Rapid Eye Movement Sleep Behavior Disorder: Modern Concept and Parkinson's Disease Correlation

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Abstract

This review describes the association between rapid eye movement (REM) sleep behavior disorder (RBD) and synucleinopathies, primarily Parkinson's disease. This article reviews the diagnostic criteria, the epidemiology of RBDs, their pathogenesis, and their association with early non-motor symptoms. The data are presented to assess the risk of phenoconversion of RBDs to Parkinson's disease or other synucleinopathies such as Lewy body dementia and multiple system atrophy. A prodromal period of RBDs may precede synucleinopathies years or decades before potential manifestation of motor, cognitive, or autonomic disorders, and this may be important for initiating the neuroprotective therapy. Other causes of RBDs are also reviewed.

Keywords: *Parkinson's disease; early stages; REM sleep behavior disorders; non-motor disorders; rapid eye movement sleep; alpha-synuclein; synucleinopathies*

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Нарушения поведения в REM-фазе сна: современная концепция и взаимосвязь с болезнью Паркинсона

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Аннотация

Обзор посвящён взаимосвязи нарушения поведения в фазе быстрого сна (фаза с быстрым движением глаз, Rapid eye movement, REM-фаза) и синуклеопатий, преимущественно болезни Паркинсона. Обсуждаются критерии постановки диагноза, эпидемиология нарушений поведения в REM-фазе сна, взаимосвязь с ранними немоторными симптомами заболевания, патогенетические причины развития нарушения поведения во сне. Представлены данные об оценке риска феноконверсии нарушений поведения в REM-фазе сна в болезнь Паркинсона или другие синуклеопатии: деменцию с тельцами Леви, мультисистемную атрофию. Продромальный период с нарушениями в REM-фазе сна может предвосхищать синуклеинопатии за годы или десятилетия до возможных явных двигательных, когнитивных или вегетативных нарушений, что может иметь важное значение для начала нейропротекторной терапии. Рассмотрены также другие причины появления нарушений в REM-фазе сна.

Ключевые слова: *болезнь Паркинсона; начальные стадии; нарушения поведения в REM-фазе сна; немоторные нарушения; фаза сна с быстрым движением глаз; альфа-синуклеин; синуклеинопатии*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dreaming, complex motor behavior, and loss of physiological muscle atonia. This behavior disorder is confused with REM sleep without atonia (RSWA), which is often detected by a sleep study. However, RSWA provides a neurophysiological substrate for full progression of RBD in the future [1]. When RBD is not associated with other apparent neurological disorders, it is called idiopathic RBD (iRBD). When accompanied by other neurological symptoms such as akinetic rigid syndrome, cognitive decline, metabolic disorders, etc., RBD is considered to be symptomatic and may be associated with neurodegenerative, autoimmune, and structural brain disorders and medications [2–16]. RBD most commonly begins in the 5th or 6th decade of life. However, in some cases, symptoms of iRBD (most notably, sleep-related motor activity) may manifest at a younger age [8, 11]. The frequency of motor events during the REM sleep can vary widely, from several episodes per night to one episode per month [8]. In each patient, the severity and frequency of RBD varies from night to night [11]. The mechanisms of such fluctuation remain unknown.

RBD was first described by S.N. Schenck et al. in 1986 [17]. No generally accepted criteria for diagnosing RBD exist to date. Questionnaires have been developed to identify RBD patients. However, they are not very specific. Patients with RBD are unaware of motor activity during sleep in 44% of cases and report good quality of sleep in 70% of cases [18]. The diagnosis of RBD usually requires an accurate observation history from a bed partner of the patient. In cases of doubt, or for patients who do not have a bed partner, a polysomnography can be performed.

According to the American Academy of Sleep Medicine's International Classification of Sleep Disorders, a sleep pattern must meet four criteria to diagnose an RBD:

1) Repeated episodes of bed activity during the dream phase corresponding to the dream content,
2) Episodes of motor activity during REM sleep, confirmed by polysomnography,
3) No REM sleep atonia confirmed by polysomnography,
4) No association with known adverse drug effects or substance abuse [19].

