Journal of the Neurological Sciences xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Dementia in Parkinson's disease

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ARTICLE INFO

Article history:
Received 26 December 2016
Received in revised form 1 January 2017
Accepted 4 January 2017
Available online xxxx

Keywords:
Parkinson's disease
Dementia
Dementia with Lewy Bodies
Cholinesterase inhibitors

ABSTRACT

Dementia can occur in a substantial number of patients with Parkinson's disease with a point prevalence close to 30%. The cognitive profile is characterized by predominant deficits in executive, visuospatial functions, attention and memory. Behavioral symptoms are frequent such as apathy, visual hallucinations and delusions. The most prominent associated pathology is Lewy body-type and biochemical deficit is cholinergic. Placebo-controlled randomized trials with cholinesterase inhibitors demonstrated modest but significant benefits in cognition, behavioral symptoms and global functions.

Contents

1. Introduction

Although considered primarily a motor disorder, non-motor symptoms may accompany Parkinson's disease (PD) from early stages onwards and be present even before the manifestation of motor symptoms. Considering its contribution to morbidity and mortality dementia constitutes one of the most significant non-motor disorders. Due to increased survival as a consequence of advances in treatment, incidence and prevalence of dementia in PD has been increasing.

2. Epidemiology

Even though subtle cognitive deficits may be detected in the early stages of PD, overt cognitive deficits usually become manifest in the late stages of the disease, especially as the age advances. The prevalence of dementia estimates varies depending on the nature of the study population and diagnostic criteria used. In a systematic review, the point prevalence of dementia was found to be 24–31% [1]. In a community-based study, 36% of newly diagnosed patients were found to have cognitive impairment based on their performance in three tests (Mini-Mental State Examination, a pattern recognition task, and the Tower of London task) at the time of diagnosis, while 57% of this cohort developed cognitive deficits within 3.5 (±0.7) years; the incidence of dementia was estimated to be 54.7 per 1000 person-years during the 10 year follow up period [2]. A prospective study showed 32.9% of drug-naive, newly diagnosed PD patients had mild cognitive

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http://dx.doi.org/10.1016/j.jns.2017.01.012
0022-510X/

impairment (MCI) at the time of diagnosis [3]. Another longitudinal study including 141 PD patients with normal cognition at baseline revealed that 47.7% developed cognitive impairment within 2–6 years observation time and all those who developed MCI progressed to dementia within 5 years [4]. In the prospectively followed-up Sydney PD cohort, 48% of surviving patients had developed dementia 15 years after the diagnosis [5] and the cumulative incidence of dementia had increased to 83% 20 years after the diagnosis [6].

The most established risk factors for Parkinson's disease dementia (PD-D) include old age at disease onset or at the time of evaluation. Older patients and those with severe disease have a 12-fold increased risk of dementia as compared to young patients with mild disease [7]. Along with severe motor disability, long disease duration, atypical neurological features such as early autonomic failure, symmetrical disease presentation and unsatisfactory response to dopaminergic treatment are other risk factors. Low cognitive scores at baseline, early development of confusion or hallucinations on dopaminergic medication, axial involvement including speech impairment, postural imbalance and excessive daytime sleepiness have also been reported to be associated with increased risk of dementia. PD patients with REM sleep behavior disorder (RBD) had a 6 fold higher occurrence of dementia than those without [8]. In a prospective cohort study several other predictors of dementia were reported, including cardiovascular autonomic dysfunction (hypertension or orthostasis) and color discrimination ability [9]. Patients with tremor-dominant phenotype have a lower risk of developing dementia. In one study, impairment in cognitive tests relying on frontal executive functions were associated with a lower risk of dementia whereas impairment in those assessing more posterior cortical functions was associated with a higher risk [2,10]. White matter hyperintensities (WMH) were suggested to be associated with cognitive decline in PD patients [11,12] but another study couldn't demonstrate an independent relationship [13]. Hippocampal volume was also reported to be a predictive factor for cognitive impairment [14]. In a cross-sectional study, heart disease was the only vascular factor significantly more prevalent in PD patients with dementia [15], whereas a longitudinal study revealed that more than two vascular risk factors and white matter leukoaraiosis in brain imaging were associated with cognitive impairment [16].

3. Genetic aspects

Presence of apolipoprotein epsilon 4 (ApoE ε4) allele was found to be a predictor of cognitive decline in non-demented PD patients. The associated cognitive profile was more typical of that seen in early Alzheimer's disease (AD) than that seen in PD [17]. Another genetic association study showed that the presence of APOE ε2 allele (the least common allele) might reduce the risk of developing dementia [18].

