fluency than patients with DLB or AD. Visuospatial function did not differ significantly between the three groups. The deficits in the cognitive domains of attention, memory, and executive function were greater in DLB patients than in PDD patients (Park et al 2011). Semantic fluency is generally more impaired than phonemic fluency in PD (Koerts et al 2013).

The assessing of PDD patients without cognitive fluctuations showed significantly less attentional, executive, and memory deficits compared to those with DLB and PDD with cognitive fluctuations (Varanese et al 2010).

Compared with AD, in PDD are visuospatial and executive function and neuropsychiatric symptoms more severe impaired and the latter also more common, while memory impairment seems to show no significant difference between the two dementias (Tang et al 2013).

One study compared the profile of cognitive deterioration in 488 patients with AD with a similar number of patients with PDD using MMSE and ADAS-cog. Alzheimer patients had a poor performance on orientation tests in ADAS-cog and PDD patients had poor results on attention tests from MMSE. Both groups showed memory impairment, but they were more significant in patients with AD (Bronnik et al 2007).

In addition to cognitive impairment, in PDD appear also neuropsychiatric symptoms. They are very common and often they precede the onset of dementia. The majority of them are more common in PD patients with dementia (Aarsland et al 2014). In a study on 537 patients with PDD, 89% presented at least one symptom in Neuropsychiatric Inventory and 77% had two or more symptoms (Aarsland D, Bronnick K et al 2007). Hallucination appear in 45%, being significantly correlated with cognitive impairment and a predictor of cognition in PDD. Visual hallucination are twice as frequent as auditory ones, but the majority are complex. Tactile hallucinations are uncommon. Paranoid ideation is frequent. Depression in PDD appears in 13% (Aarsland et al 2001; Lee et al 2012), anxiety in 57,5 % and apathy in over 52% (Lee et al 2012).

Other clinical features are falls, daytime sleepiness, poor sleep quality. These are more frequent in PDD than in other types of dementia (Boddy et al 2007).

Laboratory features

Potential markers for PDD which have been investigated are those associated with AD: ß-amyloid 1-42, tau and phospho-tau protein. Low level of ß-amyloid 1-42 is an independent predictor of cognitive decline in patients with PD (Siderow et al 2010).

Compared with the control group of healthy individuals, in patients with PDD have been found low levels of amyloid ß 1-42 in cerebrospinal fluid (CSF), but low levels were found intermittent also in some nondemented patients with PD (Compta et al 2009; Mollenhauer et al 2006; Parnetti et al 2008). Newly diagnosed patients with PD from Norwegian ParkWest cohort had low levels of amyloid ß 1-42, but not so reduced as in those with AD. These reduced levels were associated with memory impairment but not with attentia deficite or executive and visuospatial function (Alves et al 2010). Another study compared ß-amyloid 1-42, tau protein and phospho-tau protein in CSF from patients with PDD with levels in CSF from patients with cognitive impairment but without dementia. Amyloid ß 1-42 was reduced in both groups, tau-protein had similar levels and phospho-tau had significantly lower levels in patients with cognitive impairment but nondemented (Montine et al 2010).

There are also from genetical point of view studies. In CamPaIGN cohort the genotyp COMT was not associated with a cognitive decline or dementia in over 5 years of study (Williams-Gray, Evans et al 2009), but microtubule-associated protein tau (MAPT) H1 haplotype had a strong influence on the risk of PDD (Elbaz et al 2011; Trotta et al 2012). From this cohort, 132 PD patients were assessed for up to 7.9 years from diagnosis, and tau haplotypr H1 remained a strong risk factor for dementia (Evans et al 2011). The expression of this gene is thought to be important in neuronal integrity, but its specific role in the development of PDD is not fully elucidated (Setó-Salvia et al 2011). APOE-epsilon 4 has been associated with AD but in PDD have been found conflicting results. A significant effect of APOE-epsilon 4 carrier status in development of dementia or in cognitive decline has not been found in a longitudinal follow-up of CamPaIGN cohort, although there were more carriers in the PDD as in non-demented PD patients (Williams-Gray, Evans et al 2009). However, another study argues that APOE is a risk factor for development of cognitive impairment in PD, 50% of patients had developed dementia in a 10 years follow-up. The frequency of this allele was lower in patients with PDD (19%) than in DLB (31,9%) or in dementia of Alzheimer type and Lewy body (40,6%) (Anderson et al 2012). Also in a study of 212 with PD this allele was associated with faster decline (Morley et al 2012).