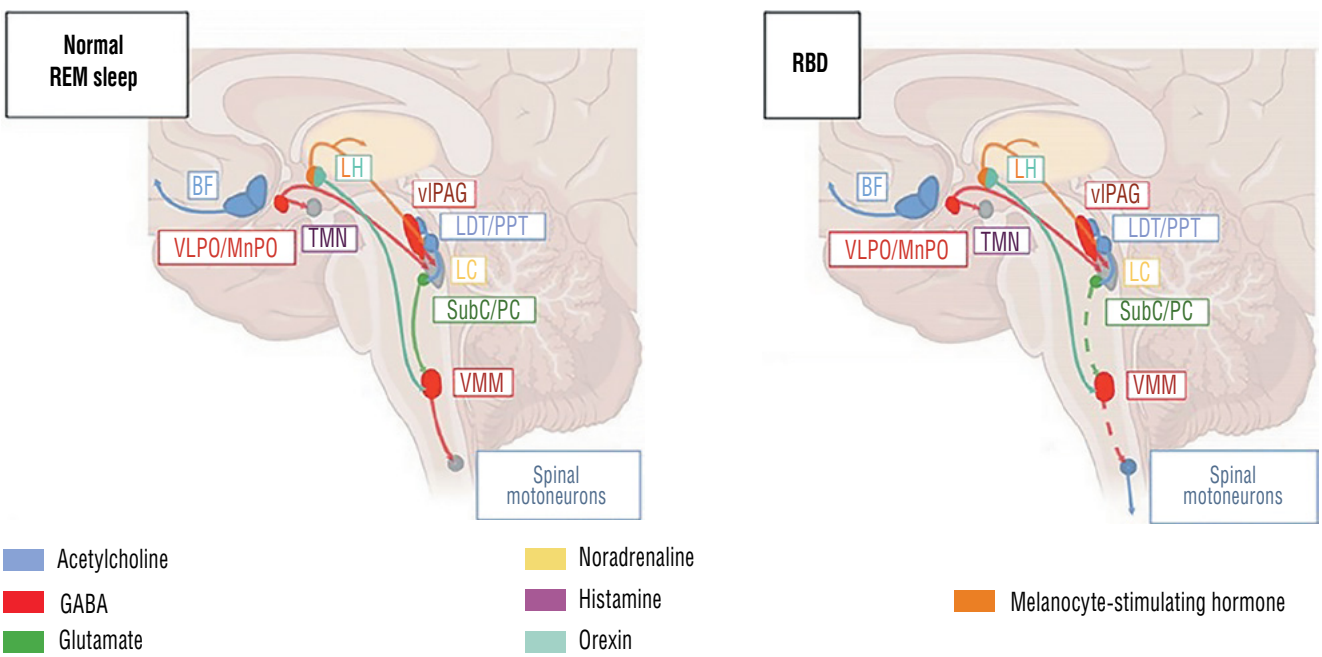
All of these factors complicate the determination of the exact RBT incidence. A large phone survey estimated the prevalence of iRBD to be 0.38% to 0.50% in the general population [20]. However, up to 4.8% of sleep clinic patients have RBD [21]. In 2013, a population-based study by S.H. Kang et al. showed that in Korea, the overall age- and sex-adjusted prevalence of RBD was 2.01% (1.15% for iRBD), and another 4.95% of the general population had isolated polysomnographically confirmed RSWA [22]. J. Haba-Rubio et al. estimated the incidence of RBD to be 1.06% in the middle-aged and elderly population in Switzerland [23]. Other population-based studies show that suspected RBD (without confirmatory polysomnography) is even more common, occurring in 5% to 6.8% of the elderly population over the age of 60–70 years [24, 25]. Although prevalence studies without confirmatory polysomnography may overestimate the incidence of RBD, their data suggest that burden of RBD has been significantly underestimated [26]. Some large studies have reported that RBD is more common in men than in women, but in patients under 50 years of age (with non-neurodegenerative RBD appearing to be more common) the incidence does not differ by sex [4, 6, 16, 18, 27–31]. The risk of RBD is 5 and 9–10 times higher in patients taking antidepressants and in those with a psychiatric diagnosis, respectively [4].

Cohort studies suggest that RBD (including iRBD) is closely associated with α-synucleinopathies, particularly Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [2–11, 13–15, 32–38]. In the largest multicenter study of RBD, B.F. Boeve et al. found that 94% of patients had abnormal accumulation of

α-synuclein at autopsy, in some cases with accumulation of β-amyloid, τ-protein, or iron [5]. At the same time, the risk of phenoconversion of RBD to PD is approximately 15–35% over the 2–5-year period and increases to 91.9% when the observation period is extended to 12–25 years, making RBD by far the most specific clinical prodromal marker for PD [10, 39]. Investigating the validity of criteria for assessing the likelihood of prodromal PD and determining the independence of prodromal markers for predicting PD or DLB, S.M. Fereshtehnejad et al. found that diagnostic accuracy of International Parkinson and Movement Disorder Society criteria was highest in people with RBD [40, 41].

The mechanism of RBD development remains unclear. The states of wake and sleep are initiated and maintained by complex interplay between multiple brainstem and diencephalic nuclei. Dysregulation, structural damage, or degeneration of these nuclei can result in various circadian rhythm disorders. RBD is thought to cause an excitation/inhibition imbalance in the brainstem nuclei controlling REM muscle tone (Figure) [42].

