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Physician and patient determinants of prognostic counseling in idiopathic REM sleep-behavior disorder

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ABSTRACT

Objectives/Background: Prognostic counseling about the risk for developing overt neurodegenerative disorders for patients with idiopathic REM sleep-behavior disorder (iRBD) and isolated REM sleep without atonia (iRSWA) is difficult, given lack of disease-modifying interventions and uncertainty in accurate prognostication for individuals. We aimed to analyze patient and physician characteristics associated with documented prognostic discussions for patients with iRBD and iRSWA.

Patients/Methods: We retrospectively reviewed the medical records for 138 (112 iRBD and 26 iRSWA) patients seen at the Mayo Clinic between 2012 and 2015. We analyzed physician and patient demographics, initial complaint, and other information discussed during office visits. We then comparatively analyzed the impact of physician and patient characteristics on documented prognostic discussions using Chi Square or Fischer's exact test.

Results: Mean iRBD patient age was 65.0 ± 13.0, and mean iRSWA age was 58 ± 15 years. Seventy-eight (69.6%) iRBD and 22 (84.6%) iRSWA patients were men. Sixty-two (55%) iRBD and three (12%) iRSWA patients received prognostic counseling about phenoconversion risk. iRBD was a secondary complaint in 67 (59.8%). Patients over age 60 years and those having iRBD as a chief complaint more frequently received prognostic discussions than those with opposite characteristics (all $p < 0.05$). Patient sex and antidepressant use were not associated with counseling. Sleep neurologists disclosed prognostic information most frequently, with male more likely than female clinicians to disclose prognoses.

Conclusions: Several patient and physician characteristics appear to influence documented prognostic counseling for iRBD/RSWA patients. Future studies of iRBD/RSWA patients' preferences are needed to clarify ethically appropriate physician-patient communication concerning prognosis.

Idiopathic rapid eye movement sleep-behavior disorder (iRBD) and its neurophysiologic substrate, polysomnographic REM sleep without atonia (RSWA), have strong associations with synucleinopathy neurodegenerative disorders, especially Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy [1–6]. Several longitudinal cohort studies examining the relationship between iRBD and synucleinopathy suggest that between 38 and 91.9% of iRBD patients can be expected to develop an overt parkinsonian or neurodegenerative disorder within 5–25 years following onset of iRBD symptoms [7,8]. This high risk for eventual phenoconversion suggests that iRBD is a prodromal neurodegenerative process within the brainstem that will likely ascend into more rostral structures in accordance with the Braak hypothesis, resulting in more clinically devastating consequences of cognitive, motor, and/

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or autonomic dysfunction given sufficient longitudinal follow-up [1,9]. Prognostic discussions concerning phenoconversion to an overt neurodegenerative disorder should be considered, to inform iRBD patients of these risks, so that they might prepare for future life planning.

The ethical tensions inherent in iRBD patient counseling include both beneficence and non-maleficence, versus respect for patient autonomy. The ethical principles of beneficence and non-maleficence suggest that given the lack of actionability for RBD prognoses and lack of insight into patient preferences for receiving this relatively bad news, practitioners should consider withholding prognostic counseling. On the other hand, respect for patient autonomy would favor frank disclosure of prognosis, to better enable patient's future life planning, access to early symptomatic treatment during phenoconversion toward overt symptomatic motor, cognitive, and autonomic neurodegenerative disorders, and, possibly, to allow participation in future neuroprotective trials.

