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Minor hallucinations in isolated rapid eye movement sleep behavior disorder indicative of early phenoconversion: A preliminary study

Running head: Minor hallucinations in isolated RBD

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YS designed the study. YS and AU performed the examinations, analyzed the data, and performed the statistical analysis. YS and AU wrote the first draft of the manuscript. YO and HK critically reviewed the analyzed data and manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

Objectives: Minor hallucinations (MH) are psychotic symptoms that can occur anywhere between prodromal to early Parkinson's disease and after onset of motor problems. MH include visual illusions, presence hallucinations, and passage hallucinations. Isolated rapid eye movement sleep behavior disorder (RBD) is a harbinger of neurodegenerative diseases. We conducted a retrospective cohort study to investigate the clinical characteristics of isolated RBD with MH and the risk of phenoconversion.

Materials and methods: We retrospectively analyzed the data of 36 patients with isolated RBD (four females; median age, 75.0 years). We defined cases reporting at least one minor hallucination as RBD with MH. Demographic data and cognitive function were compared between patients with and without MH, and Cox proportional hazards models estimated the risk of phenoconversion.

Results: We included 10 (27.8%) patients with MH and 26 (72.2%) without MH. Patients with MH were older, had less dopamine transporter accumulation, more severe autonomic dysfunction, more depressive symptoms, and lower verbal fluency and symbol coding test scores than patients without MH. After follow-up (median, 2.50 years), 13.9% (5/36) of all patients developed phenoconversion (Parkinson's disease, two patients; dementia with Lewy bodies, three patients). The rate of phenoconversion was significantly higher in patients with MH (40.0% vs. 3.8%, $p = 0.005$). The Cox

proportional hazards model adjusted for age, sex, and disease duration revealed that MH was a significant risk factor for phenoconversion (hazard ratio, 14.72; 95% confidence interval, 1.35–160.5).

Conclusions: MH may be utilized as early clinical markers for prodromal estimation of neurodegenerative diseases.

Keywords

Hallucinations, neurodegenerative disease, REM sleep behavior disorder, retrospective study

INTRODUCTION

Minor hallucinations (MH) and visual hallucinations (VH) are common psychotic symptoms in Parkinson's disease (PD) [1, 2]. MH include: (1) visual illusions (brief misperceptions of objects or living beings that differ from objective reality); (2) presence hallucinations (vivid sensations that someone is present nearby); and (3) passage hallucinations (fleeting images or brief visions of a person, animal, or object passing sideways, within the periphery of the visual field) [1, 3, 4] (Figure 1). MH are present in 42% of newly-diagnosed drug-naïve patients with PD [5] and are observed in early-stage PD [1, 6]. MH appear before VH and are on a continuous spectrum with VH [7]. MH can emerge in any phase of PD [8] and are regarded as a manifestation before the occurrence of PD motor and non-motor symptoms (i.e., rapid eye movement [REM] sleep behavior disorder [RBD], depression, VH, and cognitive impairment)[4]. MH complications in patients with PD have been associated with specific brain dysfunctions. Pareidolia, a specific subtype of visual illusion, has been reported to result from an abnormal top-down modulation of the frontal area during and prior to visual stimulation in patients with PD [9, 10]. In a recent PD study, MH were classified into the following categories according to MH appearance timing: "daytime MH" (during daytime) or "arousal MH," (during arousal from sleep during the night or early morning); it was reported in this study that daytime MH was associated with cognitive impairment and arousal MH was associated with RBD and levodopa equivalent daily dose [11].

RBD is defined as REM parasomnia characterized by dream-enacting behaviors [12]. Patients with α-synucleinopathies, such as PD, dementia with Lewy bodies (DLB), or multiple system atrophy (MSA), are frequently comorbid with RBD [12]. RBD is also a harbinger of PD, DLB, and MSA. RBD without neurodegenerative diseases was previously termed "idiopathic RBD;" however, recently, it has been regarded as the prodromal stage of an α-synucleinopathy and reconceptualized as isolated RBD (iRBD) [13].

With time, iRBD can progress to neurodegenerative disorders. The risk of developing neurodegenerative diseases (phenoconversion) has been reported to be 33.5% at 5 years, 82.4% at 10.5 years, and 96.6% at 14 years [14]. Identifying the risk factors for early phenoconversion is critical for patient care and appropriate patient selection in future disease-modifying clinical trials. A large multicenter study in 2018 identified the following risk factors for phenoconversion in patients with iRBD: abnormal quantitative motor testing, olfactory deficit, mild cognitive impairment, erectile dysfunction, motor symptoms, abnormal dopamine transporter accumulation, color vision abnormalities, constipation, REM atonia loss, and age [15].

MH are possibly related to the neurodegenerative pathology in patients with iRBD. Although idiopathic RBD patients have been reported to show more pareidolic responses than healthy subjects [16], there are few reports on MH in iRBD. Therefore, this study aimed to retrospectively evaluate the relationships between MH and other

clinical features in patients with iRBD, and the risk of early phenoconversion. We investigated the prevalence of MH in iRBD, the clinical characteristics of iRBD with MH, and the risk factors for early phenoconversion.

MATERIALS & METHODS

Patient selection

This preliminary retrospective cohort study investigated whether phenoconversion occurred between the time of comprehensive clinical assessment (baseline evaluation) and the censoring date.

Patients who satisfied the diagnostic criteria for RBD according to the International Classification of Sleep Disorders, 3rd edition [17], confirmed by polysomnography, were screened. We retrospectively analyzed medical records of patients with iRBD (without a diagnosis of PD [18], DLB [19], MSA [20], or dementia according to the Diagnostic and Statistical Manual of Mental Disorders-5 [DSM-5] [21]) who visited the Shiga University of Medical Science Hospital between April 1, 2016 and May 18, 2021. The following patients were excluded at baseline evaluation: those taking antidepressants or with severe sleep apnea (apnea-hypopnea index ≥ 30) [22]; those taking antiparkinsonian agents or with a history of schizophrenia spectrum or other psychotic disorders (DSM-5) [21]; and those with a history of stroke.

At baseline, patients underwent cognitive function assessments (described

below) between April 1, 2016 and April 23, 2021, and the censoring date was May 18, 2021. Due to the exploratory nature of the study, the required sample size was not calculated. This study was approved by the Shiga University of Medical Science Research Ethics Committee (R2017-027).

Baseline evaluation

Demographic data

Demographic data, including age, sex, years of education, disease duration from diagnosis to baseline, and disease duration from estimated onset (the first time iRBD symptoms occurred, as confirmed by family members) were collected at baseline. To assess dream-enactment behaviors, the patients were asked to complete the REM Sleep Behavior Disorder Screening Questionnaire–Japanese version (RBDSQ-J), which consists of 13 questions (cut-off score ≥ 5; maximum score, 13) [23, 24]. Motor symptoms were evaluated using the modified Hoehn and Yahr Staging Scale [25]. We used the Odor Stick Identification Test–Japanese (OSIT-J), a validated olfactory test for Japanese populations [26]. OSIT-J is a test that asks respondents to identify the correct odor from four options selected using 12 sticks with different odors (maximum score 12) with minimal false negative or positive cut-offs (< 6 or < 4, respectively) for older patients [27]. In dopamine-transporter (DAT) single-photon emission computed tomography (DAT-SPECT) with [^{123}I] N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)

nortropane, the specific-to-non-displaceable binding ratios on the right and left striatum were calculated, as well as the average value. To assess autonomic dysfunction, we administered the Scale for Outcomes in PD-Autonomic (SCOPA-AUT), a validated scale for autonomic dysfunction in PD [28]. The SCOPA-AUT contains 25 items (0–3 points/item) assessing the following domains: gastrointestinal (7), urinary (6), cardiovascular (3), thermoregulatory (4), pupillomotor (1), and sexual dysfunction (two items for males and two items for females), as well as a total score (23). Subjective and objective depressive symptoms were assessed using the Beck Depression Inventory Second Edition [29] and the Hamilton Rating Scale for Depression, both comprising 21 items with a maximum score of 63 [30]. Additionally, apathy was assessed with the Apathy Scale (14 items with a cut-off of ≥ 16 and maximum score of 42) [31, 32].

Minor hallucinations and pareidolia

We defined visual illusions, presence hallucinations, and passage hallucinations as MH, and patients with MH as "RBD with MH." The presence of MH at the time of the Brief Assessment of Cognition in Schizophrenia (BACS, described below) was evaluated by a trained physician and psychologist (YS and UA) in a semi-structured interview, using a questionnaire according to previous reports [5, 11]. We investigated the timing of MH occurrence (based on the previously described report [11]), and classified patients into three groups: daytime MH, arousal MH, or both daytime and

arousal MH. All patients had normal or corrected-to-normal vision. Furthermore, we administered a noise pareidolia test. Pareidolic responses to 32 images without a face were scored (maximum score, 32)[33] and the cut-off score was defined as ≥ 2 (in accordance with that in a PD study [10]). The severity of VH and MH at baseline and during follow-up was retrospectively assessed by the authors using the Clinical Global Impressions-Severity (CGI-S) scale [34].

Cognitive function

We evaluated patients' cognitive functions using the following examinations: 1) the Mini-Mental State Examination (MMSE): a screening examination for dementia with a cut-off score of < 24 (maximum score, 30) [35]; 2) Frontal Assessment Battery: a cognitive and behavioral examination with a cut-off score of < 12 (maximum score, 18) that is used to assess frontal lobe functions [36, 37]; 3) Montreal Cognitive Assessment (MoCA): a screening examination for mild cognitive impairment that has a cut-off score of < 23 (maximum score, 30) [38, 39].