Movement during REM sleep is controlled by two systems: the extrapyramidal system controls the input to spinal cord motor neurons to generate muscle atonia, and the pyramidal system controls motorcortex activation to suppress locomotor activity. The main generator of REM sleep is the glutamatergic Subcoeruleus/Pre-Locus Coeruleus complex (SubC/PC), which is anatomically situated just below the noradrenergic *locus coeruleus* in the pons [43] and analogous to the rat/mouse sublaterodorsal nucleus. In addition to projecting to many subcortical brain regions to promote and maintain REM sleep, the SubC/PC projects caudally to control the REM atonia [44]. Before and during REM sleep, the REM-active SubC/PC excites the inhibitory ventromedial medulla (VMM) and glycinergic neurons of the spinal ventral horn, which in turn tonically hyperpolarize spinal motor neurons [44, 45]. This results in a temporary paralysis of skeletal muscles and thus significantly reduced REM muscle tone (atonia) during REM sleep. It is not definitively known whether RBD is caused by an imbalance originating in the glutamatergic SubC/PC or downstream in the GABA/Glycinergic VMM, though animal studies suggest the latter is more likely [46]. This brainstem function disorder does not exist in isolation. Since RBD is characterized not just by an increase in small sleep twitches but also complex movements and dream enactment, it is likely that abnormal disinhibition occurs in the pyramidal motor tract during REM sleep, leading to execution of the complex movements "imagined" by the motor cortex. Neuroimaging studies have shown that RBD can also be accompanied with changes in multiple neurotransmitter systems, including the cholinergic, noradrenergic, and dopaminergic circuits [47]. Therefore, one of the key challenges in treating RBD derives from uncertainty about the underlying pathology and the extent of dysfunction throughout the brain.



Key brain regions and neurotransmitters involved in regulating and maintaining REM sleep in healthy people and RBD patients. In RBD, dysfunction within the SubC → VMM → Spinal Motor Neuron pathway results in a lack of REM sleep atonia (depicted by the dotted line). BF, basal forebrain; LC, locus coeruleus; LDT/PPT, laterodorsal tegmentum/pedunculopontine tegmentum; LH, lateral hypothalamus; Subc/PC, subcoeruleus/pre-locus coeruleus; TMN, tuberomammillary nucleus; vlPAG, ventrolateral periaqueductal gray matter; VLPO/MnPO, ventrolateral preoptic nucleus/median preoptic nucleus; VMM, ventromedial medulla.

It should be mentioned that the development of RBD in the prodromal phase of PD corresponds to the neurodegeneration concept proposed by H. Braak et al [48], according to which Lewy bodies begin to appear in the dorsal motor nucleus of the medulla (Braak stage I). Subsequently, deposits appear more rostrally, in the reticular formation and in the SubC/PC nucleus region (Braak stage II) [15, 49–52]. Therefore, patients with RBD may formally be in Braak stage II of the neurodegenerative process or in the so-called prodromal phase of PD. This was confirmed in several studies by the presence of non-specific signs of PD in the form of hyposmia and sympathetic denervation of the myocardium in these patients [4, 14, 15]. In the third and subsequent Braak stages of the neurodegenerative process, α-synuclein accumulation progresses, involving the substantia nigra, the pedunculopontine nucleus, and the amygdala. At Braak stage IV, degeneration of the substantia nigra reaches a qualitative threshold when akinetic rigid syndrome manifests clinically [48].

However, RBD may not be observed in all patients with α-synucleinopathy, and this is likely to reflect variability in the topographic onset and progression of neurodegeneration in patients. Considering this, an alternative concept of disease progression has been proposed. This unified staging system classifies Lewy body diseases by the distribution of the abnormal protein. Stage I denotes the presence of abnormal α-synuclein in the olfactory bulbs only. Then α-synuclein accumulates predominantly in the brainstem (stage IIA), in the limbic system (stage IIb), in the brainstem and limbic system (stage III), and in the neocortex (stage IV). Progression through these neurodegenerative stages correlated with increased α-synuclein density in certain regions and clinical deterioration of cognitive impairment and motor dysfunction [53]. J. Horsager et al. recently hypothesized that PD comprises two subtypes based on progression patterns: brain-first PD and body-first PD [54]. According to the "brain-first" hypothesis, abnormal α-synuclein first affects the brain and then spreads in a caudal gradient to the peripheral autonomic nervous system [54, 55]. According to the "body-first" hypothesis, abnormal α-synuclein is first formed in the peripheral autonomic nervous system and spreads rostrally into the brain along the autonomic nerves, primarily along the *n. vagus* [54, 55]. This hypothesis is consistent with the fact of intercellular transmission of abnormal α-synuclein in cellular and animal models of PD [56]. However, it remains controversial because no cases have been reported showing that abnormal α-synuclein exists only in the peripheral nervous system and not in the brain [57–59]. It should be noted that these newly proposed concepts can explain that PD is often preceded and accompanied by prodromal and progressive non-motor symptoms and signs [60, 61].

Another unsolved issue is that some patients with RBD and PD do not fit the Braak model of neurodegeneration progression. In some patients, RBD may manifest at the same time or significantly later than the development of cognitive, motor, or autonomic symptoms of PD or DLB, and these RBDs are in fact secondary/symptomatic to a neurodegenerative process [6, 62]. However, RBD has the same features as iRBD.

Some evidence suggests that PD associated with RBD is phenotypically different from PD without RBD. Patients with RBD-associated PD have more severe and diffuse neurodegeneration, which is associated with a greater deterioration in quality of life, cognitive impairment, psychiatric complications, and slowing of the awake background electroencephalogram, more severe autonomic dysfunction, akinetic rigid syndrome, and longer disease duration [63–67]. Recent studies confirm that the motor phenotype of RBD-associated PD is more severe than in PD without RBD, with a greater tendency toward akinetic rigid syndrome, poor response to levodopa, lack of tremor, earlier and more severe gait disturbances, and longer disease duration [68, 69]. Motor decline also appears to be faster in patients with PD and RBD than in patients without RBD [70]. Study results on the effect of RBD on cognitive impairment are controversial [71–73].