Yet, some sleep-medicine clinicians may feel uncomfortable or reluctant to provide prognostic information to iRBD patients concerning neurodegenerative disorders, since there are currently no neuroprotective treatments to prevent or delay progression of neurodegeneration and eventual phenoconversion. Furthermore, it remains uncertain whether practitioners should apply prognostic data derived from sleep-clinic cohorts of iRBD patients, who usually present with violent dream-enactment behaviors, to others who do not fit that profile; for example, when iRBD is discovered as an incidental or secondary issue during evaluation for other sleep disorders [10] or in patients for whom RSWA is only an incidental, isolated polysomnographic (PSG) finding without any clear history of dream enactment [11–13]. Physicians should be mindful that some iRBD patients will value prognostic information for future life planning [14], whereas providing unsolicited prognostic information to others who do not desire risk disclosure may represent possible emotional or psychological harm. For example, physicians, patients, and unaffected family members of patients with heritable neurodegenerative disorders such as Huntington's Disease and autosomal-dominant Alzheimer's disease express varying perspectives on the value of predictive testing despite their high risk for positive screening, given limited actionable treatments for these diseases. In contrast, most physicians and patients alike feel that screening for a potentially modifiable disorder such as the familial breast cancer susceptibility (BRCA) gene should be consistently offered in high risk settings for breast or ovarian cancer (such as a personal history of premature breast or ovarian cancer, or certain high risk positive family history settings), given the substantially higher lifetime risk of breast or ovarian cancer and the potential of enabling life-saving surgical and medical preventative or treatment options [15,16].

Nonetheless, recent studies have demonstrated increased interest in predictive testing for neurodegenerative conditions, specifically genetic testing for PD among individuals having PD [17,18], and almost half of first-degree relatives with a LRRK2 mutation requested counseling regarding disease-prevention strategies and discussion of phenoconversion risk [19]. Additionally, cultural background, socioeconomic status, education, and concerns about insurance eligibility appear to influence patient attitudes towards PD-predictive testing [20]. Given the variability in attitudes towards PD-predictive testing and the general lack of research of attitudes towards PD-predictive testing among populations of unknown risk, physicians frequently find themselves in difficult situations when discussing neurodegenerative disorder prognoses (and the prognoses of phenoconversion in presumably prodromal neurodegenerative disorders such as iRBD) with patients.

To our knowledge, there are no data concerning patient preferences and physician practice in iRBD prognostic counseling. We analyzed iRBD/RSWA patient and sleep physician characteristics associated with the likelihood of a documented prognosis concerning future neurodegenerative phenoconversion in our academic, multidisciplinary sleep-medicine practice.

1. Methods

1.1. Patients

We identified 138 consecutive adult patients between 2012 and 2015 at the Mayo Center for Sleep Medicine who met ICSD-2 diagnoses for idiopathic REM sleep-behavior disorder or who had isolated PSG-confirmed RSWA, as visually determined by a board-certified sleep-medicine physician without quantitative analysis, which our laboratory utilizes solely for research purposes [11,12,21]. Individuals were excluded if they were children or adolescents aged younger than 18 years, or if they previously had a synucleinopathy or symptomatic neurologic disorder diagnosis. We reviewed electronic medical records (EMRs) of these patients for patient and physician demographics, initial complaint, medication use, iRBD/RSWA diagnosis, psychiatric history, polysomnogram results, the presence or absence of completion of an advance directive document (ie, a document which details the patient's preference concerning their future care, including issues relevant to end of life decision making, that is, whether and in which circumstances they would want or not want to receive certain cares such as artificial/intravenous feeding, intubation, mechanical ventilation, or resuscitation), as well as documented prognostic discussions. The Mayo Clinic Institutional Review Board approved this study, and participating patients (or their legally authorized representatives) provided written consent to use their medical information.

1.2. Model of care

All clinicians assessed in this study actively practiced in our subspecialty sleep-medicine clinic between 2012 and 2015 and were board certified in sleep medicine. Our sleep-medicine practice is a multidisciplinary group that includes neurologists, pulmonologists, psychiatrists, and pediatricians, thus providing a naturalistic opportunity to compare the practice habits and relative counseling frequencies concerning iRBD among different types of sleep-medicine clinicians. Our practice model includes an individual comprehensive clinical patient consultation with a sleep-medicine physician before every polysomnogram, detailed review of the PSG and accompanying video by the sleep physician using our standard recording montage (as previously reported) [11,12], as well as an individual follow-up visit the morning after the study to provide results in person and permit a discussion of the plan of care in all cases. Thus, each patient has at least two opportunities to undergo questioning about a history of dream-enactment behavior, which is systematically done in all patients seen in our sleep-medicine clinic both via a standard clinical history-intake form completed by the patient and bed-partner and reviewed by the sleep-medicine practitioner, which has the following dream enacting behavior (DEB)-question format: Have you ever been told that you act out your dreams?, as well as an appropriately tailored clinical interview and examination [22–24]. Following PSG in patients without an intake history of dream enactment, if isolated RSWA is revealed, patients and their bedpartners are subsequently asked about whether they may have dream enactment to ensure whether or not there may be a diagnosis of RBD, vs. isolated RSWA in which dream enactment history, or recorded motor behaviors during PSG, are