Additionally, the Japanese version of the BACS was administered (BACS-J) [40, 41]. The scores in patients with schizophrenia are related to neurocognitive function, including verbal memory, working memory, and executive function [42]. To assess cognitive function in detail, we examined BACS scores in patients with iRBD. The BACS consists of six subsets and a composite score: (1) list learning (verbal memory,

range: 0–75); (2) digit sequencing (working memory, range: 0–28); (3) token motor task (motor speed, range: 0–100); (4) verbal fluency (lexical access and executive control ability, range: 0–without limit) [43]; (5) symbol coding (attention and speed of information processing, range: 0–110); and (6) tower of London (executive functions, range: 0–22) [40]. Normally, the subset and composite scores are compared to the standardized scores of healthy individuals according to sex and age (from 20–79, in 10-year intervals); thus, a z-score of each subset and the composite score can be calculated. As there is no relevant standardized score for patients aged ≥ 80 years, the score for the age group corresponding to 70–79 years was used.

Follow-up visit

All patients visited the hospital every 1–4 months. Follow-up examinations were not blinded, as they were administered by the authors who conducted the semi-structured interviews (YS and AU). When there was an exacerbation of parkinsonism or cognitive decline, we referred the patient to trained neurologists (not the authors) who assessed the patient for PD, DLB, or MSA—which were defined as phenoconversion upon diagnosis. The progression-free survival period was defined as baseline to the date of neurodegenerative disease diagnosis, or "the censoring date" (May 18, 2021). For patients who dropped out during follow-up, the last visit was defined as the censoring date.

Statistical analysis

Continuous variables were summarized as medians and first and third interquartile, and categorical variables were summarized as counts and percentages. For between group comparisons, continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. A one-sample Wilcoxon signed-rank test examined z-scores of the six subset and composite BACS-J scores compared to standardized scores. We used the logistic regression model to calculate the odds ratio (OR) with 95% CI for risks of MH with iRBD. Considering the limited sample size, we conducted multivariate logistic regression after controlling for age and sex. CGI-S scores of VH and MH at baseline and follow-up were compared using the Wilcoxon-signed rank test. Phenoconversion rates were estimated using the Kaplan–Meier method. We applied Cox proportional hazard models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) of developing phenoconversion in the RBD with and without MH groups. Considering results from previous clinical studies on patients with iRBD [44], adjusted covariates were included for the following indices: baseline age, sex, and disease duration. The threshold for statistical significance was set at $p < 0.05$. To evaluate the pairwise differences, effect sizes *r* were calculated and classified into small ($r = 0.1$), medium ($r = 0.3$), and large ($r = 0.5$) effect sizes [45]. All statistical analyses were performed using the R software

package (version 3.3.1; R Development Core Team, Vienna, Austria).

RESULTS

Demographic and clinical characteristics

Figure 2 shows the study flowchart. Ten (27.8%) patients with MH and 26 (72.2%) without MH were included. Eight patients with MH presented with visual illusions, 6 with presence hallucinations, and 3 with passage hallucinations. All of the RBD with MH patients had insights into the MH at baseline. Classification by timing of MH occurrence showed that 5 patients had daytime MH, 2 had arousal MH, and 3 had both daytime and arousal MH. The details of the MH and VH are summarized in Supplemental Table 1.

Table 1 shows baseline demographic and clinical characteristics. Sex or years of education were not significantly different between the two groups. Regarding the motor symptoms, all patients were in Hoehn and Yahr stage 0. Patients with MH were older than those without MH and were more likely to present with VH (40.0% vs. 3.8%, $p = 0.005$). The noise pareidolia test was administered to 23 of 26 patients without MH and 9 of 10 patients with MH. Although the percentage of patients who exceeded the cut-off score (≥ 2) on the pareidolia test was not significantly different between the two groups, the scores were significantly higher in patients with MH with a medium effect size. Although the duration from RBD diagnosis to baseline was not different between

the two groups, the duration from the estimated onset of RBD to baseline was significantly longer in patients with MH ($p = 0.028$). The RBDSQ and OSIT-J scores did not differ between groups. DAT accumulations in the right and left striatum, as well as the average values, were lower in patients with MH with medium effect sizes ($p = 0.019$, 0.040, and 0.025, respectively). Regarding autonomic dysfunction, scores in the cardiovascular, thermoregulatory, and pupillomotor dysfunction domains, and the total score on the SCOPA-AUT were significantly higher in patients with MH with medium or large effect sizes. Although there was no difference in Apathy Scale scores between the two groups, scores on the Beck Depression Inventory Second Edition and Hamilton Rating Scale for Depression were significantly higher in patients with MH with medium effect sizes.

Cognitive function

Cognitive function assessments at baseline are summarized in Table 2. Although MMSE and Frontal Assessment Battery scores did not differ between the two groups, MoCA scores were significantly lower in patients with MH with a large effect size ($p = 0.008$). Therefore, for a detailed assessment of cognitive function, we used the BACS z-scores. In the one-sample Wilcoxon signed-rank test, the z-scores for list learning, digit sequencing, token motor task, and composite z-scores were significantly lower in all patients ($N = 36$) than the standard scores for healthy individuals on the

BACS. Similarly, the results of the one-sample Wilcoxon signed-rank test revealed that the z-scores for list learning were significantly lower in patients without MH. The z-scores for token motor, verbal fluency, and symbol coding were significantly lower in patients with MH; those for verbal fluency and symbol coding were significantly lower in the RBD with MH group than the RBD without MH group with medium effect sizes ($p = 0.040$ and 0.026, respectively).

Factors associated with MH

Table 3 shows the adjusted OR of MH in patients with iRBD. Although the sample size was limited, the following variables were significantly associated with MH after adjusting for age and sex: pareidolia score; disease duration from estimated onset; DAT-SPECT uptake; SCOPA-AUT total score; HAM-D score; MMSE score; MoCA score; verbal fluency raw score; symbol coding raw score; and Tower of London raw score.

Follow-up and phenoconversion

After follow-up (median 2.50 years; first quartile 1.28 and third quartile 2.74 years; a sum of 75.1 years), 5 (13.9%) patients with iRBD developed phenoconversion, and 3 patients (2 with MH and 1 without MH) died due to cancer (Table 1, Figure 2). Of the 5 patients with phenoconversion, 2 converted to PD, 3 to DLB, and 0 to MSA or

other neurodegenerative diseases. The median time to phenoconversion was 6.53 years (first, third quartile: 1.60, 6.67 years) from RBD diagnosis and 10.09 years (first, third quartile: 8.21, 12.53 years) from estimated RBD onset. Although follow-up duration did not differ between patients with and without MH, the promotion of phenoconversion was higher in patients with MH (40.0% vs. 3.8%, $p = 0.005$), primarily related to PD ($p = 0.019$). Additionally, the progression rate to DLB was higher in patients with MH, but not significantly (20.0% vs. 3.8%, $p = 0.116$).

During follow-up, one patient in the RBD without MH group suffered a frontal lobe stroke (he remained iRBD and did not present with MH during follow-up). No other patients met conditions defined in the exclusion criteria during follow-up.

Supplemental Table 2 shows the changes in VH and MH during follow-up in the RBD with MH group. The median CGI-S at baseline was 3.5 (first, third quartile: 3.0, 5.0) and at follow-up it was 4.0 (first, third quartile: 3.3, 6.0), with a significant exacerbation during the follow-up period ($p = 0.020$). In the RBD with MH at baseline group, CGI-S worsened in the two patients who progressed to DLB, while CGI-S remained the same in the two patients who progressed to PD.

Meanwhile, of the 26 in the RBD without MH group, four presented with MH during follow-up (Supplemental Table 3). In addition, one patient who presented with MH was subsequently diagnosed with DLB.

Supplemental Tables 4-5 summarize the clinical characteristics of patients

classified according to the timing of MH occurrence and their progression to phenoconversion. Although we did not perform any statistical analysis due to the limited sample size, 20% of patients with daytime MH, 67% with arousal MH, and 50% with both daytime and arousal MH progressed to phenoconversion.

Risk of neurodegenerative diseases

Kaplan-Meier survival curves and log-rank tests revealed that RBD with MH was associated with phenoconversion ($p = 0.005$, Figure 3); however, iRBD with VH was not ($p = 0.077$, Supplemental Figure 1). An unadjusted Cox regression model showed that the risk of phenoconversion was related to MH (Table 3; HR, 11.94; 95%CI, 1.33–107.0; $p = 0.027$). The increased risk of phenoconversion in RBD with MH was significant, even after adjusting for the following factors: age at baseline and sex (model 1 in Table 3; HR, 12.27); age at baseline, sex, and disease duration from diagnosis of RBD to baseline (model 2; HR, 14.72); age at baseline, sex, and disease duration from estimated onset of RBD to baseline (model 3; HR, 11.15). However, Cox regression models showed that the risk of phenoconversion was not significantly related to VH (Supplemental Table 6).