Other synucleinopathies are also associated with RBD. For example, in DLB, which is characterized by the presence of dementia in combination with parkinsonism, visual hallucinations, and fluctuations in cognitive status and sleep/wake state, 80% of patients develop RBD several years before the appearance of other clinical signs [74, 75]. RBD is diagnosed in more than 88% of patients with multiple system atrophy [76]. RBD has been reported to be associated with clinically diagnosed Alzheimer's disease [77]. However, a concomitant Lewy body disorder should still be suspected in RBD, as the largest autopsy study of RBD patients to date found synucleinopathies in 94% of patients [5]. RBD has also been reported in association with progressive supranuclear palsy, although in contrast to synucleinopathies, RBD symptoms accompany rather than precede motor dysfunction in progressive supranuclear palsy [78]. In other primary tauopathies, RBD is very rare [79]. There are few reports on its association with Guadelupian parkinsonism (tauopathy) and the autoimmune anti-IgLON5 disease. In the latter, deposition of τ protein in the brain and hypothalamus has been demonstrated in deceased patients [80, 81].

It should be noted that iRBD occurring at a younger age, i.e. before the age of 50, is more often associated with non-neurodegenerative processes such as narcolepsy, autoimmune disorders, antidepressant use, or structural brain lesions. Almost half of patients with type 1 narcolepsy (narcolepsy with cataplexy) are reported to have

RSWA with or without RBD [82–85]. The RBD associated with narcolepsy typically develops much earlier, between the 2nd and 4th decades of life, likely due to the pathophysiology of type 1 narcolepsy with the unstable REM sleep phase in narcolepsy with hypocretin deficiency [82]. In young and elderly patients, RBD may be a manifestation of paraneoplastic and autoimmune neurological disorders such as Morvan syndrome (caused by antibodies to voltage-gated calcium channels) or autoimmune brain disorders (anti-IgLON5 disease and brainstem lesions associated with inflammatory, neoplastic, or cerebrovascular disorders) [7, 86–91]. In addition, the use of selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and tricyclic antidepressants was associated with symptoms of RBD and RSWA without RBD. It remains unclear whether the RBD/RSWA association with antidepressants is mediated by either reversible pharmacological effects, or whether antidepressants lead to RSWA and RBD detection in predisposed individuals with latent synucleinopathy [11, 14, 16, 30].

Therefore, RBDs, whether idiopathic or symptomatic, are closely associated with neurodegeneration, particularly with synucleinopathies such as PD, DLB, and MSA [92–94]. A prodromal period of RBDs may precede synucleinopathies years or decades before potential manifestation of motor, cognitive, or autonomic disorders, and this may be important for initiating the neuroprotective therapy in order to prevent RBD phenoconversion to PD, DLB, or MSA. More data is required to understand RBDs, how they progress clinically, and how to treat them.