absent. Consequently, there are at least two opportunities for prognostic counseling concerning phenoconversion related to iRBD/RSWA to occur and be documented by the sleep clinician.

1.3. Analysis

Statistical analyses used Chi-square or Fisher's exact tests utilizing JMP Statistical Software (Cary, North Carolina).

2. Results

We identified 138 consecutive patients meeting our inclusion criteria, including 114 (82.6%) with iRBD. The iRBD patients had their diagnoses by the following criteria and subgroups: 33 (28.9%) patients had clinical DEBs both by history and captured during video-PSG, with supportive RSWA; 76 (66.7%) had clinical DEBs supported by PSG RSWA, but without recorded DEBs during PSG; and five (4.4%) had no previous known clinical DEB history, and RBD diagnosed only on PSG that recorded DEB and RSWA). Furthermore, 24 (17.4%) patients had isolated RSWA (iRSWA), without clinical history or recording of DEBs. Demographics and clinical characteristics for the overall group, as well as those with iRBD and isolated RSWA, are shown in Table 1. One-hundred patients (73% overall cohort; RBD 70.2%, iRSWA 83.3%) were men, and 38 (27% overall; RBD 29.8%, iRASW 16.7%) were women, aged 19 to 87 (overall mean, 64; RBD 65, iRSWA 57) years. Moreover, 128 patients (93% overall; RBD 92.8%, iRSWA 92.3%) were white, and 10 (7% overall; RBD 7.0%, iRSWA 8.3%) were of other race/ethnicity. In 65% of patients, iRBD/RSWA diagnoses were secondary to the patient's initial sleep complaint, which included sleep apnea (42%), insomnia (7%), excessive daytime sleepiness (10%), or other issues (sleep paralysis or nightmares in 4%). In 33% of cases, iRBD, DEB, or RSWA was documented only after PSG during the follow-up visit. Fifty-two (37.7%) of patients had a psychiatric history of depression and/or an anxiety disorder, and 82 (59.4%) were taking an anti-depressant prior to the PSG. Additionally, 111 patients (80%) were married, and 63 (46%) had an advance directive. Fifty-eight (38%) patients previously or currently had a history of depression, PTSD, or an anxiety disorder.

Neurologists accounted for 71 (51%) of the consults, with other physicians, including pulmonologists, psychiatrists, and pediatricians, comprising the other 67 (49%) sleep-medicine consultants. The study included six neurologists (three women), and 13 non-neurologists (one woman). Neurologists consulted on an average of 11.8 (sd = 7.1) patients, and non-neurologists saw an average of 5.1 (sd = 4.8) patients.

A prognostic discussion concerning phenoconversion risk was documented for only 46% of the overall iRBD/RSWA cases. Sixty-two (55.4%) RBD cases and three (11.5%) iRSWA cases had a documented prognostic discussion concerning phenoconversion. The majority (65%) of documentation reflected that prognostic discussions about iRBD/RSWA occurred during the follow-up visit after PSG, indicating RBD or iRSWA as a secondary finding (61% of RBD cases, 88% of iRSWA cases). The three (13%) cases of iRSWA that had presented with known iRSWA had previously documented RSWA detected on a PSG that had been done elsewhere. Only a small minority (fewer than 5%) of notes documented that the physician offered a specific range for rates of phenoconversion, an approximate timeframe for phenoconversion, a description of specific neurodegenerative disorders, discussion of future life plans, or financial implications of future testing and/or disease management. A reference toward supplying the patient with informational material regarding iRBD, RSWA, or DEB was documented in 15% of cases.