DISCUSSION

This preliminary retrospective cohort study reveals the potential to improve

phenoconversion prediction ability, allowing for enhanced management and care in patients with iRBD. This is the first study to investigate MH in patients with iRBD. MH were present in 27.8% (10/36) of patients with iRBD. This rate is acceptable considering that 42% of patients with PD have MH [5], and that MH tend to appear before the onset of parkinsonism [7]. Patients with MH tended to be older and have a longer duration from estimated onset of RBD, lower DAT accumulation, more severe autonomic dysfunction, more depressive symptoms, and lower cognitive function compared to patients without MH (Tables 1, 2). At a median follow-up period of 2.50 years, 40% of patients with MH progressed to phenoconversion, whereas only 3.8% of patients without MH progressed to phenoconversion ($p = 0.005$). MH at baseline was a risk factor for phenoconversion after adjustment for age and sex (HR, 12.27; 95%CI 1.22–123.5: $p = 0.033$). Furthermore, after adjustment for disease duration from RBD diagnosis to baseline or disease duration from estimated RBD onset to baseline, MH was still a significant risk factor for phenoconversion (Table 4). In a previous study, 33% of patients with PD and MH reported experiencing MH 7 months to 8 years before the onset of parkinsonism, suggesting that MH could be a precursor to PD [5]. Despite the problem with the limited sample size, the present study demonstrated that MH is a risk factor for early phenoconversion in iRBD. Remarkably, VH was not a significant risk factor for early phenoconversion (Supplemental Table 6).

Factors found to be possibly associated with MH—including long disease

duration from estimated onset, score of pareidolia test, low DAT-SPECT accumulation, severe autonomic dysfunction, depressive symptoms, and cognitive impairment (Table 3)—may reflect the widespread distribution of Lewy bodies in the brain. Patients with MH had lower scores in the verbal fluency and symbol coding tests of the BACS (suggesting impaired attention and executive function), consistent with cognitive domains that are likely to be impaired in DLB or PD with dementia [46].

Regarding the question of what MH indicate in patients with iRBD, the present study suggests two possibilities: 1) RBD with MH is potentially more progressive in neurodegeneration than RBD without MH; and 2) RBD with MH may be a subtype of iRBD with a malignant phenotype.

In support of the first hypothesis, patients with MH were older with a longer disease duration, lower DAT accumulation, more cognitive impairment, and more severe autonomic dysfunction. In RBD, DAT accumulation, cognitive function, and autonomic function are expected to deteriorate over time. Therefore, patients with RBD and MH can be considered a group in which neurodegeneration has progressed further compared to patients without MH. There were no significant differences in RBDSQ scores between the longer/shorter disease duration groups (RBD with/without MH), which is consistent with the findings that symptom frequency of RBD peaks after 2–8 years of disease duration, after which the frequency decreases [47]. Among the RBD without MH group (at baseline), one patient presented MH and was subsequently diagnosed with

DLB during follow-up (Supplemental Table 3). From a different perspective, all five patients who progressed to phenoconversion presented with MH before phenoconversion. Additionally, the severity of symptoms in patients with RBD with MH at baseline deteriorated during follow-up (Supplemental Tables 1-2). These trends in MH appearance and exacerbation support the possibility that MH is a symptom reflecting the neurodegenerative process and an early manifestation of PD and DLB symptoms.

The other hypothesis is that RBD with MH is a malignant subtype of RBD with worse clinical features and higher risk of early phenoconversion. Indeed, the HR of phenoconversion was still significant after adjusting for disease duration (Table 3), supporting this second possibility. In PD, subtypes with different clinical manifestations have been recognized [48]. Merola et al. classified PD into slow progressive (benign PD) and rapidly progressive (malignant PD) types, and reported higher prevalence of depression, hallucinations, autonomic dysfunction, and RBD in malignant PD. Genetic factors may explain subtypes of PD, *e.g.*, glucocerebrosidase mutations are associated with more severe motor symptoms, cognitive impairment, psychiatric symptoms, and complications of RBD [49]. Additionally, VH, RBD, and cognitive impairment are considered risk factors for each other in patients with PD, and cholinergic dysfunction confirmed by neuroimaging is considered an underlying factor [50]. Moreover, PD with MH may form a subtype in PD, and it has been reported to cause severe non-motor

symptoms, including depression [1, 51]. The clinical features of RBD with MH in this study, such as worse depression and autonomic dysfunction, are consistent with the features of PD with MH. Considering a rapidly progressive malignant subtype of PD with a high prevalence of hallucinations or psychiatric symptoms, RBD with MH may be a malignant subtype of RBD. However, we did not investigate associations with glucocerebrosidase mutations or neuroimaging in this study; thus, the relationship remains unclear.

In both hypotheses, the finding that MH is a possible risk factor for early phenoconversion is clinically meaningful. The risk factors for phenoconversion in iRBD have been investigated in extensive multicenter studies [15]. MH may be an additional risk factor for phenoconversion. It can be assessed by interview alone, without the need for invasive testing. Therefore, it would be clinically valuable if MH could be used to estimate the risk of phenoconversion. In the future, the selection of patients for clinical trials of neurodegeneration-modifying therapies would benefit from MH screening. Interestingly, VH was revealed not to be a significant risk factor for phenoconversion (Supplemental Table 2). This is due to a lack of statistical power (VH was observed in 5/36 cases), and VH is considered less prevalent than MH in iRBD. Hence, it is more clinically appropriate to consider MH rather than VH as a risk factor for phenoconversion.

This is the first report investigating BACS performance in patients with iRBD.

The BACS provides a detailed evaluation of different cognitive functions according to six subsets. Since data on standard scores by age are available, the effect of age can be considered by calculating z-scores. In this study, by administering the BACS to patients with iRBD, we identified the characteristics of cognitive impairment in iRBD. We showed that patients with RBD and MH had lower verbal fluency and symbol coding tests scores with medium effect sizes (Table 2), suggesting impaired attention and executive function. The BACS may be helpful for a detailed assessment of cognitive impairment because subscales can be assessed individually and effects of age can be controlled for. However, standardized data are not available for patients over 80 years; thus, data from the age group corresponding to 70–79 years were used for three patients aged 80 years or older in this study and this may have resulted in low z-scores.

The possibility that frontal dysfunction is related to MH occurrence has been previously investigated. In a study of the noise pareidolia test in patients with PD, an increase of frontal low-alpha spectral power and network alterations were observed before stimulus presentation [10]. This suggests an overdependence on the top-down modulation in processing ambiguous visual information delivered from the bottom-up process; therefore, patients with PD require more time to respond to pareidolia tests and tend to experience misperceptions [9]. The impaired attention and executive function demonstrated by the BACS scores in the RBD with MH group in this study are suggestive of frontal dysfunction that may lead to MH.

This study presents future research topics related to the presence/absence of MH and other aspects of MH. First, it may be helpful to investigate whether the pathological significance differs according to the type of MH, timing of MH occurrence (daytime or arousal), and MH frequency. Although we did not perform statistical analysis due to the limited sample size in this study (Supplemental Tables 5-6), the different timing of MH occurrence may reflect different pathologies. The second topic is MH exacerbation in follow-up—during which the frequency of MH or VH increased, and the insight maintained at baseline often became insufficient (Supplemental Table 2). Insufficient insight into psychiatric symptoms may seriously hamper the patient's decision-making ability and needs to be examined. However, it should be noted that patients' recall and abilities to verbalize experiences pose limitations on MH research.

This preliminary study has some limitations. First, it had a limited sample size and follow-up period, precluding definitive conclusions. Due to the short follow-up period, progression to phenoconversion was observed in only five patients. Therefore, it is necessary to consider that the statistical analysis, including the log-rank test and Cox proportional hazards analysis, was performed within a preliminary investigation. Second, although two raters (YS and UA) assessed the presence of VH or MH in a semi-structured interview, patient reports of VH or MH were dependent on patient recall, which may have been biased. In addition, although the diagnosis of phenoconversion was made by non-authors, follow-up examinations by the authors had potential for rater

bias. In MH surveys, it may be helpful to apply a combination of recall-independent tools (e.g., the noise pareidolia test) and semi-structured interviews. Third, the symptoms of MH in this study may not all be derived from Lewy body pathology. A previous study reported that half of all healthy individuals who have lost their spouse experience hallucinations or illusions of the deceased person [52]. However, none of the 10 patients with RBD and MH reported VH or MH related to a deceased spouse, and the result that the noise pareidolia test score was higher in patients with MH than in those without MH (Table 1) supports the assumption that the MH in this study were illusions of perception that commonly occur in Lewy body disease. The single-center design is another limitation of this study. The clinical characteristics of RBD with MH and the risk of phenoconversion following MH need to be validated by future, multi-center prospective studies with larger sample sizes and longer follow-up periods.

In conclusion, 28% of patients with RBD presented with MH. Participants with RBD with MH had higher rates of phenoconversion than those without MH, and our study indicated that MH might be a risk factor for early phenoconversion. Although the sample size was limited, results suggest that MH may potentially be utilized as early clinical markers for prodromal estimation of PD or DLB symptoms.