References / Список источников

1. Darien I.L. American Academy of Sleep Medicine. International classification of sleep disorders – third edition (ICSD-3). Darien; 2014. 2313 p.
2. Boeve B.F., Silber M.H., Parisi J.E. et al. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. *Neurology*. 2003;61(1):40–45. DOI: 10.1212/01.wnl.0000073619.94467.b0
3. Boeve B.F., Silber M.H., Ferman T.J. et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. *Mov. Disord.* 2001;16(4):622–630.
DOI: 10.1002/mds.1120
4. Postuma R.B., Gagnon J.F., Vendette M. et al. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009;72(15):1296–1300.
DOI: 10.1212/01.wnl.0000340980.19702.6e
5. Boeve B.F., Silber M.H., Ferman T.J. et al. Clinicopathologic correlations I rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder. *Sleep Med.* 2013;14(8):754–762.
DOI: 10.1016/j.sleep.2012.10.015
6. Olson E.J., Boeve B.F., Silber M.H. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain.* 2000;123(Pt 2):331–339. DOI: 10.1093/brain/123.2.331
7. St Louis E.K., McCarter S.J., Boeve B.F. et al. Lesional REM sleep behavior disorder localizes to the dorsomedial pons. *Neurology*.
2014;83(20):1871–1873.
DOI: 10.1212/WNL.0000000000000978
8. Hancock K.L., St Louis E.K., McCarter S.J. et al. Quantitative analyses of REM sleep without atonia in children and adolescents with REM sleep behavior disorder. *Minn. Med.* 2014;97(5):43.
9. Boeve B.F. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann. N. Y. Acad. Sci.* 2010;1184:15–54.
DOI: 10.1111/j.1749-6632.2009.05115.x
10. Schenck C.H., Boeve B.F., Mahowald M.W. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med.* 2013;14(8):744–748.
DOI: 10.1016/j.sleep.2012.10.009
11. McCarter S.J., St Louis E.K., Sandnessd D.J. et al. Antidepressants increase REM sleep muscle tone in patients with and without REM sleep behavior disorder. *Sleep.* 2015;38(6):907–917. DOI: 10.5665/sleep.4738
12. Wing Y.K., Li S.X., Mok V. et al. Prospective outcome of rapid eye movement sleep behaviour disorder: psychiatric disorders as a potential early marker of Parkinson's disease. *Neurol. Neurosurg. Psychiatry*.
2012;83(4):470–472. DOI: 10.1136/jnnp-2011-301232
13. Frauscher B., Jennum P., Ju Y.E. et al. Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. *Neurology*. 2014;82(12):1076–1079. DOI: 10.1212/WNL.0000000000000247
14. Postuma R.B., Gagnon J.F., Tuineaig M. et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? *Sleep.* 2013;36(11):1579–1585. DOI: 10.5665/sleep.3102
15. Postuma R.B., Gagnon J.F., Vendette M., Montplaisir J.Y. Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease. *Brain.* 2009;132(Pt 12):3298–3307.
DOI: 10.1093/brain/awp244
16. Teman P.T., Tippmann-Peikert M., Silber M.H. et al. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. *Sleep Med.* 2009;10(1):60–65. DOI: 10.1016/j.sleep.2007.11.019
17. Hustad E., Aasly J.O. Clinical and imaging markers of prodromal Parkinson's disease. *Front. Neurol.* 2020;11:395. DOI: 10.3389/fneur.2020.00395
18. Fernandez-Arcos A., Iranzo A., Serradell M. et al. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. *Sleep.* 2016;39(1):121–132.
DOI: 10.5665/sleep.5332
19. Howell M., Avidan A.Y., Foldvary-Schaefer N. et al. Management of REM sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline. *J. Clin. Sleep Med.* 2023;19(4):759–768.
DOI: 10.5664/jcsm.10424
20. Ohayon M.M., Schenck C.H. Violent behavior during sleep: prevalence, comorbidity and consequences. *Sleep Med.* 2010;11(9):941–946.
DOI: 10.1016/j.sleep.2010.02.016
21. Frauscher B., Gschliesser V., Brandauer E. et al. REM sleep behavior disorder in 703 sleep-disorder patients: the importance of eliciting a comprehensive sleep history. *Sleep Med.* 2010;11(2):167–171.
DOI: 10.1016/j.sleep.2009.03.011
22. Kang S.H., Yoon I.Y., Lee S.D. et al. REM sleep behavior disorder in the Korean elderly population: prevalence and clinical characteristics. *Sleep.* 2013;36(8):1147–1152. DOI: 10.5665/sleep.2874.
23. Haba-Rubio J., Frauscher B., Marques-Vidal P. et al. Prevalence and determinants of rapid eye movement sleep behavior disorder in the general population. *Sleep.* 2018;41(2):zsx197. DOI: 10.1093/sleep/zsx197
24. Boot B.P., Boeve B.F., Roberts R.O. et al. Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study. *Ann. Neurol.* 2012;71(1):49–56.
DOI: 10.1002/ana.22655
25. Mahlknecht P., Seppi K., Frauscher B. et al. Probable RBD and association with neurodegenerative disease markers: a populationbased study. *Mov. Disord.* 2015;30(10):1417–1421. DOI: 10.1002/mds.26350
26. St Louis E.K., Boeve A.R., Boeve B.F. REM sleep behavior disorder in Parkinson's disease and other synucleinopathies. *Mov. Disord.*