Patient factors and characteristics associated with a greater likelihood of prognostic documentation for phenoconversion risk for the entire cohort were chief/primary vs. incidental/secondary complaint of iRBD (60.1% received prognostic counseling vs. 39.1% did not have documentation for counseling, $p < 0.05$); clinically overt iRBD compared to subclinical, isolated RSWA diagnosis (55.4% counseled vs. 11.5% not counseled, $p < 0.01$); and patient age >60 years (54.3% counseled vs. 33% not counseled, $p < 0.05$; Fig. 1, Table 2). There was no significant difference between men and women in documented prognostic discussions (51% men counseled vs. 37% women counseled, $p = 0.13$), nor in those patients receiving or not receiving antidepressants ($p = 0.83$).

Within the iRSWA subgroup, patient age >60 was associated with a greater likelihood of prognostic documentation for phenoconversion risk (30% vs. 0%, $p < 0.05$).

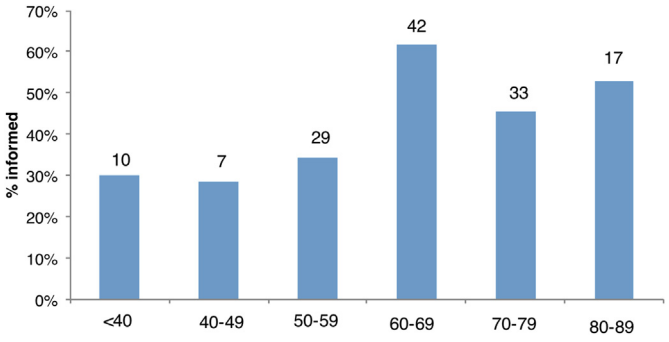

Fig. 1. Prognostic Counseling for Phenoconversion Risk in Patients with Idioapthic REM Sleep Behavior Disorder and REM Sleep without Atonia. Bar area represents percentage of individuals in each age strata that received prognostic discussion. The number above each bar indicates the number of individuals in each age strata.

Table 1
Demographic and clinical characteristics for the overall cohort and subgroups of idiopathic REM sleep behavior disorder and isolated/incidental REM sleep without atonia patients.

	Overall (n = 138)	RBD (n = 114)	iRSWA (n = 24)
Age (years, SD)	64 (13)	64 (14)	65 (12)
Sex [M (%)/F (%)]	100 (73)/38 (27)	81 (71.1)/33 (28.9)	19 (79.1)/5 (20.8)
Race/Ethnicity [White (%)/Other (%)]	128 (93)/10 (7%)	105 (92.1)/9 (7.9)	23 (95.8)/1 (4.2)
Married (%)	111 (80.4)	89 (78.1)	22 (91.7)
Possess an Advance Directive (%)	72 (52.2)	60 (52.6)	12 (50.0)
(+) DEB History (−) PSG DEB (%)	76 (55.1)	76 (66.7%)	0
(+) DEB History (+) PSG DEB (%)	33 (23.9)	33 (28.9)	0
(−) DEB History (−) PSG DEB (%)	24 (17.4)	0	24 (100)
(−) DEB History (+) PSG DEB (%)	5 (3.6)	5 (4.4)	0
Diagnoses Secondary to Initial Sleep Complaint (%)	90 (65.2%)	69 (60.5%)	21 (87.5%)
Anti-depressant Use (%)	82 (59.4%)	67 (58.8%)	15 (62.5%)
Psychiatric History (%)	52 (37.7%)	42 (36.8%)	10 (41.7%)

Table 2
Characteristics of iRBD and iRSWA Patients who Received or Did Not Receive Prognostic Counseling.

	Received prognostic counseling	Did not receive prognostic counseling	p-value
Chief/primary complaint Vs. Secondary/incidental complaint	64.4% Vs. 40.0%	54.4% Vs. 12.5%	0.022
Clinically overt iRBD diagnosis Vs. Subclinical isolated RSWA diagnosis	54.4% Vs. 12.5%	45.6% Vs. 87.5%	<0.001
Over the age of 60 years Vs. Under the age of 60 years	54.8% Vs. 31.1%	45.2% Vs. 68.9%	0.003

Characteristics significantly associated with receiving vs. not receiving prognostic counseling were iRBD as a chief/primary complaint (vs. secondary/incidental complaint), a clinically overt iRBD diagnosis vs. a subclinical iRSWA diagnosis, and older age (over 60 years) compared with age under 60 years.