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Tables:

Table 1 ***Demographic data of patients with isolated RBD with and without MH***

	All N=36	RBD without MH N=26	RBD with MH N=10	p	effect size (r)
Age, years [median (1^{st},3^{rd} quartiles)]	75.0 (70.2, 77.9)	74.2 (68.3, 77.5)	77.8 (74.9, 79.2)	**0.034**	0.309
Female [n (%)]	4 (11.1%)	2 (7.7%)	2 (20.0%)	0.293	
Education, years [median (1^{st},3^{rd} quartiles)]	13.5 (12.0, 16.0)	14.5 (12.0, 16.0)	12.0 (12.0, 15.5)	0.239	0.214
Minor hallucinations [n (%)]	10 (27.8%)	-	10 (100%)		
Visual illusions	8 (22.2%)	-	8 (80.0%)		
Presence hallucinations	6 (16.7%)	-	6 (60.0%)		
Passage hallucinations	3 (8.3%)	-	3 (30.0%)		
Visual hallucinations [n (%)]	5 (13.9%)	1 (3.8%)	4 (40.0%)	**0.005**	
Pareidolia test [median (1^{st},3^{rd} quartiles)] †	0.0 (0.0, 5.3)	0.0 (0.0, 3.0)	6.0 (0.0, 9.0)	**0.035**	0.417
Pareidolia score ≥2 [n (%)]†	12 (37.5%)	7 (30.4%)	5 (55.5%)	0.187	
Duration from diagnosis, years [median (1^{st},3^{rd} quartiles)]	2.36 (0.44, 4.54)	1.72 (0.47, 4.10)	3.98 (0.33, 6.33)	0.764	0.099
Duration from onset, years [median (1^{st},3^{rd} quartiles)]	5.23 (3.11, 8.86)	4.76 (3.07, 6.73)	9.76 (4.06, 11.02)	**0.028**	0.412
Follow-up duration, years [median (1^{st},3^{rd} quartiles)]	2.50 (1.28, 2.74)	2.52 (1.69, 2.78)	2.50 (0.59, 2.69)	0.397	0.190

RBDSQ-J [median (1^{st},3^{rd} quartiles)]	5.0 (2.8, 7.0)	5.0 (2.3, 7.0)	4.5 (3.0, 5.8)	0.957	0.002
RBDSQ score ≥ 5 [n (%)]	19 (52.8%)	14 (53.8%)	5 (50.0%)	0.836	
OSIT-J [median (1^{st},3^{rd} quartiles)]	3.0 (2.0, 5.0)	4.5 (2.8, 5.3)	2.0 (2.0, 4.3)	0.187	0.190
OSIT score < 6 [n (%)]	26 (76.5%)	18 (75.0%)	8 (80.0%)	0.754	
OSIT score < 4 [n (%)]	18 (52.9%)	11 (45.8%)	7 (70.0%)	0.198	
DAT-SPECT uptake specific binding ratio [median (1^{st},3^{rd} quartiles)]					
Striatum (Right)	3.81 (3.25, 4.65)	4.20 (3.60, 4.82)	3.24 (2.89, 3.78)	**0.019**	0.376
Striatum (Left)	3.81 (3.19, 4.70)	4.33 (3.56, 4.80)	3.13 (2.64, 3.93)	**0.040**	0.355
Striatum (Average)	3.93 (3.14, 4.72)	4.22 (3.51, 4.76)	3.13 (2.82, 3.85)	**0.025**	0.368
SCOPA-AUT [median (1^{st},3^{rd} quartiles)]					
Gastrointestinal	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	4.5 (1.5, 5.8)	0.072	0.398
Urinary	5.0 (2.0, 7.0)	4.0 (2.0, 6.0)	6.5 (3.5, 8.5)	0.090	0.368
Cardiovascular	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.5 (0.0, 2.0)	**0.015**	0.415
Thermoregulatory	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	1.5 (1.0, 2.8)	**< 0.001**	0.660
Pupillomotor	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.8)	**0.041**	0.428
Sexual	0.0 (0.0, 0.5)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.775	0.067
Total score	8.0 (5.0, 12.0)	7.0 (5.0, 9.0)	17.0 (8.0, 17.0)	**0.024**	0.480
HAM-D [median (1^{st},3^{rd} quartiles)]	1.0 (0.0, 5.0)	0.5 (0.0, 2.8)	4.5 (2.5, 8.0)	**0.003**	0.460

BDI-II [median (1^{st},3^{rd} quartiles)]	6.5 (2.0, 11.3)	5.0 (2.0, 7.8)	11.0 (7.0, 13.5)	**0.030**	0.336
Apathy scale [median (1^{st},3^{rd} quartiles)]	13.0 (6.8, 18.3)	13.5 (6.3, 17.5)	12.0 (9.0, 18.5)	0.901	0.052
Apathy scale score ≥ 16 [n (%)]	11 (30.6%)	8 (30.8%)	3 (30.0%)	0.964	
Phenoconversion [n (%)]	5(13.9%)	1 (3.8%)	4 (40.0%)	**0.005**	
Parkinson's disease	2 (5.6%)	0 (0%)	2 (20.0%)	**0.019**	
Dementia with Lewy bodies	3 (8.3%)	1 (3.8%)	2 (20.0%)	0.116	

Bold text represents statistical significance ($p < 0.05$).

Effect sizes (*r*) are shown for pairwise difference.

† Because of missing data, N = 32 in All; N = 23 in RBD without MH; N = 9 in RBD with MH.

Abbreviations: BDI-II, the Beck Depression Inventory- Second Edition; DAT-SPECT, dopamine-transporter single-photon emission tomography; HAM-D, the Hamilton Rating Scale for Depression; MH, minor hallucinations; OSIT-J, the Odor Stick Identification Test for the Japanese Population; RBD, rapid eye movement sleep behavior disorder; RBDSQ-J, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire- Japanese Version; SCOPA-AUT, the Scale for Outcomes in Parkinson's Disease-Autonomic.

Table 2 ***Cognitive assessment of patients with isolated RBD with and without minor hallucinations at baseline***

	All N=36	RBD without MH N=26	RBD with MH N=10	p	effect size (r)
MMSE [median (1^{st},3^{rd} quartiles)]	29.0 (27.0, 30.0)	29.0 (28.3, 30.0)	25.5 (25.0, 29.8)	0.061	0.420
MMSE score < 24 [n (%)]	2 (5.6%)	1 (3.8%)	1 (10.0%)	0.470	
FAB [median (1^{st},3^{rd} quartiles)]	16.0 (14.8, 17.0)	16.0 (15.0, 17.0)	15.5 (14.0, 16.0)	0.132	0.255
FAB score < 12 [n (%)]	1 (2.8%)	1 (3.8%)	0 (0.0%)	0.529	
MoCA [median (1^{st},3^{rd} quartiles)]	24.5 (23.0, 26.0)	25.5 (24.0, 27.0)	22.5 (21.0, 24.8)	**0.008**	0.506
MoCA score < 23 [n (%)]	6 (16.7%)	1 (3.8%)	5 (50.0%)	**< 0.001**	
BACS, raw score [median (1^{st},3^{rd} quartiles)]					
List Learning	33.0 (28.0, 37.0)	34.0 (29.3, 37.8)	29.0 (25.5, 34.8)	0.179	0.189
Digit Sequencing	18.0 (15.0, 20.3)	18.0 (15.3, 20.8)	17.0 (15.3, 19.0)	0.595	0.143
Token Motor	49.0 (39.5, 56.5)	51.0 (42.0, 59.5)	43.5 (34.0, 49.5)	0.093	0.251
Verbal Fluency	39.0 (32.8, 46.5)	42.0 (35.5, 52.0)	34.0 (30.0, 38.3)	**0.024**	0.382
Symbol Coding	43.0 (37.8, 51.3)	46.0 (41.3, 53.5)	38.5 (30.3, 41.3)	**0.013**	0.424
Tower of London	16.0 (15.0, 17.3)	17.0 (15.0, 18.0)	15.0 (12.5, 16.8)	0.063	0.415
BACS, z-score [median (1^{st},3^{rd} quartiles)]					

List Learning	-0.660 (-1.040, -0.180) **	-0.560 (-0.895, -0.180) *	-0.885 (-1.218, -0.557)	0.216	0.185
Digit Sequencing	-0.380 (-1.067, 0.357) *	-0.380 (-1.050, 0.440)	-0.590 (-1.145, -0.060)	0.524	0.140
Token Motor	-0.400 (-0.953, 0.013) *	-0.270 (-0.890, 0.215)	-0.795 (-1.505, -0.172) *	0.142	0.236
Verbal Fluency	-0.440 (-0.895, 0.128) *	-0.320 (-0.823, 0.390)	-0.770 (-1.140, -0.470) *	**0.040**	0.346
Symbol Coding	-0.050 (-0.522, 0.377)	0.175 (-0.365, 0.827)	-0.365 (-1.107, -0.117) *	**0.026**	0.392
Tower of London	0.170 (-0.200, 0.480)	0.330 (-0.030, 0.555)	-0.030 (-0.520, 0.260)	0.092	0.354
Composite z-score	-0.435 (-0.980, 0.185) *	-0.115 (-0.777, 0.195)	-0.890 (-1.085, -0.492)	0.116	0.321

Bold text represents statistical significance ($p < 0.05$).

Effect sizes (*r*) are shown for pairwise difference.

