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Review

Dementia – The real problem for patients with Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is meanwhile not only recognised as a disorder affecting the extrapyramidal motor system but apparently patients frequently experience non-motor symptoms, such as dementia, depression, sleep disorders, pain, autonomic and sensory dysfunction. New studies suggest that cognitive impairment or dementia would develop in each PD patient if lifetime is long enough. As these symptoms often have a greater impact on patients' quality of life than motor symptoms, worsen the prognosis and increase the personal and socioeconomic burden of PD, a major focus of prevention, recognition and treatment is mandatory and might directly improve patients' health related quality of life. Dementia associated with PD (PDD) and dementia with Lewy bodies (DLB) are likely to be part of the same disease entity and it has been shown that the cholinergic deficits are even greater than in Alzheimer's disease. Rivastigmine as a cholinesterase inhibitor provided significant benefits on cognition in comparison to placebo without worsening of parkinsonian symptoms in patients suffering from PDD and DLB.

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders of late life with an estimated prevalence of 2–3% among people aged 65 years and older and as high as 10% among those aged 80 years and older [1]. PD is clinically defined by the classic motor signs of rest tremor, rigidity, brady- and hypokinesia and postural instability but is also associated with a wide variety of non-motor symptoms such as neuropsychiatric, sleep disorders, autonomic symptoms, gastrointestinal symptoms, sensory symptoms e.g. pain and a group of other symptoms e.g. fatigue [2,3]. Depression and cognitive impairment as neuropsychiatric non-motor symptoms have been highlighted as particularly common and have a great influence on health related quality of life in PD [4,5]. Using established clinical diagnostic standards for dementia the overall rate in routine outpatient neurological care of all PD patients is 28.6%, but using more sensitive neuropsychological measures such as the Clock Drawing Test and the Parkinson Neuropsychometric Dementia Assessment (PANDA), rates for cognitive impairment might be up to 2-fold higher [6]. PD patients compared to non PD patients have a six fold increased risk for developing dementia and point prevalence of dementia in PD is approximately 30% [7]. The Sydney multicenter

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study of PD found dementia present in 83% of 20-year PD survivors and concluded an inevitability of dementia [8]. The cumulative incidence of dementia steadily increases with age and duration of PD and conditional on survival, dementia incidence increases to 80 to 90% by age 90 years [9]. As it has been shown that already a Mini Mental State Examination score of less then 25 points is associated with significantly impaired quality of life [4], the improvement of cognition should therefore become an important target in the treatment of PD [10].

State of the art

The four milestones defining advanced PD are frequent falls, visual hallucinations, dementia and the need of residential care [11]. Kempster et al. showed that these milestones occur at a similar time from death in five different age-at-death groups (<70, 70–74, 75–79, 80–84, >84 years) [11]. The milestone of cognitive disability showed the greatest consistency in time to death across these groups. Furthermore grouping the assessed patient cohort by age at PD onset in five groups (24–53, 54–59, 60–65, 66–72, 73–80 years), the intervals between milestones and death vary again only little across the five groups, but the effect of age at PD onset on disease duration was apparent with a significant negative correlation between the age at onset and the time to the first and to the mean milestone occurrence [11]. These findings support the state of the art that young onset PD is associated with a longer disease course and longer preservation of cognition in comparison with older onset PD patients [6,12]. This was also found by the Sydney Multicentre Study [13] and in contrast later age of PD onset is associated with more rapid cognitive decline and poorer prognosis. A patient with PD onset aged 75 years is 4.8 times as likely as a patient with a PD onset aged 55 years to develop dementia [13]. Particular susceptibility for the evolution of cognitive decline was mainly suspected around 70 years of age [9,13,14]. This seems to be in contrast to the finding that the onset of cognitive impairment is independent of age at disease onset, disease duration and age-at-death but the time course to death of advanced PD after onset of cognitive decline is similar at whatever age it starts. Clinical PD course seems to be subdivided into a variable long early and middle stage followed by a more stereotyped final period of advanced PD [11]. All PD patients pass through the advanced stage at an individual age but with a similar duration with disease- and age-related factors being hard to disentangle.