Radiological and neurophysiological features

From the encephalographic point of view has been found in patients with mild cognitive impairment (MCI) an increase of

posterior theta amplitude, and in patients with PDD an increase posterior delta wave amplitude (Fonseca et al 2009).
In patients with selective executive dysfunction have been reported an increase in slow wave activity and decrease of alpha and fast wave activity at the frontal pole (Kamei et al 2010).
The medial temporal lobe atrophy observed in MRI is comparable in PD patients without cognitive impairment and in patients with PDD. AD and DLB (in DLB less as in AD) present a more marked atrophy of medial temporal lobe. A greater involvement of the hippocampus in AD compared to PDD and DLB is correlated with clinic, cognition and pathological differences between diseases (Tam et al 2005). PD patients with cognitive dysfunction also in early PD and those with PDD has been found to have an atrophy of the head of the caudate nuclei and enlargement in the posterior regions of the lateral ventricles, what was also with MMSE score associated (Apostolova et al 2010; Dalaker et al 2011). Pagonabarraga (2013) assessing cortical thickness found in PDD patients, but not in PD-MCI patients, an association between reduced alternating verbal fluency and cortical thinning in right parahippocampal gyrus, left lingual gyrus and left precuneus.
By using FDG (18 F-fluorodeoxyglucose) PET (Positronen-Emissions-Tomographie) for the investigation of changes in regional metabolism associated with mild cognitive impairment has been found in PD patients with MCI an increased expression of abnormal metabolic pattern in relation with cognition. The results of this study, performed on a cohort of PD patients has shown that patients with PDD had a higher expression of metabolic pattern as patients with MCI and without cognitive impairment together. The pattern expresion increased linearly with disease duration over a period of 15 years and represents a biomarker which may be used to asses the progression of cognitive impairment in PD (Poston et al 2009). In another study using FDG-PET has been found that cognitive dysfunction in PD patients was correlated with increased posterior cingulate metabolism and decreased temporoparietal lobe metabolism (Huang et al 2013).
By using magnetic resonance spectroscopy has been found in patients with PD a loss of neuronal integrity in the anterior cingulate which was associated with poor performances on executive function mesurements (Lewis et al 2012).
Voxel-based morphometry was used to compare the amount of gray matter in the brains of PD patients to identify specific regions responsible for cognition dysfunction in PD. Compared with Parkinson's disease patients without dementia, in those with PDD it has been found decreased gray matter volume in the bilateral superior temporal gyrus, bilateral posterior cingulate and left cingulate gyrus, right parahippocampal gyrus and hippocampus, right precuneus and right cuneus, left inferior frontal gyrus and left insular lobe (Xia et al 2013). Compared with healthy subjects, in patients with PDD has been found a significant loss of volume of the neocortex and hippocampus but there were no distinct changes associated with MCI in PD (Ramirey-Ruiy et al 2005). In a comparison between PD patients without cognitive impairment and PD patients with MCI, in the latter has been found an atrophy of hippocampus and in those with dementia also an atrophy of medial temporal lobe (Weintraub et al 2011). Another study using voxel-based morphometry explored the pattern of cortical atrophy in DLB and in PDD. In patients with DLB has been found a more pronounced atrophy in temporal, parietal and occipital lobes as in patients with PDD. Patients with AD have a reduced gray matter concentration in temporal lobe bilateral including the amygdala than those with PDD. Compared with those with DLB, patients with AD have temporal and frontal atrophy. Despite similar severity of dementia in enrolled patients, DLB patients have a more pronounced cortical atrophy than those with PDD (Beyer et al 2007).