* $p < 0.05$ in one-sample Wilcoxon signed-rank test

** $p < 0.01$ in one-sample Wilcoxon signed-rank test

Abbreviations: BACS, the Brief Assessment of Cognition in Schizophrenia; FAB, Frontal Assessment Battery; MH, minor hallucinations; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RBD, rapid eye movement sleep behavior disorder

Table 3 ***Association between patient features and minor hallucinations***

	Unadjusted			Multivariable adjusted		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Pareidolia score	1.022	0.876 to 1.191	0.785	1.257	1.007 to 1.569	**0.044**
Duration from diagnosis (years)	0.881	0.742 to 1.047	0.150	1.119	0.870 to 1.440	0.382
Duration from onset (years)	0.970	0.915 to 1.028	0.300	1.171	1.002 to 1.368	**0.047**
DAT-SPECT uptake specific binding ratio (Striatum average)	0.755	0.623 to 0.913	**0.004**	0.385	0.163 to 0.909	**0.029**
RBDSQ-J score	0.857	0.745 to 0.985	**0.030**	0.960	0.739 to 1.247	0.757
OSIT-J score	0.803	0.670 to 0.964	**0.019**	0.768	0.557 to 1.060	0.108
SCOPA-AUT total score	0.988	0.937 to 1.043	0.669	1.244	1.038 to 1.491	**0.018**
HAM-D score	1.021	0.893 to 1.167	0.761	1.302	1.040 to 1.631	**0.021**
BDI-II score	0.966	0.900 to 1.037	0.343	1.127	0.985 to 1.289	0.082

Apathy scale score	0.947	0.899 to 0.997	0.037	1.001	0.902 to 1.111	0.986
MMSE score	0.964	0.939 to 0.990	**0.007**	0.681	0.498 to 0.931	**0.016**
FAB score	0.937	0.894 to 0.983	**0.007**	0.686	0.458 to 1.028	0.068
MoCA score	0.958	0.929 to 0.987	**0.005**	0.619	0.428 to 0.897	**0.011**
BACS						
List learning raw score	0.970	0.948 to 0.992	**0.007**	0.923	0.834 to 1.020	0.116
Digit sequencing raw score	0.947	0.909 to 0.986	**0.008**	0.891	0.748 to 1.061	0.194
Token motor raw score	0.979	0.964 to 0.994	**0.006**	0.950	0.894 to 1.010	0.100
Verbal fluency raw score	0.973	0.955 to 0.991	**0.004**	0.888	0.802 to 0.984	**0.024**
Symbol coding raw score	0.974	0.958 to 0.991	**0.003**	0.898	0.818 to 0.985	**0.023**
Tower of London raw score	0.928	0.884 to 0.975	**0.003**	0.732	0.541 to 0.991	**0.043**
Composite z-score	0.826	0.472 to 1.448	0.505	0.752	0.381 to 1.484	0.412

The association between patient features and MH is shown in the logistic regression model, adjusted for age and sex

in the multivariable adjusted model. For the BACS composite z-score, the multivariable adjusted model is adjusted

for sex.

Bold text represents statistical significance ($p < 0.05$).

Abbreviations: BACS, the Brief Assessment of Cognition in Schizophrenia; BDI-II, the Beck Depression Inventory-Second Edition; DAT-SPECT, dopamine-transporter single-photon emission tomography; FAB, Frontal Assessment Battery; HAM-D, the Hamilton Rating Scale for Depression; MH, minor hallucinations; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; OSIT-J, the Odor Stick Identification Test for the Japanese population; RBD, rapid eye movement sleep behavior disorder; RBDSQ-J, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire- Japanese Version; SCOPA-AUT, the Scale for Outcomes in Parkinson's Disease-Autonomic.

Table 4 ***Hazard ratios for development of neurodegenerative diseases in patients with isolated RBD with minor hallucinations***

	Hazard ratio	95% CI	p
Unadjusted	11.94	1.33 to 107.0	**0.027**
Model 1	12.27	1.22 to 123.5	**0.033**
Model 2	14.72	1.35 to 160.5	**0.027**
Model 3	11.15	1.13 to 110.5	**0.039**

Bold text represents statistical significance ($p < 0.05$).

Model 1: adjusted for age at baseline, sex

Model 2: adjusted for age at baseline, sex, disease duration from diagnosis of RBD to baseline

Model 3: adjusted for age at baseline, sex, disease duration from estimated onset of RBD to baseline

Abbreviations: CI, confidence interval; RBD, rapid eye movement sleep behavior disorder.

Figure legends

Figure 1. ***Illustrations of minor hallucinations***

These illustrations represent examples of minor hallucinations.

(1) Visual illusions: To the patient, the clothes look as if they are a person for a while.

(2) Presence hallucinations: The patient feels as if someone is next to her.

(3) Passage hallucinations: The patient sees a black shadow pass by in his peripheral vision, though when he turns around, he finds that nothing is there.

Figure 2. ***Flowchart of patient enrollment and follow-up***

Follow-up periods are shown as median (first, third quartiles) or mean ± standard deviation.

Abbreviations: DLB, dementia with Lewy bodies; iRBD, isolated rapid eye movement sleep behavior disorder; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder

Figure 3. ***Kaplan–Meier survival curves of patients with isolated RBD with and***

without MH

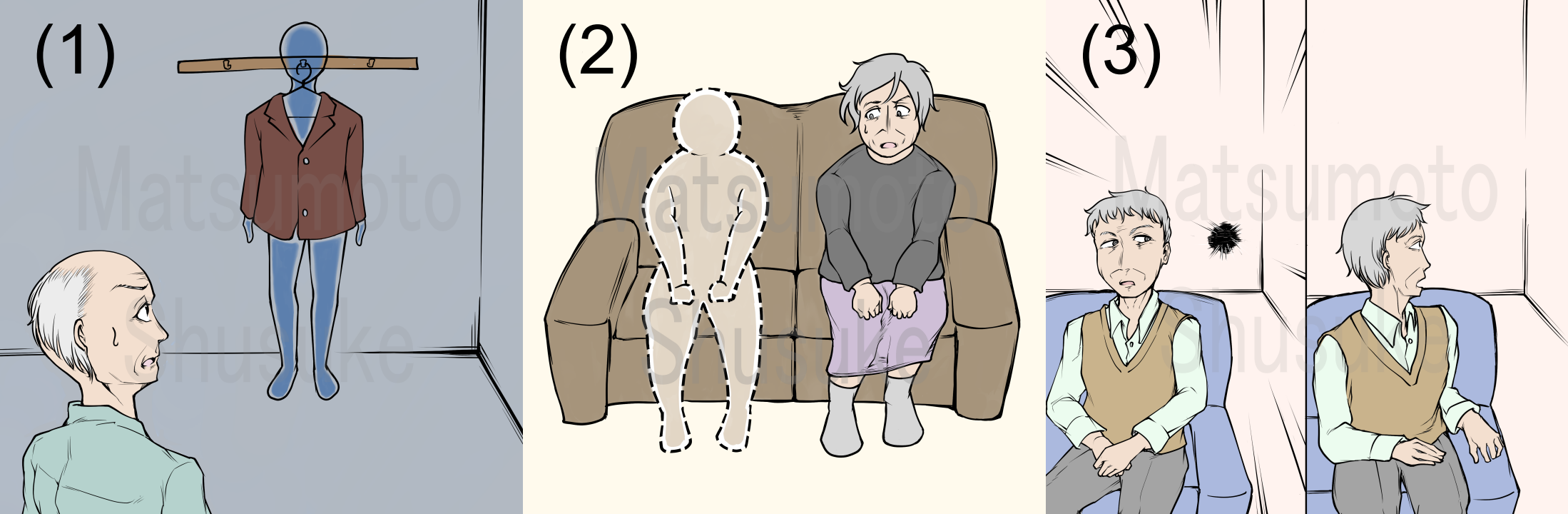
Cumulative risk of developing phenoconversion for patients with and without isolated RBD. The number of at-risk patients at each time point is presented below the horizontal axis.

Abbreviations: CI, confidence intervals; HR, hazard ratio; MH, minor hallucinations; RBD, rapid eye movement sleep behavior disorder

Supplemental Figure 1 ***Kaplan–Meier survival curves in patients with isolated iRBD with and without VH***

Cumulative risk of developing phenoconversion in patients with isolated iRBD with and without VH. The number of at-risk patients at each time point is presented below the horizontal axis.

Abbreviations: CI, confidence intervals; HR, hazard ratio; iRBD, idiopathic rapid eye movement sleep behavior disorder; VH, visual hallucinations


