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Review article

Interactions of visual hallucinations, rapid eye movement sleep behavior disorder and cognitive impairment in Parkinson's disease: A review

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ABSTRACT

Patients with Parkinson's disease may develop various non-motor symptoms during the course of the illness. Visual hallucinations (VH) and cognitive impairment (CI) are two common non-motor symptoms of Parkinson's disease. Studies have reported association of both VH and CI with presence of rapid eye movement sleep behavior disorder (RBD). Presence of visual hallucinations and cognitive impairment has been described as risk factors for emergence of each other. There is marked overlap in the risk factors for development of RBD, VH and CI in patients with PD. Results of clinical and epidemiological studies as well as studies based on neuroimaging, electrophysiology especially transcranial magnetic stimulation and neuropsycholgical evaluations in PD patients have suggested presence of certain common neurobiological process leading to emergence of RBD, VH and CI. Structural neuroimaging studies using voxel-based morphometry have often reported grey matter atrophy of hippocampus and parahippocampal cortices in PD patients with RBD, VH and CI. Cholinergic dysfunction is common in PD patients with RBD, VH and CI. This review explores the complex interactions of RBD, VH and CI in patients with PD and their potential implications.

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by motor symptoms such as tremor at rest, rigidity, bradykinesia and postural instability [1]. Patients with PD may develop various non-motor symptoms such as psychosis, cognitive dysfunction, depression, sleep disturbances and autonomic dysfunctions during the course of the illness [2]. Psychosis is one of the common and debilitating non-motor symptoms of PD and visual hallucinations (VH) are the commonest manifestation of psychosis in PD [3]. VH is usually preceded by minor hallucinations such as presence and passage hallucinations, whereas delusions, illusions and hallucinations of modalities other than visual (auditory, gustatory, tactile) are rare and usually coexist with VH [3,4]. Though the exact pathogenesis and natural course of VH in PD is not known, various factors such as older age of the patients, higher stage and severity of PD, medications (dopaminergic and anticholinergic), visual dysfunctions, sleep disturbances, presence of rapid eye movement sleep behavior disorder (RBD) and cognitive impairment (CI) have been described as risk factors for emergence of VH [5,6]. RBD is a common feature of synucleinopathies and is characterized by loss of normal skeletal muscle atonia during REM sleep and behaviors related to dream enactment [7]. Approximately 35–50% of the patients with PD may have RBD, onset of which usually precedes the onset of symptoms of PD [8]. CI is one of the major non-motor symptoms of PD, which may be present even at the earlier stages of the disease [9]. The spectrum of CI in PD may range from mild cognitive impairment (PD-MCI) to dementia (PDD). Though the point prevalence of PDD is approximately 40% [10], longitudinal studies have reported development of dementia in more than three quarters of the patients with PD [11,12]. The risk factors for development of CI in PD often overlap

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with that of development of VH [11,13].

Several studies have attempted to determine the relationships between VH and RBD, RBD and CI, VH and CI in patients with PD. Since patients with PD may develop VH, RBD and CI in various combinations, it is interesting to explore whether the presence of any of the three symptoms (VH, RBD, CI) increases the risk of developing the other two. It is however unclear whether VH, RBD and CI are risk factors for each other in a patient with PD or their combined presence is just an association. Considering the remarkable overlap in the clinical characteristics and risk factors for development of VH, RBD and CI in patients with PD, it is imperative to explore the complex interactions between VH, RBD and CI, which may have important clinical implications. This review explores the interactions between the aforementioned non-motor symptoms with insights from previous epidemiological studies as well as studies based on neuroimaging and electrophysiology.

2. Methodology

We searched the literature published in last 20 years from PubMed and PsycINFO database from the year 1995 to July 2015 focusing on PD patients with VH and RBD, RBD and CI, VH and CI. A broad search strategy was applied by using a number of terms and combinations, details of which are given in Table 1. A large number of studies, which are not relevant to the article, were excluded after screening the titles, abstracts or full texts of articles obtained from the two databases using the key words and combinations. Some publications in the initial searches were duplicates of those obtained during subsequent searches, which were subsequently removed and the remaining articles were assessed for inclusion using a set of criteria. Studies were considered for review if: (1) they were either original or review articles, (2) full text was available in English, (3) either RBD or VH or CI or any combination was present in the PD cohort, (4) in case of original articles, PD was diagnosed according to UK PD society brain bank clinical diagnostic criteria, and (5) the severity and stage of PD were estimated by appropriate scales. Details of the steps of database search are given in a flow chart in Fig. 1.

