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Electroencephalographic Finding in Idiopathic REM Sleep Behavior Disorder

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Key Words

Electroencephalography \cdot Idiopathic form \cdot Power spectral analysis \cdot Mild cognitive impairment \cdot REM \cdot Sleep behavior disorder \cdot α -Synucleinopathies

Abstract

The REM sleep behavior disorder (RBD) is a type of parasomnia manifested by vivid, often frightening dreams associated with motor behaviors during REM sleep, sometimes causing injuries to patients themselves or to their bed partners. The polysomnographic features of RBD include increased muscle activity during REM sleep (REM sleep without atonia). The majority of RBD-affected persons are older men. The disorder might be idiopathic (iRBD) or secondary to neurological disorders of various kinds. iRBD management with pharmaceutical measures is usually straightforward and effective. Several longitudinal studies have revealed that a high proportion of iRBD patients convert to α-synucleinopathies such as Parkinson's disease and dementia with Lewy body disease (DLB). Considering this, many studies have been conducted to identify common clinical markers between α-synucleinopathies and iRBD or indicators for the future development of α-synucleinopathies in iRBD patients. In this context, electroencephalographic (EEG) slowing occurring while awake and asleep, which is frequently observed in DLB, has received much attention. Clarification of the association between EEG slowing and the presence of mild cognitive impairment, which is also commonly seen in early

stages of DLB, has been particularly expected to offer a breakthrough for the identification of cases which might convert to α-synucleinopathies. In this article, we introduce the progress in quantitative EEG research in iRBD during the past decade. We also discuss the relationship between EEG findings and cognitive decline as well as the mechanisms of EEG changes or cognitive abnormalities in patients with the disorder.

Disease Concept, Prevalence and Clinical Correlates of the REM Sleep Behavior Disorder

The REM sleep behavior disorder (RBD) is characterized by dream-enacting behaviors during REM sleep with increased muscle activity in the submentalis or limb muscle (REM sleep without atonia) [1]. Violent behaviors associated with RBD can result in repeated injury, including ecchymoses, lacerations and fractures. The disorder, which affects mainly older men, may occur alone [idiopathic RBD (iRBD)] or in association with various neurological disorders.

A previous study including a phone survey of >4,900 people aged 15–100 years indicated an overall prevalence of violent behavior in this population during sleep of 2% [2]. One quarter of them were regarded as having RBD, giving an overall prevalence of RBD of 0.5%. Another survey estimated the prevalence of RBD as 0.38% in elderly

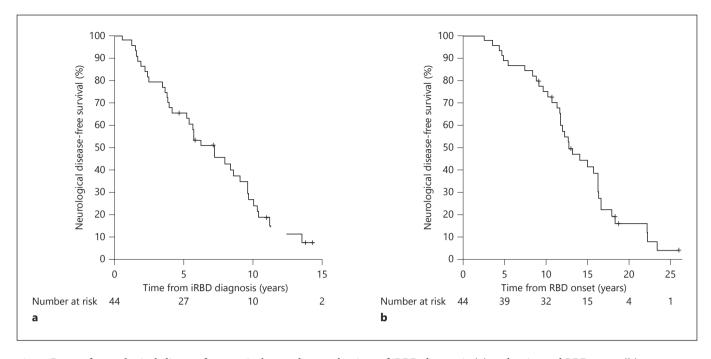


Fig. 1. Rates of neurological-disease-free survival according to the time of iRBD diagnosis (a) and estimated RBD onset (b).

people [3]. These rates imply that the disorder is rare among the general population. However, one recent study from Korea using video-polysomnography (PSG) showed that the prevalence rate of RBD was 2.01%. Moreover, the rate of subclinical RBD, in which increased muscle activities are clearly observed with no history of abnormal REM sleep behavior, was estimated as 4.95% in elderly Koreans [4], suggesting that a nonnegligible number of people are affected by the disorder.