Clinical presentation of dementia associated with Parkinson's disease and differential diagnoses to dementia with Lewy bodies and Alzheimer's disease

Dementia associated with PD (PDD) is a "dysexecutive syndrome" characterised by impaired mental planning and concentration. A core feature of PDD is impairment of executive functions and attention – the cognitive abilities to plan, initiate and regulate goal-directed activities. In addition, the condition is characterised by bradyphrenia (cognitive slowing), impaired memory, visuospatial functions and communication impairment. Communication impairment has been associated with prefrontal cortical dysfunction in PD affecting verbal fluency, sentence comprehension and narrative production [15,16]. By contrast, there are reports that semantic, but not phonemic fluency is a useful predictor of cognitive impairment in PD and that semantic fluency imply a posterior cortical rather than a frontostriatal basis for dementia in PD [14]. The severity of vocabulary impairment differs in PD patients dependent on the time of onset of dementia in the disease duration (classified as mid-stage vs. late-stage PDD) [13]. Together with neuropsychiatric symptoms, this leads to a decline in performance and in the inability to carry out daily activities [17,18].

Memory problems in PDD are thought to be due to inefficient *retrieval* of memory – possibly due to poor retrieval strategies as a result of executive dysfunction – as opposed to the memory *storage* problems typically seen in Alzheimer's disease (AD) [19,20]. Similar to dementia with Lewy bodies (DLB), "attention" deficits may fluctuate throughout the day [21]. This may help in the differential diagnosis to AD. Cognitive problems such as aphasia, apraxia and agnosia are relatively absent in patients with PDD compared with those with AD [17,19].

The symptom profile of PDD is similar to that seen in DLB patients with typical parkinsonian motor (extrapyramidal) symptoms, cognitive deficits mainly in attention and executive function, which may be fluctuating, as well as psychiatric symptoms, such as visual hallucinations. Particularly when fully established in later stages of PDD and DLB, patients may be indistinguishable, clinically as well as pathologically, when their history is unknown. So far the separation between PDD and DLB was done on an arbitrary basis considering the temporal course of the onset of dementia and the parkinsonian motor symptoms [22]. Appropriate to the DLB consortium [23] PDD should be diagnosed when symptoms of dementia occur in the context of a well-established PD (consequently long after the onset of motor symptoms), compared with DLB in whom dementia symptoms typically occur before or simultaneously with motor symptoms. However in research studies the former one year rule between the onset of dementia and parkinsonian motor symptoms for DLB should be still used. In fact, there is much evidence that dementias associated with PD and DLB are probably both part of the same disease entity differing in the spatial and temporal evolution of the disease process [24], with the major hallmark of Lewy body pathology in the brain in areas comprising the brainstem, as well as subcortical and cortical regions [17,22].

Caregivers may provide specific cues for the onset of cognitive impairment or dementia by reporting of, e.g. "lack of motivation", "loss of concentration", "distractibility" or "inability to coordinate/organize". Also, caregiver reports of noticeable changes specifically in the behavioural status of patients may indicate significant caregiver distress and suggest a particular need to test cognitive pattern and eventually initiate treatment. Physicians might need to treat these signs as potential warnings for the onset of cognitive decline in PD patients.

Neuropathology

Neuropathological progression of PD has been described by Braak et al. in a topographically, caudal to rostral, six-stage scheme culminating in widespread cortical Lewy body degeneration [25,26]. The classification correlates with the clinical observation of a symptomatic pre-motor stage such as the recognition of prodromal hyposmia, autonomic symptoms and sleep disorders in patients developing motor PD later [26]. In clinically well-documented cases of PD a good correlation between alpha-synuclein deposition and clinical disability supporting a link between Lewy body burden and the clinical manifestations of advanced PD has been shown, but without any significant differences in disease duration across different age groups, nor in the severity and distribution of Lewy body and other pathologies [11].

Clinicopathological studies of patients being younger at PD onset and suffering from minimal cognitive impairment have shown a slow infiltration of Lewy bodies in the limbic system that underlie their neurocognitive deficits [27]. In the final phase of clinical PD, the results of Kempster et al. [11] support the two Braak postulates that progression occurs according to factors that are