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

Youngsin Jung, Brendon P. Boot, Michelle M. Mielke, Tanis J. Ferman, Yonas E. Geda, Eric McDade, Teresa J. H. Christianson, David S. Knopman, Erik K. St Louis, Michael H. Silber, Ronald C. Petersen, Bradley F. Boeve

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.

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

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.
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

| 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 | 65                          | 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

This research was funded by the following NIH grants: National Institute on Aging U01 AG06786 (B.F.B., Y.E.G., T.J.H.C., D.S.K., and R.C.P.), P50 AG016574 (B.F.B., D.S.K., and R.C.P.), R01 AG15866 (B.F.B., T.J.F., and M.H.S.), and K01 MH068351 (Y.E.G.), as well as the Harold Amos Medical Faculty Development Program (RWJ foundation) (Y.E.G.), and Robert H. and Clarice Smith and Robert D.S.K., and R.C.P.), RO1 AG15866 (B.F.B., T.J.F., and M.H.S.), and K01 MH068351 (Y.E.G.), as well as the Harold Amos Medical Faculty Development Program (RWJ foundation) (Y.E.G.), and Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program (B.F.B., Y.E.G., T.J.H.C., D.S.K., and R.C.P.). The authors thank the staff of MCSA and especially the subjects and family members involved in the study.

The authors have declared that no conflict of interest exists.

References

[1] Schenck CH, Mahowald MW. REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in SLEEP. Sleep 2002;25:120–38.
[2] Molano J, Boeve B, Roberts R, Geda Y, Christianson T, Knopman D, et al. Frequency of sleep disorders in the community-dwelling elderly: The Mayo Clinic Study of Aging. Neurology 2009;72:A107.
[3] Boot BP, Boeve BF, Roberts RO, Ferman TJ, Geda YE, Pankratz VS, et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. Ann Neurol 2012;71:49–56.
[4] Boeve BF, REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. Ann N Y Acad Sci 2010;1184:15–54.
[5] Boeve BF, Silber MH, Ferman TJ, Lin SC, Benarroch EE, Schmeichel AM, et al. Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. Sleep Med 2013;14:754–62.
[6] Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicot-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296–300.
[7] Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. Sleep Med 2013; 14:744–8.
[8] Iranzo A, Fernandez-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. PLoS One 2014;9:e89741.

[9] Roberts RO, Geda YE, Knopman DS, Cha RH, Pankratz VS, Boeve BF, et al. The Mayo Clinic Study of Aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology 2008;30:58–69.

[10] Boeve BF, Molano JR, Ferman TJ, Smith GE, Lin SC, Bieniek K, et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. Sleep Med 2011;12:445–53.

[11] McKeith IG, Dickson DW, Lowe J, Emre M, O’Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–72.

[12] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement 2011;7:263–9.