Of note, RBD has been reported as strongly associated with a category of α-synucleinopathies, such as Parkinson's disease (PD), dementia with Lewy body disease (DLB) and multiple system atrophy [5–12]. Results from longitudinal studies from three different groups have shown that a large proportion of patients with iRBD at baseline eventually presented with α-synucleinopathies at the long-term follow-up [7, 8, 13, 14]. In the first series, PD developed in 11 (38%) of 29 patients nearly 4 years after the diagnosis of iRBD [5]. After 16 additional years of follow-up, 21 patients with iRBD from the original cohort developed PD, DLB or multiple system atrophy [13]. In the second series, 26 (28%) of 93 patients with iRBD developed PD, DLB or multiple system atrophy after a mean follow-up of 5 years [8]. In the third series of studies done by Iranzo et al. [7], 20 (45%) of 44 patients with iRBD developed a defined neurodegenerative syndrome after a mean follow-up of 5 years. Their recent report with 7 years of additional follow-up has demonstrated that most of the patients diagnosed with iRBD at baseline developed a defined neurodegenerative syndrome (fig. 1) [14]. These very high rates of conversion strongly suggest that iRBD represents a prodromal phase of α -synucleinopathies.

Many potential markers are related to early stages of α -synucleinopathies, including sensory, motor, autonomic functional, olfactory and cognitive dysfunction, as well as structural and functional neuroimaging [15–21]. However, these markers are not present in all iRBD patients, suggesting considerable heterogeneity, which reduces the capacity of these markers to identify which iRBD patients are at the highest risk of developing α -synucleinopathies.

Considering that quantitative electroencephalographic (EEG) analysis has been regarded as a useful tool for characterizing patients in early-stage Alzheimer's disease, DLB and PD with dementia [22], many researchers have aimed to ascertain possible associations of quantitative EEG findings while both awake and asleep to cognitive findings or descriptive RBD variables [23–25]. Here, we introduce the progress in quantitative EEG research in iRBD during the past decade and discuss the clinical significance and mechanism of abnormal EEG findings in patients with the disorder.

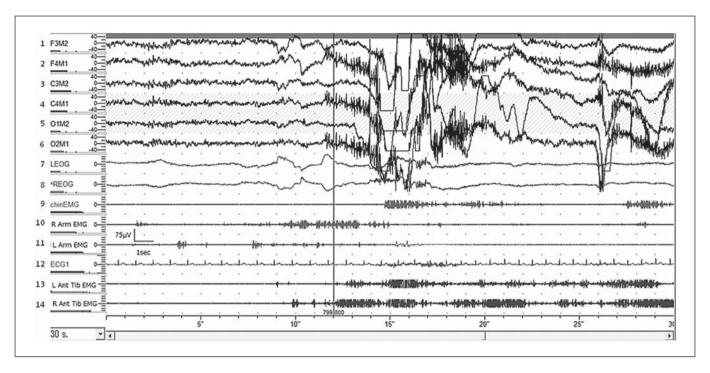


Fig. 2. REM sleep PSG showing submental EMG activity (9) despite the emergence of gross arm and leg movements that are noted by the technician and reflected by prominent twitching in the upper and lower extremity EMGs (10, 11, 13, 14). REM (7, 8) im-

mediately precedes the onset of complex behavior. F = Frontal; M = mastoid; C = central; O = occipital; LEOG/REOG = left/right electrooculogram; Ant Tib = anterior tibialis.

Quantitative and Qualitative EEG Findings in iRBD

The diagnosis of RBD requires confirmation not only of the existence of dream enactment behavior with a thorough clinical interview but also PSG-determined positivity for REM sleep without atonia (fig. 2) [26]. Reportedly, a normal non-REM (NREM)-REM cycle is well maintained in patients with iRBD [27], and REM sleep without atonia, in which phasic electromyographic (EMG) activity defined as 3-second mini-epochs including phasic EMG activity with any burst of EMG activity lasting between 0.1 and 5.0 s and an amplitude exceeding twice the background EMG activity, or tonic EMG activity with an amplitude of at least twice the background EMG muscle tone or more than 10 µV for more than 50% of a 30-second epoch, is mixed into normal REM episodes. In the upcoming third edition of *The Internation*al Classification of Sleep Disorders (ICSD-3), any (tonic/ phasic) chin EMG activity combined with bilateral phasic activity of the flexor digitorum superficialis muscles in >27% of REM sleep, scored in 30-second epochs, is recommended to distinguish RBD patients reliably from controls [28].