There is some evidence that variations in the tau (*MAPT*) gene may determine the genetic risk of dementia in PD, the H1/H1 haplotype being associated with a greater rate of cognitive decline and development of early dementia [2,19,20].

Heterozygote mutations in the glucocerebrosidase gene (GBA) has been reported to be a significant risk factor for PD and DLB. A community-based incident cohort study showed that GBA mutations are present at a frequency of 3.5% in the PD population and progression to dementia is 5.7 fold higher and occurs earlier than in non-carriers [21]. In mutation carriers cognitive dysfunction was found to be present even without motor features of PD at the time of investigation [22]. A large, longitudinal study revealed that GBA E326K polymorphism is associated with a 3.34-fold more rapid progression of cognitive impairment and dementia compared with non-carriers [23].

There is a robust association between cognitive impairment and duplication, and even more so with the triplication of the alpha-synuclein gene [24,25]. The frequency of dementia in autosomal dominant LRRK2 mutations may be lower than that in sporadic PD. The risk of dementia seems to be lower in patients with PINK1, DJ-1 and Parkin mutations [26].

4. Clinical features of PD-D

Typically, the cognitive profile of dementia in PD-D is a dysexecutive syndrome (characterized by impairment in planning, abstract thinking, mental flexibility and apathy) with early and prominent impairment of attention and visuo-spatial functions, moderately impaired episodic memory and relatively preserved core language functions. Deficits in attention/executive functions, naming, visuospatial/constructional abilities and retrieval in episodic memory are present in early stages [27]. Behavioral symptoms are pervasive, most notably apathy and psychosis.

Dementia is preceded by mild cognitive impairment, which may affect a variety of domains. Mild cognitive impairment, it should be noted, may not progress to dementia. In early stages, designated as Parkinson's disease mild cognitive impairment (PD-MCI), the most frequent subtype is multi-domain MCI [28–31], with the most frequently impaired domains being memory and visuo-spatial functions [32–34]. Deficits in more posterior cortical functions, such as visuo-spatial functions, were found to be associated with a higher risk of dementia than frontal-subcortical deficits [2].

PD-D patients are more apathetic, with more prominent impairment of attention as compared to AD patients in comparative studies [35]. Impaired attention is an important determinant of the ability to undertake activities of daily living. Working memory, explicit visual and verbal memory and implicit memory such as procedural learning can all be impaired in PD-D. In typical cases the memory impairment is characterized by a deficit in free recall with relatively preserved recognition, however, memory impairment with impaired recognition resembling that seen in AD, can also be seen in a sub-population of PD-D patients [36]. Impairment in visuo-spatial functions is another early feature, which is typically more severe than in patients with typical, amnestic AD [37].

A wide range of neuropsychiatric symptoms are seen in PD-D. The most common are hallucinations, apathy, depression, anxiety and insomnia. At least one neuropsychiatric symptom is present in more than 90% of PD patients [38]. Visual hallucinations are similar to those seen in Dementia with Lewy Bodies (DLB), with well-formed figures of humans or animals, often with preserved insight and little emotional content. Delusions, usually paranoid in nature are not uncommon. Delusional misidentification syndromes were found in 17% of PD-D patients [39] in one study.

Autonomic disturbances including notably urinary incontinence, orthostatic and postprandial hypotension (which can result in syncope and falls) are frequent in PDD, it was suggested that orthostatic hypotension and cognition may be interrelated [40]. Excessive sweating, reduced heart rate variability predisposing to ventricular arrhythmias can also occur [41].

5. Pathological and biochemical correlates

Pathologically, PD-D is characterized by a variable combination of Lewy Body (LB)-type degeneration, cellular loss in subcortical nuclei and cortical AD-type pathology [42]. Dementia and more rapid cognitive decline best correlate with neocortical LB pathology, although some degree of AD-type pathology (more plaques than tangles) usually co-exists, a combination of both pathologies being more detrimental [43–45].

Degeneration of subcortical nuclei results in various neurochemical abnormalities including cholinergic, dopaminergic, serotoninergic and noradrenergic deficits, of which cholinergic loss is the most prominent. Loss of cholinergic cells in the nucleus basalis of Meynert (nbM) is greater than that seen in AD, LBs are frequently found in nbM cells. It has been suggested that the pattern of neuronal loss in the nbM of patients with Lewy body disease is different than that seen in AD [46].

Please cite this article as: H.A. Hanagasi, et al., Dementia in Parkinson's disease, J Neurol Sci (2016), http://dx.doi.org/10.1016/j.jns.2017.01.012