2.1. RBD and VH in PD: a continuum or two distinct phenomena?

RBD has long been regarded as a potential clinical biomarker for synucleinopathies such as PD, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) as it usually precedes the onset of symptoms of these disorders by many years [14]. VH is a common symptom in both PD and DLB and recent studies have reported significant association of RBD in hallucinating PD patients compared to those without VH [15]. Neuropathologic studies also support the fact that RBD is a harbinger of PD and various non-motor symptoms of PD such as VH and CI. Degeneration of sub-laterodorsal nucleus, which has been speculated to result in REM sleep without atonia and RBD, corresponds to stage-2 of the Braak staging system for PD [16]. Hence clinically and pathologically RBD precedes not only the onset of parkinsonian signs (Braak stage-3 and 4) but also that of VH (Braak stage-6) and cognitive impairment in PD (Braak stage-4, 5,6) [17–19]. Patients with PD and RBD have been speculated to have a different clinical course from those without RBD. Various studies have reported significant association of RBD with non-tremor phenotype of PD, higher prevalence of other non-motor symptoms, and poor response to levodopa [20]. Several studies have also reported a strong association of RBD with presence of VH in patients with PD, which supports the observation that presence of RBD probably leads to a clinical course which is different from those without RBD.

2.1.1. Evidence from clinical and epidemiological studies

Vivid dreams and nightmares, which are typically found in RBD, have also been reported in patients with PD. Pappert et al. have reported that sleep fragmentations, vivid dreams and nightmares are more frequently observed in PD patients with hallucinations/illusions than those without hallucinations/illusions [21]. Gjerstad et al. in a study on 231 patients with PD (with RBD: 34, without RBD: 197) have reported that frequency of hallucinations in PD patients with RBD (29.4%) is double the frequency of those without RBD (14.7%) [22]. Sinforiani et al., in a longitudinal study reported higher risk of emergence of VH in patients with PD and RBD than those without RBD after a two year follow up [23]. In this study none of the PD patients without RBD at baseline had developed VH during the follow up after two years whereas 38% of the PD patients with RBD had developed VH during the follow up. In a recent questionnaire based postal survey, PD patients with a RBD screening questionnaire (RBDSQ) score of $\geq$6 more frequently had hallucinations compared to those with a score $\leq$6 [24]. A study based on polysomnography has reported reduced sleep efficiency, total REM sleep duration and REM sleep percentage in PD patients with VH compared to those without VH [25]. Several other studies have also reported increased frequency of VH in PD patients with RBD compared to those without RBD [15,26–28]. Though majority of the studies have reported significant association of VH and RBD in patients with PD, there are few studies, which did not find any significant association [29,30]. However disparities in the results may be secondary to differences in methodologies and patient characteristics.

Though controversial, a continuum hypothesis has been proposed to explain the association of sleep disturbances, altered dream phenomena and hallucinations in patients with PD [31]. This hypothesis suggests that drug induced psychosis in PD is possibly secondary to dopaminergic kindling. This may begin with sleep disruption, which may be subsequently followed by vivid dreams, hallucinatory and delusionary experiences and later by delirium. Later Pappert et al. in a study involving 174 patients reported that the three behavioral symptoms (sleep fragmentation, altered

Table 1
Results of PubMed and PsycINFO database search with various key words and combinations.

Key words	Number of publications	
	PubMed	PsycInfo
Parkinson's Disease AND visual hallucination AND REM Sleep behavior disorder	72 (22)	11 (6)
Parkinson's Disease AND visual hallucination AND RBD	49 (15)	9 (5)
Parkinson's Disease AND visual hallucination AND cognitive impairment	167 (32)	58 (12)
Parkinson's Disease AND visual hallucination AND dementia	481 (56)	140 (22)
Parkinson's Disease AND REM Sleep behavior disorder AND Cognitive impairment	77 (21)	51 (12)
Parkinson's Disease AND RBD AND Cognitive impairment	57 (19)	41 (12)
Parkinson's Disease AND REM Sleep behavior disorder AND Dementia	184 (38)	111 (29)
Parkinson's Disease AND RBD AND Dementia	120 (38)	86 (34)