Slow-wave sleep is thought to play an important role in memory consolidation, brain plasticity, synapse strength and sleep homeostasis [29-31]. In previous studies, PSG findings of patients with iRBD indicated an increased percentage of slow-wave sleep [32, 33]. In 2005, Massicotte-Marquez et al. [24] reported that iRBD patients spent more time in slow-wave sleep on PSG compared with controls. Their spectral analysis also demonstrated that iRBD patients had increased all-night δ power in comparison with controls. Based on these findings, they speculated that abnormal EEG patterns during slow-wave sleep, possibly due to cortical neural desynchronization, might constitute a physiological marker of iRBD. However, the same team reported a negative result to this finding in 2011 [34]. As the reason for this discrepancy, they stated that they had possibly overlooked early parkinsonism or dementia in the subjects examined in the prior study. Consequently, abnormality of EEG during NREM is minimal or absent, suggesting that the neurophysiological substrates responsible for NREM sleep are preserved in iRBD.

Different from slow-wave sleep, substantial EEG abnormality during REM sleep and wakefulness of patients with iRBD has been reported by several researchers. In

2003, Fantini et al. [23] reported that, during wakefulness, iRBD patients showed a considerably higher θ power in frontal, temporal and occipital regions with a lower β power in the occipital region compared with age-matched elderly controls. The dominant occipital frequency was significantly lower in iRBD. Results also indicate that β power in the occipital region during REM sleep was lower in the affected patients. That study was the first to show impaired cortical activation during both wakefulness and REM sleep in iRBD although changes in sleep architecture were absent. The results were replicated by studies conducted in later years [25, 35].

When interpreting EEG findings of iRBD patients, the age effect on EEG slowing must be considered [36, 37] because most iRBD-affected people are elderly. To clarify this issue, we conducted a similar EEG power spectral analysis in younger iRBD patients (60.5 \pm 5.3 years) and age-matched controls [35]. The results demonstrated that iRBD patients exhibited significantly lower α and β power in the central and occipital regions during wakefulness and REM stage (but not during NREM sleep) than controls (fig. 3) [35]. Although clearly increased power in the low-frequency band was not seen in our patients, this finding raised the possibility of the existence of decreased cortical activation, even in this young iRBD patient population.

Relationship between EEG Slowing and Cognitive Impairment in iRBD

Mild cognitive impairment (MCI), which is characterized by cognitive deficits that do not interfere with daily activities, is a transitional stage between normal aging and dementia. This condition is generally accepted as an important risk factor for developing dementia [38]. MCI with deficits in visuospatial function, attention/executive function, verbal episodic memory or nonverbal memory occurs in approximately 50% of iRBD patients, a rate that is markedly higher than the 8% found in age- and sexmatched healthy controls [39, 41]. The type of MCI most frequently encountered in iRBD is single-domain nonamnestic MCI. However, results vary across studies depending on which cognitive domain is impaired (table 1) [39]. Population heterogeneity, small sample sizes and the use of different cognitive tasks with variable sensitivity to detect deficits and variable specificity to a cognitive domain might explain these discrepancies. However, in general, attention, executive functions, episodic verbal memory (mainly free-recall capacities) and nonverbal learning are the most affected domains in iRBD [43]. In addition, two

recent studies have revealed that iRBD patients have impaired decision making ability, a frontal-related cognitive function, irrespective of other cognitive variables [44, 45].

EEG slowing in an awake state and REM sleep might represent an early stage of central nervous system dysfunction, perhaps associated with cognitive decline. The Montreal team investigated the relation between the result of waking EEG spectral analysis and the cognitive variables in 42 untreated iRBD patients [46]. That study found that RBD + MCI patients had a higher slow-to-fast EEG frequency ratio than RBD - MCI patients and controls in the parietal, temporal and occipital regions. RBD + MCI patients also had higher relative θ power in the parietal, temporal and occipital regions, and lower relative a power in the occipital region compared to RBD – MCI patients and controls. Moreover, RBD + MCI patients had higher relative θ power in the frontal and central area and lower relative β power in the central, parietal and temporal regions compared to controls. The dominant occipital frequency was also slower in RBD + MCI patients compared to controls. It is particularly interesting that no between-group differences were observed between RBD - MCI and controls. These findings strongly affected the relationship between cognitive decline and EEG slowing in patients with iRBD. In line with this report, our study also revealed that MCI determined using the Montreal cognitive assessment scale [47] was observed in more than 75% of the iRBD patients, and that age and $log(\theta)$ power during REM sleep) was significantly associated with the this score in multiple regression analysis in this patients population [35]. In addition, a decrease in the score of the Sniffin' Stick test (thresholddiscrimination-identification score), which is known as an early LBD marker [48], was significantly associated with the Montreal cognitive assessment score in this analysis. The results presented in these two reports support the idea that EEG slowing during wakefulness or REM sleep is related with the process of cognitive decline possibly brought about by Lewy body pathology.