2017;32(5):645–658. DOI: 10.1002/mds.27018
27. Wing Y.K., Lam S.P., Li S.X. et al. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. *J. Neurol. Neurosurg. Psychiatry*. 2008;79(12):1415–1416. DOI: 10.1136/jnnp.2008.155374
28. Iranzo A., Fernandez-Arcos A., Tolosa E. et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One*. 2014;9(2):e89741. DOI: 10.1371/journal.pone.0089741
29. Bonakis A., Howard R.S., Ebrahim I.O. et al. REM sleep behaviour disorder (RBD) and its associations in young patients. *Sleep Med*. 2009;10(6):641–645. DOI: 10.1016/j.sleep.2008.07.008
30. Ju Y.E., Larson-Prior L., Duntley S. Changing demographics in REM sleep behavior disorder: possible effect of autoimmunity and antidepressants. *Sleep Med*. 2011;12(3):278–283. DOI: 10.1016/j.sleep.2010.07.022
31. Bodkin C.L., Schenck C.H. Rapid eye movement sleep behavior disorder in women: relevance to general and specialty medical practice. *J. Womens Health (Larchmt)*. 2009;18(12):1955–1963. DOI: 10.1089/jwh.2008.1348
32. Boeve B.F., Silber M.H., Ferman T.J. REM sleep behavior disorder in Parkinson's disease and dementia with Lewy bodies. *J. Geriatr. Psychiatry Neurol.* 2004;17(3):146–157. DOI: 10.1177/0891988704267465
33. Ferman T.J., Boeve B.F., Smith G.E. et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology*. 2011;77(9):875–882. DOI: 10.1212/WNL.0b013e31822c9148
34. Ferman T.J., Boeve B.F., Smith G.E. et al. Dementia with Lewy bodies may present as dementia and REM sleep behavior disorder without parkinsonism or hallucinations. *J. Int. Neuropsychol. Soc.* 2002;8(7):907–914.
DOI: 10.1017/s1355617702870047
35. McCarter S.J., St Louis E.K., Boeve B.F. Mild cognitive impairment in rapid eye movement sleep behavior disorder: a predictor of dementia? *Sleep Med.* 2013;14(11):1041–1042. DOI: 10.1016/j.sleep.2013.08.780
36. McCarter S.J., St Louis E.K., Boeve B.F. REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. *Curr. Neurol. Neurosci. Rep.* 2012;12(2):182–192.
DOI: 10.1007/s11910-012-0253-z
37. Molano J., Boeve B., Ferman T. et al. Mild cognitive impairment associated with limbic and neocortical Lewy body disease: a clinicopathological study. *Brain*. 2010;133(Pt 2):540–556. DOI: 10.1093/brain/awp280
38. Murray M.E., Ferman T.J., Boeve B.F. et al. MRI and pathology of REM sleep behavior disorder in dementia with Lewy bodies. *Neurology*. 2013;81(19):1681–1689. DOI: 10.1212/01.wnl.0000435299.57153.f0
39. Chan P.C., Lee H.H., Hong C.T. et al. REM sleep behavior disorder (RBD) in dementia with lewy bodies (DLB). *Behav. Neurol.* 2018;9421098.
DOI: 10.1155/2018/9421098
40. Fereshtehnejad S.M., Montplaisir J.Y., Pelletier A. et al. Validation of the MDS research criteria for prodromal Parkinson's disease: longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. *Mov. Disord.* 2017;32:865–873. DOI: 10.1002/mds.26989
41. Berg D., Postuma R.B., Adler C.H. et al. MDS research criteria for prodromal Parkinson's disease. *Mov. Disord.* 2015;30(12):1600–1611.
DOI: 10.1002/mds.26431
42. Roguski A., Rayment D., Whone A.L. et al. A neurologist's guide to REM sleep behavior disorder. *Front. Neurol.* 2020;11:610.
DOI: 10.3389/fneur.2020.00610
43. Valencia G.S., Libourel P.A., Lazarus M. et al. Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder. *Brain*. 2017;140(2):414–428.
DOI: 10.1093/brain/aww310
44. Arrigoni E., Chen M.C., Fuller P.M. The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. *J. Physiol.* 2016;594:5391–5414. DOI: 10.1113/JP271324
45. Fraigne J.J., Torontali Z.A., Snow M.B., Peever J.H. REM sleep at its core – circuits, neurotransmitters, and pathophysiology. *Front. Neurol.* 2015;6:123. DOI: 10.3389/fneur.2015.00123
46. Peever J., Luppi P.H., Montplaisir J. Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. *Trends Neurosci.* 2014; 37:279–288. DOI: 10.1016/j.tins.2014.02.009
47. Knudsen K., Fedorova T.D., Hansen A.K. et al. In vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study. *Lancet Neurol.* 2018;17:618–628.
DOI: 10.1016/S1474-4422(18)30162-5
48. Braak H., Ghebremedhin E., Rüb U. et al. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res.* 2004;318(1):121–134. DOI: 10.1007/s00441-004-0956-9
49. Miyamoto T., Miyamoto M., Inoeu Y. et al. Reduced cardiac ^{123}I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. *Neurology*. 2006;67(12):2236–2238.
