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Diagnostic Assessment & Prognosis

Phenoconversion from probable rapid eye movement sleep behavior disorder to mild cognitive impairment to dementia in a population-based sample

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Abstract

Introduction: Rapid eye movement sleep behavior disorder (RBD) is strongly associated with synucleinopathies. In 2012, we reported an increased risk of mild cognitive impairment (MCI) and Parkinson disease (PD) in cognitively normal Olmsted County, Minnesota, residents, aged 70 to 89 years with probable RBD. Here, we examine their progression to dementia and other neurodegenerative phenotypes.

Methods: Fifteen participants with RBD who were diagnosed with either MCI or PD were longitudinally followed, and their subsequent clinical courses were reviewed.

Results: Over 6.4 ± 2.9 years, six of the 14 participants with MCI developed additional neurodegenerative signs, five of whom had Lewy body disease features. Four of them progressed to dementia at a mean age 84.8 ± 4.9 years, three of whom met the criteria for probable dementia with Lewy bodies. One subject with PD developed MCI, but not dementia.

Discussion: Our findings from the population-based sample of Olmsted County, Minnesota, residents suggest that a substantial number of RBD patients tend to develop overt synucleinopathy features over time, and RBD patients who develop MCI and subsequent dementia have clinical features most consistent with dementia with Lewy bodies.

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Keywords: Rapid eye movement sleep behavior disorder; Mild cognitive impairment; Dementia with Lewy bodies; Parkinson disease; Synucleinpathy

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by complex motor behaviors (e.g., shouting, screaming, kicking, and punching) suggestive of dream enactment [1]. The prevalence of RBD increases in older adults, especially in those with neurodegenerative conditions [2,3]. In particular, RBD is strongly associated with synucleinopathies, including Parkinson disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy [4,5]. Longitudinal cohort studies of patients with idiopathic RBD suggest that most of these patients ultimately develop an overt neurodegenerative phenotype

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with the rate of phenoconversion as high as 91% at 14 years [6–8]. However, these studies are based on sleep center cohorts in which referral bias toward more severe disease is likely to be present, and therefore may not reflect findings in the general population.

To assess population-based risk of neurodegenerative disease in RBD, we previously studied cognitively normal individuals aged 70 to 89 years with probable RBD (pRBD) in Olmsted County, Minnesota, and reported a 2.2-fold–increased risk of developing mild cognitive impairment (MCI) or PD over 4 years [3]. Since the initial report, we have longitudinally followed the participants with pRBD who developed MCI or PD as part of the Mayo Clinic Study of Aging (MCSA), a longitudinal population-based study of aging [9]. Here, we examine their progression to dementia and other neurodegenerative phenotypes.

2. Methods

The details of subject recruitment and diagnostic evaluation are described in our previous report [3]. Briefly, the original cohort included the MCSA participants aged 70 to 89 years who were randomly selected residents of Olmsted County, Minnesota, using the medical records linkage system of the Rochester Epidemiology Project. All individuals in the original cohort were cognitively normal without PD at the time of their initial enrollment in the MCSA. These participants were longitudinally followed based on a standardized protocol [9]. The diagnosis of pRBD was made using the Mayo Sleep Questionnaire [10]. A consensus diagnosis of MCI, dementia, or PD was made according to our previously published criteria [9].

A total of 15 participants with pRBD who were diagnosed with either MCI or PD at the time of our original analysis

were included in the present study. Follow-up and autopsy data were obtained from the MCSA and/or review of their medical records.

Informed consent was obtained from the participants and their family members or significant others. All study protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

3. Results

The demographic and clinical characteristics of the participants are summarized in the Table 1. The participants were followed for an average 6.4 ± 2.9 years after their MCI or PD diagnosis. Of the 14 participants with MCI, four with amnestic MCI developed dementia at a mean age 84.8 ± 4.9 years: three met the criteria for probable DLB [11] and one for Alzheimer disease dementia [12]. The estimated onset of dementia began 13.8 ± 6.2 years after pRBD diagnosis and 4.3 ± 2.8 years after MCI diagnosis. All participants with probable DLB had well-formed visual hallucinations, and one of them also had parkinsonism. One participant with nonamnestic MCI developed visual hallucinations 2 years after the MCI diagnosis and another developed parkinsonism 4 years after the MCI diagnosis, but neither met criteria for dementia. One participant with PD subsequently developed nonamnestic multidomain MCI 10 years after the PD diagnosis. The remainder of the participants continued to have MCI until their death or last follow-up (5.9 ± 2.9 years), except for one who was reclassified as having normal cognition 7 years before her death and remained cognitively normal until the death. Her prior cognitive insufficiency was presumed related to suboptimally controlled depression and/or polypharmacy. This individual underwent autopsy and