(1)
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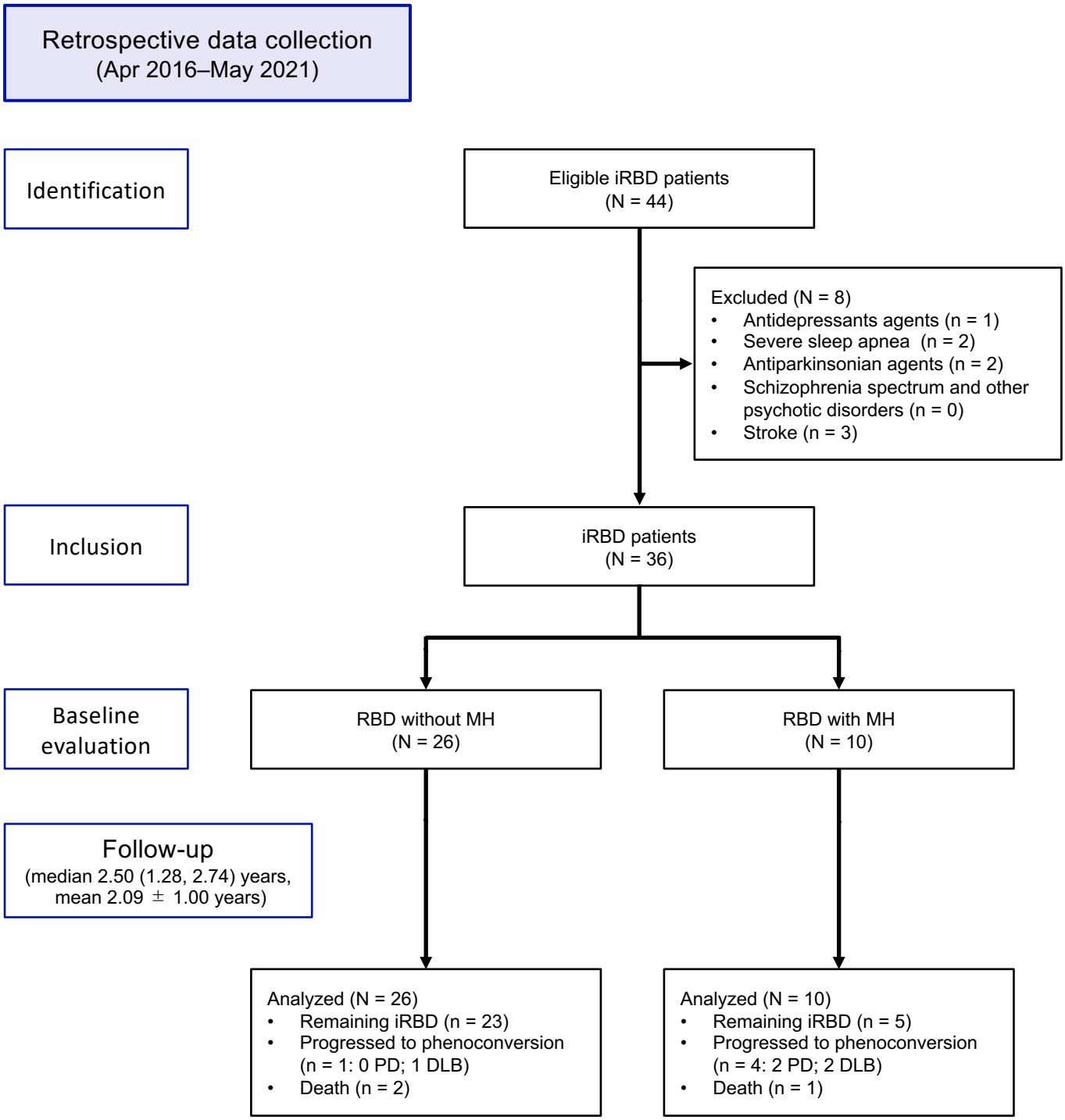
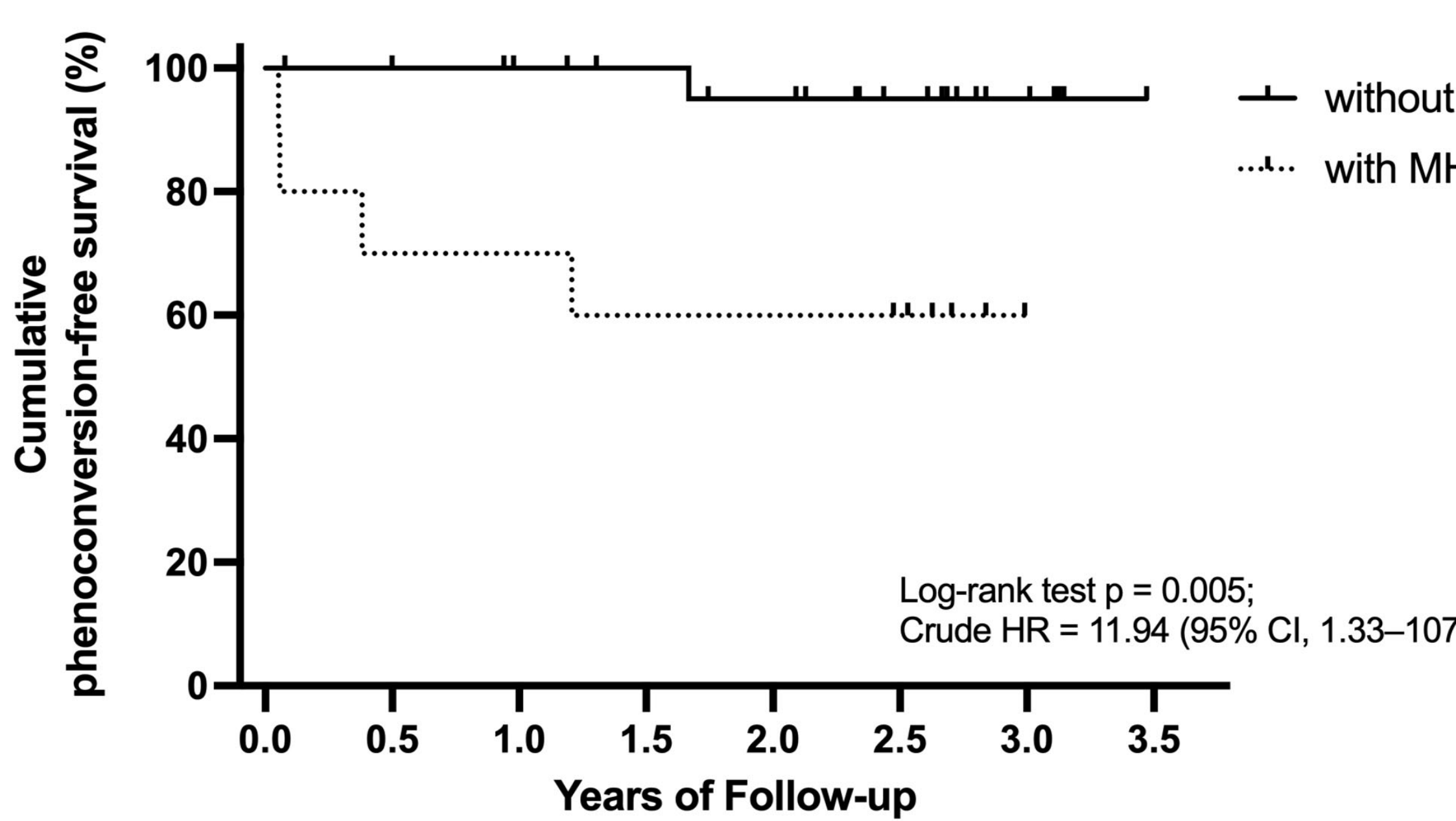

Retrospective data collection
(Apr 2016–May 2021)
Identification
Eligible iRBD patients
(N = 44)
Excluded (N = 8)
• Antidepressants agents (n = 1)
• Severe sleep apnea (n = 2)
• Antiparkinsonian agents (n = 2)
• Schizophrenia spectrum and other psychotic disorders (n = 0)
• Stroke (n = 3)
Inclusion
iRBD patients
(N = 36)
Baseline evaluation
RBD without MH
(N = 26)
RBD with MH
(N = 10)
Follow-up
(median 2.50 (1.28, 2.74) years,
mean 2.09 ± 1.00 years)
Analyzed (N = 26)
• Remaining iRBD (n = 23)
• Progressed to phenoconversion (n = 1: 0 PD; 1 DLB)
• Death (n = 2)
Analyzed (N = 10)
• Remaining iRBD (n = 5)
• Progressed to phenoconversion (n = 4: 2 PD; 2 DLB)
• Death (n = 1)



nber at risk

out MH	26	24	22	20	18	13	5	0
MH	10	7	7	6	6	5	0	0

Supplemental Table 1: Details of misperceptions of RBD with MH at baseline.

Patient	Age	Sex	CGI-S	Kind of false perception (timing of occurrence)	Description
RBD with MH #1	75	M	6	Visual hallucination (daytime and arousal)	He saw someone standing beside him during daytime. He saw someone lying in a room during night.
				Visual illusions (daytime and arousal)	To him, the hanging clothes looked as if they were adults or children; however, when he looked closer, he quickly realized that they were just clothes.
				Presence hallucinations (daytime and arousal)	He felt as if someone was next to him during daytime and midnight.
				Passage hallucinations (daytime and arousal)	He saw something like a black shadow or a mass pass by in his peripheral vision two or three times a day; however, there was nothing present when he turned his head.
RBD with MH #2	78	F	5	Visual hallucination (arousal)	She often saw her granddaughter toweling her hair in the living room when she awoke at night on her way to the restroom. As she looked into what she believed to be her granddaughter's face, the shape disappeared, and she realized that it was a hallucination.
				Visual illusions (arousal)	To her, the blanket sometimes looked as if it were a cat. When she looked closer, she realized that it was just a blanket.
				Presence hallucinations (arousal)	She felt as if someone was behind her when she was walking at night.
RBD with MH #3	76	M	3	Visual illusions (daytime)	He saw that there seemed to be a cicada on his pants that were hanging out to dry. However, when he went to look closer, he found that there were no cicadas.