Within the iRBD cohort, prognostic discussions were documented by neurologists in 63% of cases, compared with only 27% of cases by non-neurology sleep-medicine physicians ($p = 0.03$), whereas for the iRSWA subgroup, counseling was no different between neurologists and non-neurology sleep clinicians. Among sleep neurologists, male clinicians were more likely than female clinicians to have documented prognostic discussions for RBD patients (83% male neurologists counseled patients vs. 46% of female neurologists who counseled patients, $p = 0.01$), but this difference was not seen for the iRSWA subgroup.

3. Discussion

Currently, guidance regarding ethical aspects of prognostic counseling in iRBD has been sparce. Thus, physicians have had to decide on a case-by-case basis when providing such information to patients may be appropriate. Our findings suggest that the patient's age and presenting complaint, as well as neurology subspecialty and male physician sex, are determinants for prognostic counseling. Neither older patient age (>60 years in our cohort) or sleep neurology provider type are surprising as factors associated with prognostic counseling, but the finding of male physician sex as a possible counseling determinant is difficult to interpret, and will require further confirmation in a future larger prospective study. Fewer than half of our patients with iRBD or RSWA had documented prognostic discussion. This preliminary data suggests the need for further research on physician prognostic counseling practices as well as the need for development of recommendations on how to counsel iRBD patients, and to encourage the completion of advance directives, as only 46% of the patients in our cohort had completed an advance directive for future care preferences.

Although motivational factors influencing physician counseling were not assessable in this study, some likely use a “watchful waiting” approach rather than offer prognostic information at initial diagnosis. Watchful-waiting tactics may be reasonable, since longitudinal annual neurological follow-up may reveal a more accurate individualized assessment of phenoconversion risk over time, and doctor-patient rapport and trust may also grow, which could then inform and better enable prognostic discussions. Watchful-waiting tactics are frequently observed when counseling patients with treatable conditions such as prostate cancer, kidney stones, and lumbar stenosis. Typically, both patient and physician feel comfortable with a watchful approach until the benefits of intervention outweigh the potential risk or harm of an early intervention. However, circumstances are different when considering iRBD, since no medical intervention is currently available to prevent or slow phenoconversion. Yet, it is also possible that an intervention may become available during the watchful-waiting period. Then patients unaware of their neurodegenerative risk and who are not advised to seek annual neurological follow-up would be unaware of potentially beneficial interventions and might also be deprived of an opportunity to plan proactively for their future.

A surprising revelation of our study was that the majority (59.8%) of iRBD patients presented with an alternative primary sleep complaint, meaning that 40.4% of our iRBD cohort had discovery of their RBD diagnoses only after PSG. This frequency is even higher than a recent large cohort study of iRBD from a dedicated neurologic sleep center, which reported up to 11% of iRBD cases as secondary diagnoses that were only identified by specific questioning about DEBs and, therefore, were incidental to the primary presenting sleep complaint [10]. Notably, in this study, patients with iRBD as a chief/primary or a secondary sleep complaint had a similar risk for phenoconversion to an overt neurodegenerative disease [10]. However, until further confirmatory prospective cohort studies clarify the impact on prognosis, it currently remains unclear whether the same prognostic risks apply to iRBD patients presenting with dream enactment as a chief complaint, versus those whose iRBD is discovered as a secondary issue during sleep-medicine consultation. Physicians in our practice may have been reluctant to disclose information concerning phenoconversion to iRBD patients who were not seeking care for their dream-enactment history. Of potential relevance to iRBD and RSWA patients identified as a secondary sleep complaint, the American College of Medical Genetics (ACMG) in 2013 released a policy statement regarding the analysis and reporting of secondary findings in clinical genome-scale sequencing, recommending that all secondary findings be reported to the ordering physician [25]. Many physicians and patient advocacy organizations criticized this statement as a significant limitation to patient autonomy, depriving the patient of the ability to determine which prognostic information she or he may have desired to learn [26–28]. Similarly, the decision to inform iRBD patients of their prognostic risk for neurodegenerative disease resides either with the treating sleep physician or the physician who ordered the sleep study. One solution might be to inform patients of the possibility of an incidental discovery of a medical or neurological disorder such as RBD and allow them to decide whether they want to be made aware of that information [29–31]. However, patients are likely to learn later about phenoconversion risk via the internet as they seek additional information, as suggested by several recent reports concerning patient-search habits in other neurological disorders [32,33]. Patients with iRBD may benefit from initial counseling about phenoconversion risk—even in very general terms—to avoid becoming alarmed later when reading about this association on the internet without benefit of the perspective of the physician familiar with their individual case history. Other related considerations are whether social workers, psychologists, psychiatrists, and pastoral-care resources should also be available and integrated into RBD patient counseling and how referring primary care providers might be best informed and involved in counseling practices. The preferences of iRBD patients for receiving prognostic counseling remain unknown, as does the psychosocial ramifications for RBD patients following prognostic discussions, which are topics deserving future prospective study.