Table 1
Demographic and clinical characteristics of the updated probable RBD cohort

Subject	Sex	Age at the onset of RBD (year)	Age at the onset of MCI (year)	MCI type	Age at the onset of dementia (year)	Dementia type	Age at death (year)	Age at last follow-up (year)	Other features
1	Male	71	77	A	84	Probable DLB	85	n/a	VH, parkinsonism
2	Male	63	84	A	85	Probable DLB	89	n/a	VH
3	Female	78	85	A	91	Probable DLB	n/a	92	VH
4	Male	72	76	A	79	Probable AD	81	n/a	
5	Female	32	82*	n/a	n/a	n/a	91	n/a	
6	Male	66	87	A	n/a	n/a	88	n/a	
7	Male	23	85	A	n/a	n/a	n/a	93	
8	Male	82	84	A	n/a	n/a	n/a	93	
9	Male	71	81	A, M	n/a	n/a	85	n/a	
10	Male	69	74	A, M	n/a	n/a	n/a	82	
11	Female	84	86	NA	n/a	n/a	89	n/a	VH
12	Male	27	78	NA	n/a	n/a	84	n/a	Parkinsonism
13	Male	30	78	NA	n/a	n/a	n/a	86	
14	Male	47	76	NA, M	n/a	n/a	78	n/a	PD
15	Male	34	84	U	n/a	n/a	87	n/a	

Abbreviations: A, amnestic; AD, Alzheimer disease; DLB, dementia with Lewy bodies; M, multidomain; MCI, mild cognitive impairment; n/a, not applicable; NA, nonamnestic; PD, Parkinson disease; RBD, rapid eye movement sleep behavior disorder; U, unknown type; VH, visual hallucinations.

*Classification changed from amnestic MCI to normal 7 years before her death.

was found to have neither Lewy body disease nor Alzheimer pathology. No other participant underwent autopsy.

4. Discussion

In our pRBD cohort ascertained in a population-based sample, six of the 14 MCI participants developed additional neurodegenerative signs, five of whom had Lewy body disease features, including visual hallucinations and parkinsonism. Three of the four participants who progressed to dementia satisfied the criteria for probable DLB. Our findings from the population-based sample of Olmsted County, Minnesota, residents are consistent with the findings from the previous studies of sleep center cohorts [6–8] and suggest that RBD patients tend to develop overt synucleinopathy features when followed over time, and those RBD patients who develop MCI and subsequent dementia have clinical features most consistent with DLB.

Potential limitations of our findings include use of a questionnaire for RBD diagnosis. We used the Mayo Sleep Questionnaire, which has a high sensitivity and specificity for RBD diagnosis in older adults relative to RBD diagnosis by polysomnography [10]. This lends confidence to RBD ascertainment despite absence of polysomnographic confirmation, which was not feasible in this population-based cohort. Another limitation was that our participants were older adults with an average age of 81 years at the time of their MCI diagnosis. Most participants died of causes unrelated to their neurodegenerative conditions. This, in turn, limited our longitudinal follow-up, which may have resulted in underestimation of the proportion progressing to dementia. Plus, pathologic confirmation of underlying Lewy body disease in this cohort is lacking either because the subjects are still alive or autopsy was not performed in those who have died. However, our population-based design heightens the generalizability of these findings. We plan future longitudinal studies of younger cohorts with pRBD and MCI to provide further insight into progression to dementia, including neuropathologic examination when feasible.

Acknowledgments

RESEARCH IN CONTEXT

1. Systematic review: Literature review was done using traditional search engines (e.g., PubMed/Medline, Google scholar). Several longitudinal studies of sleep center cohorts have suggested an increased risk of neurodegenerative disorders in patients with idiopathic rapid eye movement sleep behavior disorder (RBD), but population-based risk assessment has been limited. Our previous population-based study of individuals with probable RBD showed an increased risk of mild cognitive impairment and Parkinson disease, but the duration of follow-up was limited. We sought to further explore whether other neurodegenerative phenotypes develop in these patients.

2. Interpretation: Our findings provide further evidence for the association between RBD and synucleinopathies in a population-based sample and suggest most RBD patients who develop mild cognitive impairment and subsequent dementia have clinical features most consistent with dementia with Lewy bodies.

3. Future directions: Longitudinal studies of younger cohorts with RBD will provide further insight into progression to dementia.

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