Diagnosis of Parkinson's disease dementia

"Movement Disorder Society Task Force" proposed new diagnostic criteria for PDD. The defining characteristic for this is that dementia develops in the context of diagnosed PD. The diagnose of dementia should be based on the presence of deficite in at least two cognitive domains (attention, memory, executive function and visuospatial function) and to be severe enough to affect the normal daily living. These guidelines are based on two levels, the first is primarily used by clinicians without experience in neuropsychological methods and contains in addition to medical history and medical history provided from carers, the MMSE, clock drawing test and the 4-items of Neuropsychiatric Inventory. The second level, which is more specific, is used especially to establisch the pattern and severity af dementia and also for the detailed clinical monitoring, research studies or pharmacological trials (Litvan et al 2012).
According to the Alzheimer's Association, the diagnosis of cognitive impairment and dementia should not be based on a single test (Cordella et al 2013).
For the assessment of cognitive impairment in PD are a wide variety of test available. Among them are Mini-Mental State Examination (MMSE), Mattis Dementia Rating Scale (DRS), Mini-Mental Parkinson (MMP), Montreal Cognitive Assessment (MoCA), Scalles for Outcomes of Parkinson's disease-cognition (SCOPA-COG), Parkinson Neuropsychometric Dementia Assessment (PANDA).
MMSE is often used for screening and for evaluation of severity of cognition in PD, but it is not a specific instrument for this, due to the high proportion of items focused on cortical cognitive aspects and two items are influenced from motor impairments. Also, MMSE does not adequately assess executive and visuospatial functions, typically deteriorated in PD (Chaudhuri et al 2009).
DRS is often used in studies on PD. The scale includes items for the exploration of executive function to, which make it valid for screening of PDD and also MCI in PD (Pirogovski et al 2014; Villeneuve et al 2011).
MMP is rarely used and has not been independently validated. Additionally several metric properties have never been tested. This scale is not recommended (Chaudhuri et al 2009).
PANDA includes tests which evaluates the immediate and delayed recall memory, alternating verbal fluency, visuospatial abilities, and working memory and attention. Kalbe et al (2008) examined healthy subjects, patients with PD but without cognitive impairment, PD patients with mild cognitive impairment and patients with PDD, and it has been reported that PANDA discriminates between all of these. As disadvantage, it lacks

assessment of language function, data on clinimetric scale properties, construct validity, and test-retest reliability. However, in some countries (Germany) the test has been validated as tool for cognitive impairment evaluation on patients with PD and the test was also in other languages translated and in studies used with good results (Gasser et al 2011; Pignatti et al 2014). MoCA is in the recent years increasingly used for the evaluation of cognitive impairments in PD. Also, there are more and more studies, that demostrates a better sensitivity compared to MMSE and that MoCA is an adequate test for screening of cognition in PD (Dalrymple-Alford et al 2010; Hoops et al 2009) as well as in predicting cognitive decline in early PD (Kandiah et al 2014). One study found evidence of caudate nucleus dopaminergic denervation at patients with normal scores in MMSE but abnormal MoCA scores. This study also sugested that although MoCA preferentially detects executive dysfunction, should not be used alone to make the diagnosis, due to its limited diagnostic accuracy for mild cognitive impairment in PD (Chou et al 2014).

SCOPA-COG assesses specifically the cognitive domains where problems appear in PD, is short, reliable, valid and sensitiv to the specific cognitive deficits in PD (Marinus et al 2003), but has been created to measure the severity of cognitive impairment and not for the screening or diagnosis. In advanced dementia, the scale has a limited usefulness (Chaudhuri et al 2009).

Differential diagnosis

Differential diagnoses of dementia in PD are vascular parkinsonism, Alzheimer disease, delirium, depressive pseudo-dementia, dementia with Lewy bodies. PDD and DLB are close related, and oft confused with each other. They are separated by the „one year rule" which says that if the extrapiramidal motor symptoms were present one year or more before the onset of dementia, we can talk about PDD, but if dementia appears in less then one year from onset of motor symptoms, the diagnosis is of DLB. Both are now regarded as part of Lewy bodies dementias, determinated by abnormalities of α-sinuclein metabolism (Diener et al 2012). Recently, it has been demonstrated important differences regarding MCI between DLB and PD, these suggest that differences in pathologic substrates between PDD and DLB may begin in the MCI stage of the two diseases and may lead to differences in cognitive profiles (Yoon et al 2014).

