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Review article

REM sleep behavior disorder portends poor prognosis in Parkinson's disease: A systematic review

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ABSTRACT

REM sleep behavior disorder (RBD) is a parasomnia wherein a loss of REM sleep atonia manifests as dream-enactment, often violent. Aside from its significance as a predictor of PD, RBD in PD may imply more than merely screaming at night and experiencing sleep fragmentation. To probe its significance as a prognostic factor in PD, we performed a systematic literature review. Analysis of prospective studies reveals baseline RBD confers a higher risk of developing dementia and hallucinations. In cross-sectional studies, RBD is associated with the non-tremor predominant motor phenotype and autonomic dysfunction. Clinical, imaging, and autopsy studies support the presence of dense and diffuse pathology extending beyond the brainstem in PD with RBD. As RBD in PD is associated with a greater disease burden and an increased risk of mortality, we propose the RBD subtype in PD to highlight that RBD may mark a distinct subtype with relatively poor prognosis.

1. RBD as a predictor of PD

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of normal REM sleep atonia that allows, or rather disinhibits the affected to act out his dreams, often violently. The significance of RBD as a potent predictor of PD lies in its specificity. While the prevalence of idiopathic RBD (iRBD) is less than 1% in the general population [1,2], the prevalence of RBD in PD is estimated to be 15–60% [3–16]. Owing to its high specificity, RBD has a higher positive likelihood ratio than any other prodromal markers of PD [17]. Other potential prodromal markers such as olfactory deficits [18], constipation [19–21], and depression [22], which are experienced by up to 25% of the population, are insufficient to be used alone as prodromal markers due to their low specificity.

The concept of RBD as a harbinger of evolving synucleinopathies was introduced in 1996 when 38% (11/29) of iRBD patients were described to have developed PD after four-year follow-up [23]. In the extension of the study, after 16 additional years of follow-up, 81% (21/26) developed a Parkinsonian disorder or dementia [24]. In another longitudinal study of iRBD patients, 45% (20/44) developed PD, dementia with Lewy bodies (DLB), multiple system atrophy (MSA) or mild cognitive impairment (MCI) after a mean follow-up period of 5 years [25]; after 7 years of additional follow-up, 82% (36/44) of the original cohort developed one of the defined neurodegenerative diseases [26]. In a similar fashion, other longitudinal studies of iRBD patients witnessed emergence of Parkinsonism or dementia in 33.3% (93/279) after 2.5 years [27], 34% (15/44) after 3.8 years [28], 30% after 3 years, 47% after 5 years, and 66% after 7.5 years [29] (Fig. 1).

2. RBD in PD

For a PD patient to have RBD, does it mean more than merely screaming at night and experiencing sleep fragmentation? Subtyping based on non-motor symptoms (NMS) has gained much attention recently as the specific patterns of NMS have been shown to correspond reasonably well to differential pathways of neuronal degeneration involving non-dopaminergic areas pertinent to the NMS of interest [30]. Of the several non-motor subtypes thus presented, "park sleep" refers to a phenotype dominated by either excessive daytime sleepiness or RBD and is considered to represent the brainstem-dominant route of pathology spread. The depiction

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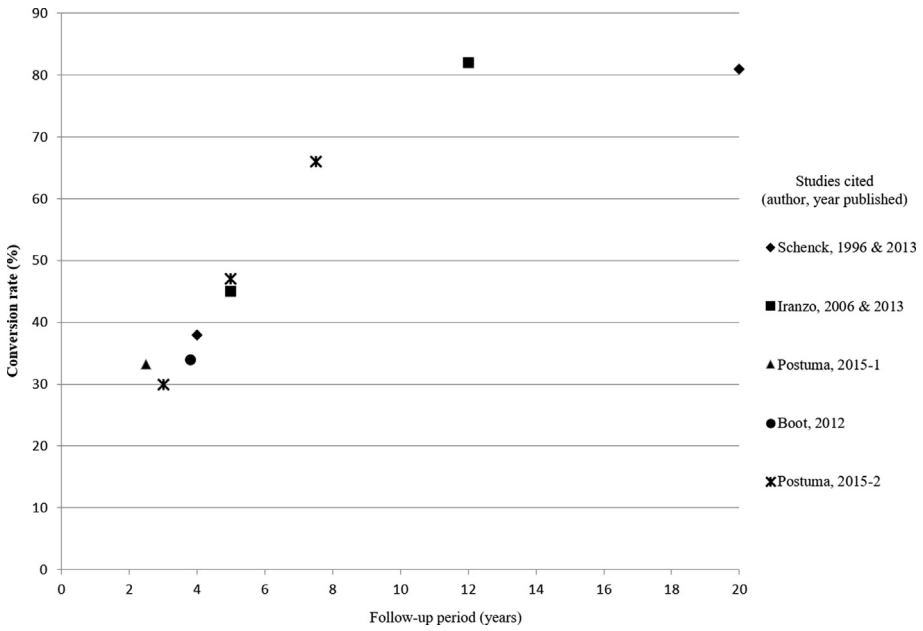