RBD with MH #4	78	F	3	Visual illusions (arousal)	When she woke up during the night, she felt afraid because she saw a bag that looked like a dog. She soon realized that it was a visual illusion.
RBD with MH #5	67	M	5	Visual hallucination (daytime and arousal)	He sometimes saw someone behind a utility pole while driving, but after a while, the person disappeared. When he woke during the night, he saw a woman washing dishes. He was curious and looked closer, and the woman's shape immediately disappeared.
				Visual illusions (daytime and arousal)	He saw that the paper towels looked like creatures for a little while, but a closer look revealed that they were paper towels.
				Presence hallucinations (daytime and arousal)	He sometimes felt as if there were strangers in the room. After looking around and confirming that nobody was in the room, he recognized that it was just his imagination.
RBD with MH #6	80	M	5	Visual hallucination (arousal)	He sometimes saw a young woman lying on his bed at night. After turning on the light, he realized that it was a visual hallucination.
				Visual illusions (arousal)	To him, the grandfather clock sometimes looked like a woman. He looked at it for a while and realized that it was a grandfather clock, but he continued to feel that someone was there and that someone was watching him.
				Presence hallucinations (arousal)	Presence hallucinations occurred simultaneously with the visual illusions described above.
RBD with MH #7	79	M	4	Visual illusions (daytime)	He saw a small hole in the wall that looked like a wriggling worm. To him, the clothing sometimes "looked like a dog," but upon a closer look, he realized that it was just clothing.

				Presence hallucinations (daytime)	He felt that there was someone in the room, but he was aware that it was just his imagination.
				Passage hallucinations (daytime)	He sometimes perceived a mouse running in his peripheral vision without fear. He often experienced passage hallucinations in the corner of a well-lit room.
RBD with MH #8	79	M	3	Visual illusions (daytime)	To him, a vacuum cleaner looked like a little child.
RBD with MH #9	82	M	3	Passage hallucinations (daytime)	He saw a cat running across the right side of the room. He felt strange and went to look in the corner of the room and realized it was just his imagination and that there was no cat.
RBD with MH #10	75	M	3	Presence hallucinations (daytime)	He felt that someone was in the room.

Abbreviations: CGI-S, the Clinical Global Impressions-Severity; MH, minor hallucinations; RBD, rapid eye movement sleep behavior disorder.

***Supplemental Table 2**: Changes in misperceptions during follow-up in RBD with MH at baseline.*

Patient	Age	Sex	Phenoconversion	CGI-S	Description
RBD with MH #1	75	M	DLB	7	Detailed and vivid hallucinations appeared every day, and insight into the visions was no longer maintained. He developed rage and paranoia toward his family related to the hallucinations.
RBD with MH #2	78	F	DLB	6	The frequency of visual hallucinations increased, and whereas before, the visual hallucinations and visual illusions appeared primarily upon arousal, they began to also appear during the daytime. Moreover, sometimes insights of VH were not maintained. Visual hallucinations (daytime and arousal): She saw her deceased mother and her previous cat. She looked at the carpet and mentioned that there was a wriggling worm and tried to remove it. Visual illusions (daytime and arousal): The hats and coats looked like a person.
RBD with MH #3	76	M	PD	3	The MH remained less frequent and insight was maintained.
RBD with MH #4	78	F	PD	3	Visual illusions during arousal continued, but their frequency did not change and insight was maintained.
RBD with MH #5	67	M	Remaining iRBD	6	MH persisted. Insight was maintained, however, the frequency of visual hallucinations gradually increased. (e.g., He saw a person on the roof, but he was aware that it was a hallucination.)
RBD with MH #6	80	M	Remaining iRBD	6	He was occasionally affected by visual hallucinations--for example, he would state that his son was coming to his house—but after a while he realized that they were just hallucinations. Visual illusions rarely occurred anymore.

					He sometimes experienced presence hallucinations, however, insight was maintained.
RBD with MH #7	79	M	Remaining iRBD	4	MH during the daytime persisted, but the frequency did not change much, and insight was maintained.
RBD with MH #8	79	M	Remaining iRBD	4	In addition to visual illusions during the daytime, visual hallucinations and presence hallucinations appeared, but insight was maintained. Visual hallucinations (arousal): He saw bugs in the room, but after a while he realized there were no bugs. Presence hallucinations (daytime): He had a feeling that his son and daughter were nearby.
RBD with MH #9	82	M	Remaining iRBD	4	He died of cancer during the follow-up. Presence hallucinations (daytime) occurred with insight. He sometimes felt as if his wife was on his left. He realized that it was just his imagination after he turned around and noticed that no one was around.
RBD with MH #10	75	M	Remaining iRBD	3	MH occurred with less frequency.

Abbreviations: CGI-S, the Clinical Global Impressions-Severity; DLB, dementia with Lewy bodies; iRBD, isolated rapid eye movement sleep behavior disorder; MH, minor hallucinations; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.

Supplemental Table 3: Changes in misperceptions during follow-up in RBD without MH at baseline.

Patient	Age	Sex	Phenoconversion	CGI-S	Kind of false perception (timing of occurrence)	Description
RBD without MH #1	75	M	DLB	3	Presence hallucinations (daytime)	He sometimes felt the presence of a person nearby. As he stared carefully in the direction of the presence, the sensation of someone's presence disappeared.
RBD without MH #2	74	M	Remaining iRBD	3	Visual illusions (daytime and arousal)	Metamorphopsia, a subtype of visual illusion used to indicate spatial or temporal misperceptions, appeared. Parts of the door and drawer appeared to be distorted or moving. He felt that something was wrong with his vision.
					Presence hallucinations (daytime and arousal)	During daytime, he felt as if someone was nearby, but he could not see anyone. When he went to the restroom at midnight, he sometimes felt as if there was someone nearby.
RBD without MH #3	71	M	Remaining iRBD	3	Visual illusions (arousal)	At night, he saw the flowers in the vase as if it was the cat moving. He looked closer and noticed that it was a flower.
RBD without MH #4	70	M	Remaining iRBD	3	Passage hallucinations (daytime)	At the edge of his vision, he saw a small insect-like shadow moving quickly.

Of 26 patients with RBD without MH, four patients presented with MH during follow-up.

Abbreviations: DLB, dementia with Lewy bodies; iRBD, isolated rapid eye movement sleep behavior disorder; MH, minor hallucinations; RBD, rapid eye movement sleep behavior disorder.

Supplemental Table 4 ***Demographic data of patients with isolated RBD classified according to the timing of minor hallucination occurrence***

	daytime MH	arousal MH	both daytime and arousal MH
	N=5	N=3	N=2
Age, years [median (1^{st},3^{rd} quartiles)]	79.1 (75.5, 79.2)	77.8 (77.8, 79.0)	70.6 (68.6, 72.7)
Female [n (%)]	0 (0.0%)	2 (66.7%)	0 (0.0%)
Education, years [median (1^{st},3^{rd} quartiles)]	16.0 (12.0, 16.0)	12.0 (12.0, 12.0)	13.0 (12.5, 13.5)
Minor hallucinations [n (%)]			
Visual illusions	3 (60.0%)	3 (100%)	2 (100%)
Presence hallucinations	2 (40.0%)	2 (66.7%)	2 (100%)
Passage hallucinations	2 (40.0%)	0 (0.0%)	1 (50.0%)
Visual hallucinations [n (%)]	0 (0.0%)	2 (66.7%)	2 (100%)
Pareidolia test [median (1^{st},3^{rd} quartiles)] †	4.0 (0.0, 8.8)	9.0 (7.5, 10.0)	0.5 (0.3, 0.8)
Pareidolia score ≥ 2, [n (%)] †	2 (50.0%)	3 (100%)	0 (0.0%)
Duration from diagnosis years [median (1^{st},3^{rd} quartiles)]	5.91 (3.84, 6.64)	0.31 (0.26, 0.35)	5.29 (4.70, 5.88)
Duration from onset years [median (1^{st},3^{rd} quartiles)]	9.70 (9.55, 14.77)	19.13 (12.41, 25.86)	11.54 (9.84, 13.23)
Follow-up duration years [median (1^{st},3^{rd} quartiles)]	2.63 (2.53, 2.70)	1.21 (0.63, 2.10)	1.27 (0.66, 1.87)
RBDSQ-J [median (1^{st},3^{rd} quartiles)]	3.0 (3.0, 5.0)	4.0 (3.0, 6.5)	7.0 (6.0, 8.0)
RBDSQ score ≥ 5 [n (%)]	2 (40.0%)	1 (33.3%)	2 (100%)
OSIT-J [median (1^{st},3^{rd} quartiles)]	2.0 (2.0, 5.0)	2.0 (1.0, 5.5)	2.0 (2.0, 2.0)
OSIT score < 6 [n (%)]	4 (80.0%)	2 (66.7%)	2 (100%)
OSIT score < 4 [n (%)]	3 (60.0%)	2 (66.7%)	2 (100%)
DAT-SPECT uptake specific binding ratio [median (1^{st},3^{rd} quartiles)]			
Striatum (Right)	3.39 (2.99, 3.50)	3.08 (2.55, 4.37)	3.40 (2.90, 3.90)
Striatum (Left)	3.33 (2.03, 3.61)	2.70 (2.27, 4.26)	3.28 (2.68, 3.89)
Striatum (Average)	3.16 (3.09, 3.56)	2.89 (2.41, 4.32)	3.35 (2.79, 3.90)