However, EEG slowing in iRBD can be hypothesized as an indicator for the future development of cognitive dysfunction. To test this hypothesis, Iranzo et al. [25] blindly quantified EEG spectral power from PSG findings of 23 iRBD patients without MCI and 10 healthy controls. After a mean follow-up of 2.4 years from the baseline evaluation, 10 patients developed MCI (RBD + MCI) and 13 patients continued to show normal cognitive function (idiopathic at follow-up). Patients with RBD + MCI had marked EEG slowing (increased θ and δ activity) in central and occipital regions during wakefulness and REM

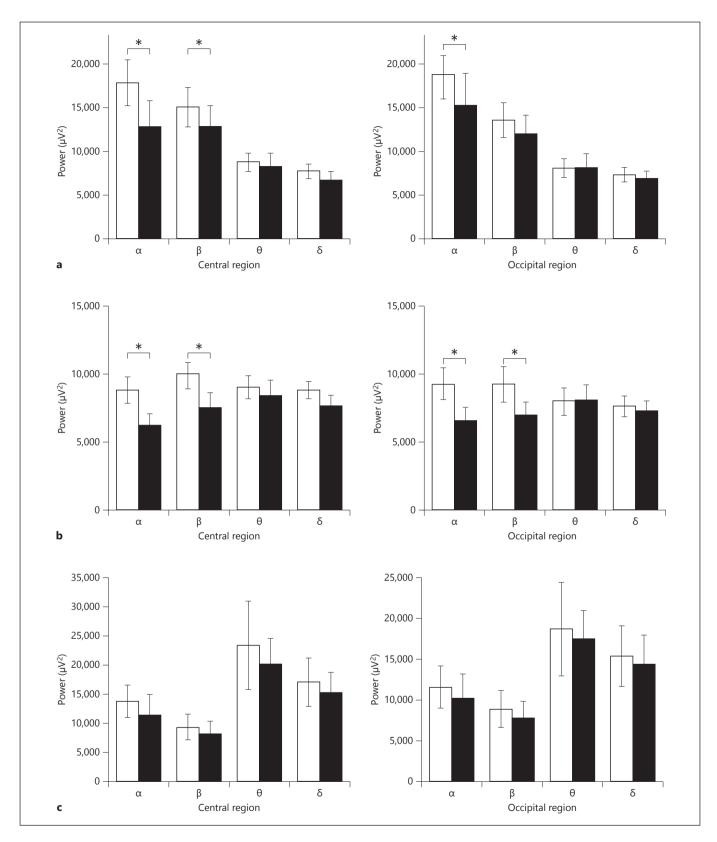


Fig. 3. Comparison of EEG spectral power during wake (**a**), REM sleep (**b**) and NREM sleep (**c**) in patients with iRBD and controls. \blacksquare = Younger RBD group; \square = age-matched control group. * p < 0.05, means ± SD.

Table 1. Controlled studies of cognitive performance in iRBD

Cognitive domains	Terzaghi et al. [40] (2008)	Massicotte- Marquez et al. [16] (2008) ^a	Gagnon et al. [41] (2009) ^a	Marques et al. [42] (2010)	Ferini- Strambi et al. [15] (2004) ^b	Fantini et al. [70] (2011) ^b
Attention/executive functions	Yes	Yes	Yes	Yes	Yes	Yes
Verbal episodic memory	Yes	Yes	Yes	Yes	Yes	Yes
Nonverbal memory	Yes	_	_	_	Yes	Yes
Visuospatial abilities	No	No	No	Yes	Yes	Yes

Yes = Patients show poorer performance than controls (p < 0.05); No = similar performance between patients and controls. $^{a, b}$ Share common participants.

sleep at baseline, particularly in the right hemisphere, in comparison with controls and, to a lesser degree, iRBD patients without MCI at the follow-up. The EEG spectral pattern of the RBD + MCI group was similar to that found in patients with DLB or PD associated with dementia [22, 49]. Based on these findings, they speculated that the presence of EEG slowing on spectral analysis might predict the development of MCI within a short period in patients initially receiving a diagnosis of iRBD.