DOI: 10.1212/01.wnl.0000249313.25627.2e
50. Frauscher B., Normura T., Duerr S. et al. Investigation of autonomic function in idiopathic REM sleep behavior disorder. *J. Neurol.* 2012;259(6):1056–1061. DOI: 10.1007/s00415-011-6298-0
51. Postuma R.B., Gagnon J.F., Vendette M. et al. Olfaction and color vision identify impending neurodegeneration in rapid eye movement sleep behavior disorder. *Ann. Neurol.* 2011;69(5):811–818. DOI: 10.1002/ana.22282
52. Fantini M.L., Postuma R.B., Montplaisir J., Ferini-Strambi L. Olfactory deficit in idiopathic rapid eye movements sleep behavior disorder. *Brain Res. Bull.* 2006;70(4–6):386–390. DOI: 10.1016/j.brainresbull.2006.07.008
53. Beach T.G., Adler C.H., Lue L. et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. *Acta Neuropathol.* 2009;117(6):613–634.
DOI: 10.1007/s00401-009-0538-8
54. Horsager J., Andersen K.B., Knudsen K. et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain*. 2020;143:3077–3088. DOI: 10.1093/brain/awaa238
55. Bohnen N.I., Postuma R.B. Body-first versus brain-first biological subtyping of Parkinson's disease. *Brain*. 2020;143:2871–2873.
DOI: 10.1093/brain/awaa293
56. Horsager J., Knudsen K., Sommerauer M. Clinical and imaging evidence of brain-first and body-first Parkinson's disease. *Neurobiol. Dis.* 2022;164:105626. DOI: 10.1016/j.nbd.2022.105626
57. Bloch A., Probst A., Bissig H. et al. α-Synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. *Neuropathol. Appl. Neurobiol.* 2006;32:284–295.
DOI: 10.1111/j.1365-2990.2006.00727
58. Blesa J., Foffani G., Dehay B. et al. Motor and non-motor circuit disturbances in early Parkinson disease: which happens first? *Nat. Rev. Neurosci.* 2022;23:115–128. DOI: 10.1038/s41583-021-00542-9
59. Warnecke T., Schäfer K.H., Claus I. et al. Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. *NPJ Parkinsons Dis.* 2022;8:1–13. DOI: 10.1038/s41531-022-00295-x
60. Adler C.H., Beach T.G. Neuropathological basis of nonmotor manifestations of Parkinson's disease. *Mov. Disord.* 2016;31(8):1114–1119.
DOI: 10.1002/mds.26605
61. Залялова З.А., Хасанова Д.М. Эволюция предикторов ранней болезни Паркинсона. *Бюллетень Национального общества по изучению болезни Паркинсона и расстройств движений*. 2022;(2):72–75.
DOI: 10.24412/2226-079X-2022-12438
Zalyalova Z.A., Khasanova D.M. Early Parkinson's disease predictors' evolution. Bulletin of the National Society for the Study of Parkinson's Disease and Movement Disorders. 2022;(2):72–75. DOI: 10.24412/2226-079X-2022-12438
62. Хасанова Д.М., Залялова З.А., Мунасипова С.Э. Нарушения сна у впервые выявленных пациентов с ранними стадиями болезни Паркинсона. *Практическая медицина*. 2020;18(5):117–123.
Khasanova D.M., Zalyalova Z.A., Munasipova S.E. Sleep disorders in early Parkinson's disease de novo patients. *Practical medicine*. 2020;18(5):117–123.
63. McCarter S.J., St. Louis E.K., Boeve B.F. Is rapid eye movement sleep behavior disorder in Parkinson disease a specific disease subtype? *Sleep Med.* 2013;14(10):931–933. DOI: 10.1016/j.sleep.2013.06.004
64. Nomura T., Xiong K.P., Li J. et al. Clinical significance of REM sleep behavior disorder in Parkinson's disease. *Sleep Med.* 2013;14(2):131–135.
DOI: 10.1016/j.sleep.2012.10.011
65. Chahine L.M., Kauta S.R., Daley J.T. et al. Surface EMG activity during REM sleep in Parkinson's disease correlates with disease severity. Parkinsonism *Relat. Disord.* 2014;20(7):766–771. DOI: 10.1016/j.parkreldis.2014.04.011
66. Sixel-Doring F., Trautmann E., Mollenhauer B. et al. Associated factors for REM sleep behavior disorder in Parkinson disease. *Neurology*. 2011;77(11):1048–1054. DOI: 10.1212/WNL.0b013e31822e560e
67. Залялова З.А., Хасанова Д.М., Угрюмов М.В. Катехоламины плазмы крови у пациентов с ранними нелеченными стадиями болезни Паркинсона. *Альманах клинической медицины*. 2018;46(8):792–801.
DOI: 10.18786/2072-0505-2018-46-8-792-801
Zalyalova Z.A., Khasanova D.M., Ugrumov M.V. Plasma catecholamine levels in the early stages of treatment-naïve Parkinson's disease. *Almanac of Clinical Medicine*. 2018;46(8):792–801. DOI: 10.18786/2072-0505-2018-46-8-792-801
68. Postuma R.B., Gagnon J.F., Vendette M. et al. REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features.