SCOPA-AUT [median (1^{st},3^{rd} quartiles)]			
Gastrointestinal	3.0 (1.0, 4.0)	5.0 (3.0, 5.5)	7.0 (6.0, 8.0)
Urinary	6.0 (3.0, 11.0)	7.0 (4.5, 8.0)	6.0 (5.5, 6.5)
Cardiovascular	0.0 (0.0, 2.0)	1.0 (0.5, 1.5)	1.0 (0.5, 1.5)
Thermoregulatory	1.0 (1.0, 2.0)	1.0 (0.5, 2.0)	2.5 (2.3, 2.8)
Pupillomotor	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	1.5 (1.3, 1.8)
Sexual	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	1.0 (0.5, 1.5)
Total score	11.0 (7.0, 17.0)	17.0 (10.0, 17.0)	19.0 (18.0, 20.0)
HAM-D [median (1^{st},3^{rd} quartiles)]	4.0 (2.0, 5.0)	4.0 (3.0, 6.5)	8.0 (6.5, 9.5)
BDI-II [median (1^{st},3^{rd} quartiles)]	11.0 (6.0, 12.0)	11.0 (6.5, 16.0)	12.0 (11.0, 13.0)
Apathy scale [median (1^{st},3^{rd} quartiles)]	12.0 (12.0, 20.0)	14.0 (8.0, 17.0)	9.0 (7.5, 10.5)
Apathy scale score ≥ 16 [n (%)]	2 (40.0%)	1 (33.3%)	0 (0.0%)
Phenoconversion [n (%)]	1 (20.0%)	2 (66.7%)	1 (50.0%)
Parkinson's disease	1 (20.0%)	1 (33.3%)	0 (0.0%)
Dementia with Lewy bodies	0 (0.0%)	1 (33.3%)	1 (50.0%)

Abbreviations: BDI-II, the Beck Depression Inventory- Second Edition; DAT-SPECT, dopamine-transporter single-photon emission tomography; HAM-D, the Hamilton Rating Scale for Depression; MH, minor hallucinations; OSIT-J, the Odor Stick Identification Test for the Japanese population; RBD, rapid eye movement sleep behavior disorder; RBDSQ-J, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire- Japanese Version; SCOPA-AUT, the Scale for Outcomes in Parkinson’s Disease- Autonomic.

Supplemental Table 5 ***Cognitive assessment of patients with isolated RBD classified according to the timing of MH occurrence at baseline***

	daytime MH N=5	arousal MH N=3	both MH N=2
MMSE [median (1^{st},3^{rd} quartiles)]	25.0 (25.0, 30.0)	26.0 (24.5, 27.5)	27.5 (26.3, 28.8)
MMSE score < 24 [n (%)]	0 (0.0%)	1 (33.3%)	0 (0.0%)
FAB [median (1^{st},3^{rd} quartiles)]	16.0 (14.0, 16.0)	12.0 (12.0, 14.5)	15.5 (15.3, 15.8)
FAB score < 12 [n (%)]	0 (0.0%)	0 (0.0%)	0 (0.0%)
MoCA [median (1^{st},3^{rd} quartiles)]	22.0 (21.0, 25.0)	23.0 (21.0, 23.5)	22.5 (20.8, 24.3)
MoCA score < 23 [n (%)]	3 (60.0%)	1 (33.3%)	1 (50.0%)
BACS, raw score [median (1^{st},3^{rd} quartiles)]			
List Learning	29.0 (29.0, 35.0)	23.0 (22.5, 28.5)	31.0 (28.0, 34.0)
Digit Sequencing	18.0 (16.0, 19.0)	19.0 (17.0, 20.0)	13.0 (12.0, 14.0)
Token Motor	48.0 (46.0, 52.0)	34.0 (34.0, 37.5)	42.0 (38.0, 46.0)
Verbal Fluency	36.0 (36.0, 39.0)	30.0 (30.0, 31.0)	34.0 (30.5, 37.5)
Symbol Coding	39.0 (31.0, 39.0)	38.0 (34.0, 42.0)	36.5 (27.8, 45.3)
Tower of London	15.0 (14.0, 15.0)	16.0 (8.5, 16.5)	9.5 (5.8, 13.3)
BACS, z-score [median (1^{st},3^{rd} quartiles)]			
List Learning	-0.790 (-0.790, -0.050)	-1.650 (-2.080, -1.315)	-0.880 (-1.080, -0.680)
Digit Sequencing	-0.320 (-0.860, -0.060)	-0.060 (-0.650, 0.210)	-1.840 (-2.010, -1.670)

Token Motor	-0.270 (-0.400, -0.010)	-1.250 (-1.525, -1.220)	-1.035 (-1.482, -0.588)
Verbal Fluency	-0.470 (-0.470, -0.240)	-1.730 (-1.730, -1.260)	-0.965 (-1.073, -0.857)
Symbol Coding	-0.320 (-1.040, -0.320)	-0.410 (-1.375, -0.135)	-0.905 (-1.512, -0.297)
Tower of London	-0.030 (-0.220, -0.030)	0.170 (-3.365, 0.315)	-1.150 (-1.870, -0.430)
Composite z-score	-0.680 (-0.800, -0.430)	-0.980 (-2.765, -0.980)	-0.675 (-1.528, 0.177)

Results are presented as median (first, third quartiles) or number (percentage).

Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia; FAB, Frontal Assessment Battery; MH, minor hallucination; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RBD, rapid eye movement sleep behavior disorder

Supplemental Table 6 ***Hazard ratios for the development of neurodegenerative diseases in patients with isolated RBD and visual hallucinations***

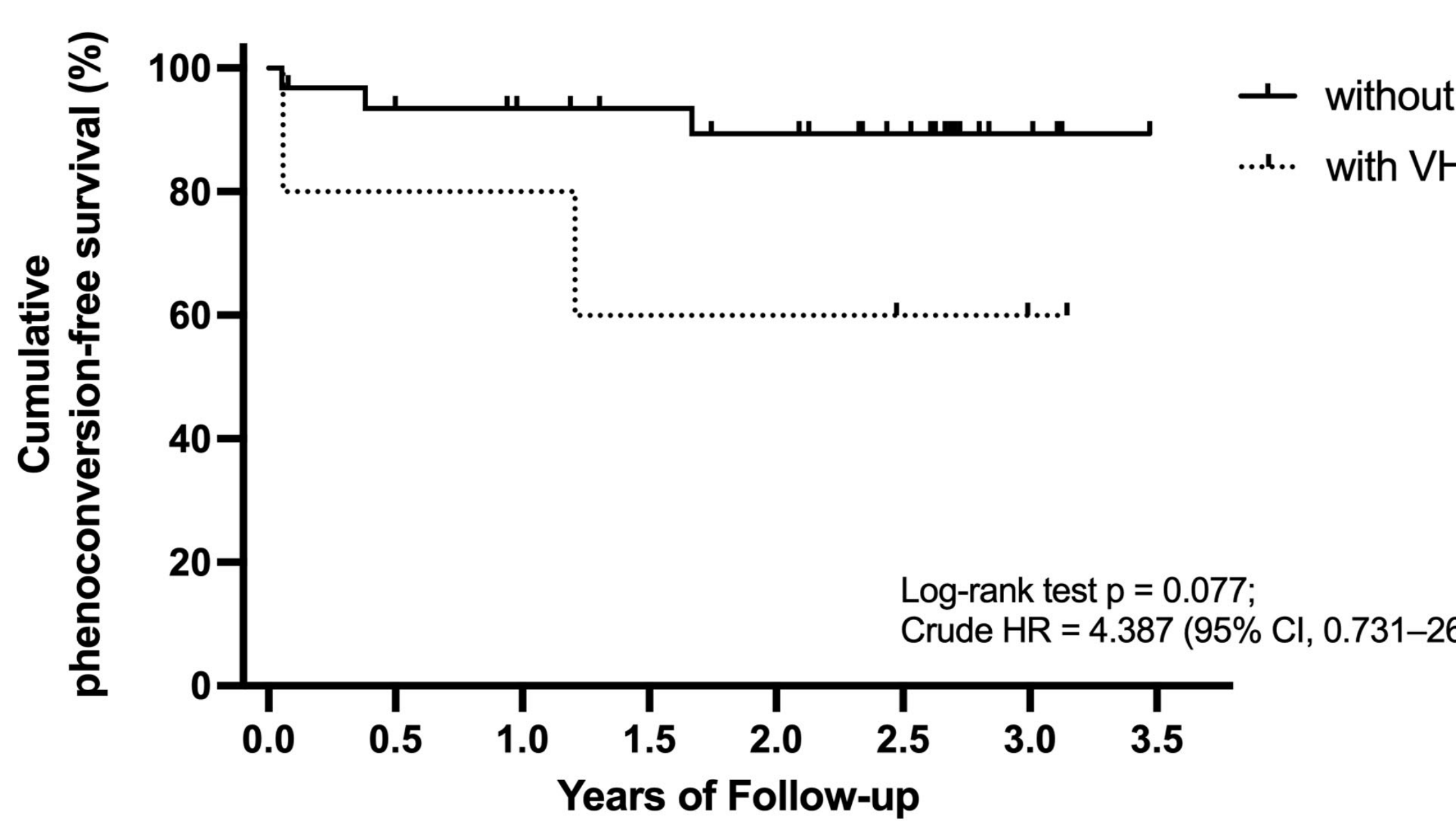
	Hazard ratio	95% CI	p
Unadjusted	4.387	0.731 to 26.31	0.106
Model 1	3.467	0.542 to 22.18	0.189
Model 2	5.340	0.656 to 43.44	0.117
Model 3	4.007	0.641 to 25.04	0.138

Model 1: adjusted for age at baseline, sex

Model 2: adjusted for age at baseline, sex, and disease duration from diagnosis of RBD to baseline

Model 3: adjusted for age at baseline, sex, and disease duration from estimated onset of RBD to baseline

Abbreviations: CI, confidence interval; RBD, rapid eye movement sleep behavior disorder



mber at risk

hout VH	31	27	25	23	21	16	4	0
h VH	5	4	4	3	3	2	1	0