Treatment of dementia in Parkinson's disease

Nonpharmacological treatment

Nonpharmacological treatment plays an important role in primary and secondary prevention of cognitive decline in many neurodegenerative diseases (Palavra et al 2013; Mowszowski et al 2010). Cognitive training in nondemented PD patients has been found to improve performance in tests in many domains: attention, information processing speed, memory, visuospatial and visuoconstructive abilities, semantic verbal fluency and executive functions (Paris et al 2011).

Pharmacological treatment

A recent review supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on cognitive function, behavioral disorders and daily activities but there are no sure evidence to support their use in patients with PDD and MCI (Rolinski et al 2012).

In the EXPRESS study, study of rivastigmine and EDON, study of donepezil were recruted patients with mild-moderate dementia. The studies assesed severity of dementia using MMSE and they were conducted over 24 weeks. Significant improvements of cognition, daily activities and psychiatric symptoms were observed in both studies (Chaudhuri et al 2009).

Efficacy of rivastigmine on cognitive function has been proven in several studies. Cochrane Collaboration evaluated rivastigmine, despite the insufficient data, as a product having a moderate, but clinically significant effect in 15% of patients (Diener et al 2012). Rivastigmine is the only approved medication from Food and Drug Administration in PDD (Goldman & Holden 2014). Also the long-term safety of rivastigmine as 12 mg/day capsules and 9,5 mg/24 h patch was supported by a study of 583 patients over 76 weeks using Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI-10), Mattis Dementia Rating Scale (MDRS) and MMSE (Emre et al 2014).

In a multicenter, placebo-controlled study was demonstrated the efficacy of Memantine 20 mg on the generall condition and cognitive speed, but without any significant effect on psychiatric symptoms, behavior or daily functionality (Emre et al 2010). Another review supports the beneficial effects of Piribedil through dual action mode - partial agonist of D2/D3 receptor and additionally antagonist of noradrenergic alpha 2 A+C receptor- on alertness, cognition and affection (Millan 2010).

The concomitent administration of memantine and donepezil is associated with a significant neuronal damage (Creeley et al 2008).

Affective disorders may be ameliorated by dopaminergic treatment (particularly through dopamine agonists, such as pramipexol and ropinirol) (Storch et al 2010), but also through tricyclic antidepressants or selective serotonin reuptake inhibitors. Their use is also limited by side effects.

Important in order to avoid the development or exacerbation of psychiatric symptoms is to reduce as possible the antiparkinsonian therapy and gradual withdrawal of anticholinergics, selegiline, dopamine antagonists and of catecholamine-o-methyltransferase inhibitors (Chaudhuri et al 2009). The european, canadian and american guidlines suggest clozapine, pointing that olanzapine should not be used in psychosis in PDD. Another alternative may be quetiapine (Grimes et al 2012; Sorbi et al 2012).

Among atypical antipsychotics that need no monitoring, the only with benefits and without worsening the parkinsonisn is quetiapine (25-150 mg/day) (Goldman & Holden 2014). New atypical antipsychotic agents are: ziprasidone, antagonist at 5HT2A and dopamine D2 receptors, pimavanserin a 5HT2A inverse agonist/antagonist (Chaudhuri et al 2009).

Conclusions

1. Dementia in PD appears usualy in the advanced stages of disease, but the cognitive impairment is present since early stages and may be a predictor for the development of dementia. Other predictors are older age, age on onset, male gender, long duration of disease, axial impairment, symmetric symptoms, akinetic-rigid form, depression, etc.

2. For the diagnosis of dementia in PD, "Movement Disorder Society Task Force" proposed new criteria. For the screening and evaluation of cognitive impairment and dementia have been designed more tests, some of them were also validated.
3. The most affected cognitive domains in PDD are executive function and visuospatial function. Data from literature on deterioration degree of atention and memory are controversed, what proves the heterogeneous profile of cognitive impairment in PDD.
4. Analysis of CSF offers more information in the recent years about PDD, but not specific markers for it. From the neuroimagistic point of view, FDG-PET may be use for the specific evaluation of progresion of cognitive impairment in PD. To discover the biomarkers for PDD further studies are needed.
5.The better resultes of cognitive training in nondemented PD patients encourage to its use in PD patients in ordert to delay the evolution of cognitive impairment and development of PDD.

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