J. Neurol. Neurosurg. Psychiatry. 2008;79(10):1117–1121. DOI: 10.1136/jnnp.2008.149195
69. Lee J.E., Kim K.S., Shin H.W., Sohn Y.H. Factors related to clinically probable REM sleep behavior disorder in Parkinson disease. *Parkinsonism Relat. Disord.* 2010;16(2):105–108. DOI: 10.1016/j.parkreldis.2009.08.005
70. Sommerauer M., Valko P.O., Werth E. et al. Revisiting the impact of REM sleep behavior disorder on motor progression in Parkinson's disease. *Parkinsonism Relat. Disord.* 2014;20(4):460–462. DOI: 10.1016/j.parkreldis.2014.01.005
71. Postuma R.B., Bertrand J.A., Montplaisir J. et al. Rapid eye movement sleep behavior disorder and risk of dementia in Parkinson's disease: a prospective study. *Mov. Disord.* 2012;27(6):720–726. DOI: 10.1002/mds.24939
72. Vendette M., Gagnon J.F., Decary A. et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*. 2007;69(19):1843–1849. DOI: 10.1212/01.wnl.0000278114.14096.74
73. Plomhause L., Dujardin K., Duhamel A. et al. Rapid eye movement sleep behavior disorder in treatment-naive Parkinson disease patients. *Sleep Med.* 2013;14(10):1035–1037. DOI: 10.1016/j.sleep.2013.04.018
74. McKeith I.G., Dickson DW, Lowe J. et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872. DOI: 10.1212/01.wnl.0000187889.17253.b1
75. Pao W.C., Boev B.F., Ferman T.J. et al. Polysomnographic findings in dementia with Lewy bodies. *Neurologist*. 2013;19(1):1–6. DOI: 10.1097/NRL.0b013e31827c6bdd
76. Palma J.A., Fernandez-Cordon C., Coon E.A. et al. Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis. *Clin. Auton. Res.* 2015;25(1):69–75. DOI: 10.1007/s10286-015-0279-9
77. Gagnon J.F., Petit D., Fantini M.L. et al. REM sleep behavior disorder and REM sleep without atonia in probable Alzheimer disease. *Sleep.* 2006;29(10):1321–1325. DOI: 10.1093/sleep/29.10.1321
78. Arnulf I., Merino-Andreu M., Bloch F. et al. REM sleep behavior disorder and REM sleep without atonia in patients with progressive supranuclear palsy. *Sleep.* 2005;28(3):349–354.
79. Boeve B.F., Lin S.C., Strongosky A. et al. Absence of rapid eye movement sleep behavior disorder in 11 members of the pallidopontonigral degeneration kindred. *Arch. Neurol.* 2006;63(2):268–272. DOI: 10.1001/archneur.63.2.268
80. De Cock V.C., Lannuzel A., Verhaeghe S. et al. REM sleep behavior disorder in patients with guadeloupean parkinsonism, a tauopathy. *Sleep.* 2007;30(8):1026–1032. DOI: 10.1093/sleep/30.8.1026
81. Sabater L., Gaig C., Gelpi E. et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. *Lancet Neurol.* 2014;13(6):575–586. DOI: 10.1016/S1474-4422(14)70051-1
82. Schenck C.H., Mahowald M.W. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. *Ann. Neurol.* 1992;32(1):3–10. DOI: 10.1002/ana.410320103
83. Dauvilliers Y., Rompre S., Gagnon J.F. et al. REM sleep characteristics in narcolepsy and REM sleep behavior disorder. *Sleep.* 2007;30(7):844–849. DOI: 10.1093/sleep/30.7.844
84. Ferri R., Franceschini C., Zucconi M. et al. Searching for a marker of REM sleep behavior disorder: submentalis muscle EMG amplitude analysis during sleep in patients with narcolepsy/cataplexy. *Sleep.* 2008;31(10):1409–1417.
85. Nightingale S., Orgill J.C., Ebrahim I.O. et al. The association between narcolepsy and REM behavior disorder (RBD). *Sleep Med.* 2005;6(3):253–258. DOI: 10.1016/j.sleep.2004.11.007
86. McCarter S.J., Tippmann-Peikert M., Sandness D.J. et al. Neuroimaging-evident lesional pathology associated with REM sleep behavior disorder. *Sleep Med.* 2015;16(12):1502–1510. DOI: 10.1016/j.sleep.2015.07.018
87. Compta Y., Iranzo A., Santamaria J. et al. REM sleep behavior disorder and narcoleptic features in antiMa2-associated encephalitis. *Sleep.* 2007;30(6):767–769. DOI: 10.1093/sleep/30.6.767
88. Cornelius J.R., Pittock S.J., McKeon A. et al. Sleep manifestations of voltage-gated potassium channel complex autoimmunity. *Arch. Neurol.* 2011;68(6):733–738. DOI: 10.1001/archneurol.2011.106
89. Iranzo A., Graus F., Clover L. et al. Rapid eye movement sleep behavior disorder and potassium channel antibody-associated limbic encephalitis. *Ann. Neurol.* 2006;59(1):178–181. DOI: 10.1002/ana.20693
90. Josephs K.A., Silber M.H., Fealey R.D. et al. Neurophysiologic studies in Morvan syndrome. *J. Clin. Neurophysiol.* 2004;21(6):440–445. DOI: 10.1097/00004691-200411000-00008
91. Tippmann-Peikert M., Boeve B.F., Keegan B.M. REM sleep behavior disorder initiated by acute brainstem multiple sclerosis. *Neurology*. 2006;66(8):1277–1279. DOI: 10.1212/01.wnl.0000208518.72660.ff
92. Илларионшкин С.Н., Власенко А.Г., Федотова Е.Ю. Современные возможности идентификации латентной стадии нейродегенеративного процесса. *Анналы клинической и экспериментальной неврологии*. 2013;7(2):39–50.
Illarioshkin S.N., Vlasenko A.G., Fedotova E.U. Modern possibilities of identification of the latent stage of the neurodegenerative process. *Annals of Clinical and Experimental Neurology*. 2013;7(2):39–50.
93. Нодель М.Р., Украинцева Ю.В., Яхно Н.Н. Синдром нарушения поведения в фазе сна с быстрыми движениями глаз при болезни Паркинсона. *Неврологический журнал*. 2015;20(6):28–34.
Nodel M.R., Ukraintseva Yu.V., Yakhno N.N. Syndrome of behavior disorders in the rapid eye movements phase with in Parkinson's disease. *Neurological Journal*. 2015;20(6):28–34.
94. Рождественский А.С., Делов Р.А., Маркс Е.А. и др. Изучение фундаментальных и прикладных аспектов болезни Паркинсона в рамках международного консорциума GEoPD. *Нервные болезни*. 2020;(1):10–15. DOI: 10.24411/2226-0757-2020-12146
Rozhdestvensky A.S., Delov R.A., Marks E.A. et al. Study of fundamental and applied aspects of Parkinson's disease within the framework of the international GEoPD consortium. *Nervous diseases*. 2020;(1):10–15. DOI: 10.24411/2226-0757-2020-12146

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