Mechanism of EEG Slowing and Cognitive Decline in iRBD

To describe the mechanism of EEG slowing and cognitive decline in iRBD patients, one must consider some functional or anatomical abnormalities in the brain. The pathogenesis of iRBD and the neurobiological significance of the cognitive decline and EEG slowing have not been clearly elucidated. Evidence of the involvement of several brain stem structures mainly located in the pons, which include the ventral mesopontine junction, the pedunculopontine nucleus, the laterodorsal tegmental nucleus, the locus ceruleus (LC) and the peri-LC area, derives from animal models [50, 51] and from neuropathological observations in human RBD [52-54]. The pedunculopontine nucleus and the LC, which represent the largest clusters of cholinergic and noradrenergic neurons within the brain stem reticular formation, respectively, are known to play a role in arousal, cortical activation and cognitive function, including attentional processes [55–58]. Therefore, a dysfunctioning cholinergic subcortical system might contribute to cognitive impairment and EEG slowing in iRBD patients. The fact that cholinergic activity promotes REM sleep, in which EEG

slowing was observed in the studies described above [23, 25, 35], and that cholinergic denervation of the limbic cortex is a robust determinant of hyposmia [59], which was recognized in our study using threshold-discrimination-identification scores on Sniffin' Stick tests [35], might support this idea.

In vivo evaluation of some cholinergic circuits of the human brain has recently been introduced using a transcranial magnetic stimulation protocol that might yield information about the function of some cholinergic circuits in the human brain. This technique relies on short latency afferent inhibition (SAI) off the motor cortex [60]. SAI is significantly reduced in hypocholinergic forms of dementia, such as dementia of the Alzheimer type, DLB and MCI. In these patients, it can be increased by administration of acetylcholinesterase inhibitors [61-63]. Based on the hypothesis that cognitive performance and cortical activation in iRBD patients are associated with a dysfunctioning cholinergic system, Nardone et al. [64] applied the SAI technique in a group of 10 mostly drug-naïve iRBD patients (MCI was observed in 6 of them) and a group of 15 age-matched healthy controls. They found that mean SAI was significantly reduced in patients with iRBD compared with the controls, and that those SAI values correlated strongly with tests measuring episodic verbal memory and executive functions. This finding also supports the hypothesis of cholinergic dysfunction in some patients with iRBD who develop cognitive impairment.

Abnormalities in central cholinergic functions, as well as EEG slowing and cognitive decline in iRBD patients, might be caused either by cortical pathology or damage to the brain stem structure that regulates REM sleep and activates the neocortex [23, 24]. Several neuropathological studies performed on iRBD patients have shown neural alterations in several brain stem nuclei (i.e. substantia nig-

ra, pedunculopontine nucleus and the LC-sub-LC complex). All of these brain stem structures have diffuse projections to the cerebral cortex, and perturbations in these neural networks might explain the presence of cognitive decline or EEG slowing. A recent single-photon emission computed tomography study [65] revealed that iRBD + MCI patients showed hypoperfusion in the occipital cunei and superior temporal gyri compared to iRBD - MCI patients and controls, suggesting an underlying anatomical substrate specific to the presence of MCI in iRBD, which can also explain the mechanism of the EEG slowing. A diffusion tensor imaging study revealed microstructural changes in the white matter, particularly in the left superior temporal lobe and the right occipital lobe [66]. In addition, studies using voxel-based morphometry showed gray matter density anomalies in both hippocampi and the left parahippocampal gyrus in iRBD patients [67, 68]. This evidence suggests that structural changes in the brain are responsible for EEG slowing and cognitive decline, although none of these studies simultaneously conducted cognitive function measurements and quantitative EEG analyses during both wakefulness and sleep.

Concluding Remarks

To date, few studies have examined longitudinal changes in the cognitive function of iRBD patients [14, 69, 70], and no conclusive information has been obtained. Moreover, no study has evaluated changes in quantitative EEG findings along with the disease course of RBD. Thus, it remains unclear whether EEG slowing and deteriorated cognitive variables in iRBD represent a true early marker of subsequent development of α -synucleinopathies. The scientific community interested in RBD requires further efforts to clarify this issue.

Disclosure Statement

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