Fig. 1. Rate of conversion of idiopathic REM sleep behavior disorder to synucleinopathies over time as witnessed in multiple studies.

of RBD subtype in PD as having a higher prevalence of orthostatic symptoms, visual hallucinations, non-tremor predominant phenotype, falls and freezing [30] however is based on merely a few studies at most [12,16].

To ultimately understand the significance of RBD in PD, we performed a systematic literature review to see whether 1) having RBD at baseline entails poor prognosis and 2) having RBD is associated with a greater disease burden concurrently.

2.1. Search Strategy and Selection Criteria (Fig. 2)

We searched PubMed and Embase for articles published up to December 2016. Using the search builder available in both databases, we identified potentially relevant studies as follows: rapid eye movement sleep behaviour disorder[Title/Abstract] OR rapid eye movement sleep behavior disorder[Title/Abstract] OR rapid eye movement behaviour disorder[Title/Abstract] OR rapid eye movement behavior disorder[Title/Abstract] OR REM sleep behaviour disorder[Title/Abstract] OR REM sleep behavior disorder [Title/Abstract] OR REM behaviour disorder[Title/Abstract] OR REM behavior disorder[Title/Abstract] OR RBD[Title/Abstract] OR REM sleep without atonia[Title/Abstract] OR RSWA[Title/Abstract] OR dream enactment[Title/Abstract] AND Parkinson[Title/Abstract].

The initial search returned a total of 458 articles – 209 articles from PubMed and 249 articles from Embase. Duplicate studies were excluded. A study had to meet the following minimum criteria: 1) The study was written in English. 2) The article was an original research article, and not an editorial, supplement to an original article, case report, brief report, or correspondence. Studies were excluded if they met at least one of the following criteria: 1) The study was concerned with non-PD patients only (e.g., iRBD, DLB, and other neurodegenerative diseases). 2) The study did not compare clinically probable RBD with no RBD. 3) The study was concerned with aspects or sleep events of PD other than RBD. 4) The study fulfilled the minimum inclusion criteria, but was not relevant to the purpose of this review. Two authors (Y.K. and E.P.) independently evaluated the 458 articles to select articles for inclusion. Disagreement between the two authors was resolved by discussion. In the end, the two finally agreed on 19 articles out of 458 to be included for the review.

A further search was done by meticulously inspecting the reference lists of the included articles. This returned a total of 20 additional studies. In summary, this paper is based on a total of 39 studies: 5 prospective studies for Section 2.2 *RBD as a Prognostic Factor in PD* and 33 cross-sectional and 1 retrospective studies for Section 2.3 *RBD as a Marker of a Specific PD Subtype with a Greater Disease Burden*. Note studies that are prospective with regards to data collection but cross-sectional with respect to data analysis were classified as cross-sectional for the purpose of this review. In essence, we adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [31] in conducting this systemic review. However, as the topic requires a qualitative approach rather than a quantitative one, we neither assessed risk of bias nor calculated summary measures (e.g., risk ratio and difference in means).

2.2. RBD as a Prognostic Factor in PD (Table 1)

Analysis limited to prospective studies reveals having RBD at baseline confers a higher risk of developing dementia or hallucinations and possibly faster progression of bradykinesia in PD. For clarification of terminology, clinically probable RBD (cRBD) denotes the presence of RBD in PD reported by patient or informant-completed questionnaires, but not confirmed by PSG. P-RBD stands for PSG-confirmed RBD in PD and NRBD for absence of RBD irrespective of PSG-confirmation. PD with RBD includes both cRBD and P-RBD.

Two longitudinal follow-up studies conducted specifically to determine whether RBD predicts future development of PD dementia (PDD) confirmed the association. After a mean follow-up period of four years, 48% of P-RBD developed dementia compared to 0% of NRBD [32]. In another study, after 1.8 years of follow-up, 32.1% of P-RBD developed dementia compared to 8.7% of NRBD [9]. Likewise, two prospective studies specifically investigating the emergence of hallucinations in relation to baseline RBD in PD indeed demonstrated a significantly higher percentage of cRBD patients developing hallucinations compared to NRBD

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