As seen in previous studies from both other centers and our own, antidepressant use was frequent in this cohort, and has been reported in between 26.1 and 56% of patients with iRBD

[10,12,35,36]. In the present series, 38% of patients had a psychiatric history of depression and/or an anxiety disorder, and 59.4% were taking an anti-depressant medication. Antidepressant medications are strongly associated with RSWA, especially isolated RSWA, and antidepressant use, especially for depression, has been associated with RBD in the general population [12,37,38]. We suspected that antidepressant use may be impactful to prognostic counseling, given a key recent study which found similar neurodegenerative biomarker positivity between RBD patients receiving or not receiving antidepressant treatment, yet a lower phenoconversion risk to a defined neurodegenerative disease for the antidepressant-treated RBD patients [39]. We were somewhat surprised to see that prognostic counseling between those RBD patients receiving or not receiving antidepressants was similar. Future larger confirmatory prospective studies will need to determine if antidepressant use influences counseling of patients with RBD, and further prospective cohort studies defining the natural history of these RBD patient subgroups are needed to inform appropriate counseling. Likewise, further research into the natural history of isolated/incidental RSWA found at PSG is needed. To our knowledge, thus far only one pilot study has systematically investigated the frequency of neurodegenerative marker positivity and prognosis in patients with isolated RSWA, and this study found that 10 (71.4%) of 14 isolated RSWA patients had presence of neurodegenerative markers (such as hyposmia, color vision, cognitive, motor, or autonomic functional test impairments), while one (7.3%) progressed to develop RBD. Further larger confirmatory studies are needed to clarify the natural history of isolated RSWA to inform prognostic counseling for this thus far enigmatic group of patients.

Our study has several significant limitations. These findings at our single-center, tertiary-referral practice may not be generalizable to other practice settings. Physicians may have discussed prognosis but failed to document this in the medical record, either due to error of omission, time limitations in a busy clinical practice, or alternatively, due to concerns about discoverability of information in the medical records that might impact the patient's future insurability or vulnerability to discrimination. However, a long-held medico-legal maxim in the United States is that “if it's not written, it didn't happen [34],” making medical records the most accurate approximation of physician-patient communication and personal interactions during each office visit. Determining which factors underlie physician documentation concerning prognostic counseling will require further prospective study.

4. Conclusions

Our findings suggest that iRBD patient factors of older age and a chief complaint of dream enactment favor their receiving prognostic counseling, and that sleep-medicine physician factors of neurology subspecialty and male sex also may favor prognostic disclosure. Future studies are needed to clarify iRBD patient preferences for counseling, to inform the optimal timing for counseling, and to determine specific information most valuable to patients concerning neurodegenerative prognoses. Future surveys of patient preferences and physicians' opinions and biases are needed to inform the development of guidelines for delivery of neurodegenerative prognostic information to iRBD patients.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.010.

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