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Review

Critically appraised topic on Rapid Eye Movement Behavior Disorder: From protein misfolding processes to clinical pathophysiology and conversion to neurodegenerative disorders

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Abstract: *Background:* REM Behavior Disorder (RBD) is considered one of most powerful prodromal condition in different neurodegenerative disorders, mainly alpha-synucleinopathies. A large amount of research recently explored this relationship. *Objective and Design:* The present critically appraised review undertakes this topic, from the perspective of the pathogenetic interplay between clinical manifestations in RBD patients and the misfolding processes that characterize neurodegeneration. In particular, evidence in favor and against the role of RBD as a biomarker of neurodegeneration is discussed. *Results and Conclusion:* The selected papers were functional to structure the review into three main sections: 1) Protein misfolding in neurodegenerative disorders with focus on alpha-synuclein; 2) Clinical features, diagnosis, and pathophysiology of RBD; 3) RBD as a clinical biomarker of protein misfolding. Data herein highlights the current knowledge and the areas of uncertainties in the relationship between RBD and neurodegenerative disorders; we went through preclinical, prodromal and clinical stages of neurodegenerative processes as a useful reference for clinicians involved in brain pathological aging and future research in this field.

Keywords: REM Behavior Disorder; REM parasomnias; REM Without Atonia (RWA); alpha-synuclein; parkinsonism; neurodegenerative disorders; prodromal Parkinson's disease; protein misfolding

1. Introduction (rationale and objective)

Neurodegenerative Disorders are becoming one of the most prevalent groups of diseases in an aging population worldwide, with nearly 5% of people aged >50 years old suffering a form of "non pure vascular dementia" and prevalence exponentially increasing with aging [1]. They include several very different disorders–from Alzheimer's disease (AD) to Parkinson's disease (PD), from Frontotemporal dementias (FTD) to Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) to Corticobasal Degeneration, etc. but they are thought to be associated by a common prion-like pathogenetic process that leads to cellular dysfunction and finally to cell death. The most important goal of basic, translational, and clinical Research around neurodegenerative disorders is to characterize their early clinical manifestations, and possibly their preclinical stages. In turn, these conditions will be the best target for effective disease-modifying therapies. Rapid Eye Movement (REM) behavior disorder (RBD) is considered one of the most powerful predictors of future a-synucleinopathy, above all PD [2]. However, it has been observed also in AD and other diseases different from PD itself; moreover, several RBD patients feature an isolated RBD even decades after diagnosis, without a clear phenoconversion into a full-blown neurodegenerative disease. Thus, the speed of phenoconversion and the occurrence of co-pathologies within the same patient are just two examples of the several areas of uncertainty still debated about the relationship between RBD occurrence and the pathophysiology of neurodegenerative disorders.

In this paper we reviewed the published evidence on the relationship between RBD occurrence and neurodegeneration. Within the particular focus on alpha-synuclein misfolding process, we will go through the main RBD clinical and pathophysiological features. We aimed above all at highlighting the unsolved issues on this topic, as a useful reference for future research and clinicians involved in disordered brain aging.

2. Materials and methods

The search process for this critically appraised topic was based on the following keywords: "alpha-synuclein", "RBD AND neurodegeneration", "REM sleep Behavior Disorder", RBD", "prodromal Parkinson disease". Databases searched using these keywords were: PubMed, Science Direct, Medline, EMBase and Web of Science. Searches were replicated between May 31, 2022 and December 31, 2022 to determine whether new studies had been published since the initial search.

Peer-reviewed journal papers were included if they were published between the period of 2000–2022 (unless of particular interest for this topic), written in English, and involving human participants. At the same time the following exclusion criteria were applied: i. papers without complete data; ii. case reports, unless of peculiar interest for the topic; articles in languages different from English.

All Authors independently evaluated the titles, abstracts and the full text of all publications identified by our searches for potentially relevant publications. The final selected papers with a disagreement between two Authors have been discussed together with all the other Authors.

We chose to categorize collected information into four categories. 1) Papers with relevant data on protein misfolding in neurodegenerative disorders; 2) Data on alpha-synuclein properties in neurodegenerative disorders; 3) Data on clinical features and diagnosis of RBD; 4) RBD as a clinical biomarker of protein misfolding.

3. Results

3.1. Protein misfolding

3.1.1. Protein misfolding in the pathophysiology of neurodegenerative diseases

The phenomenon of "protein misfolding" has been a clearly recognized common mechanism in the pathophysiology of neurodegenerative diseases. It implies an incorrect organization of the tertiary structure of endogenous polypeptides. This lends to them a higher propensity to aggregate, and through the formation of inclusions within the Central Nervous System (CNS) causes cellular dysfunction and damage. The specific inductor events that modify the protein tertiary structure are still unknown, but neurotoxic substances [3], infectious/inflammatory agents [4] and metabolic imbalance [5] have all been advocated as epigenetic factors that could start or enhance the process.

In recent years, specific misfolded proteins have been described in different systemic and, most of all, neurodegenerative diseases: In AD, misfolded and aggregated phosphorylated Tau and Amyloid-beta (Aβ) has been documented in intracellular and extracellular environment, respectively; in PD, Multiple System Atrophy (MSA) and Lewy Body Dementia (LBD), misfolded and aggregated alpha-synuclein (α-Syn) was found in the so-called Lewy Bodies and Lewy Neurites; in spongiform encephalopathies like Creutzfeldt-Jakob Disease (CJD), a misfolded form of the native prion protein, PrPSc, has been demonstrated; TDP-43 aggregates have been documented in cases of FTD, LATE and Amyotrophic Lateral Sclerosis (ALS) [6–8].

How can misfolded and aggregated proteins lead to neurodegenerative processes? Protein enzymatic functions strictly rely on a precise and well-defined three-dimensional molecular structure. In this perspective, it is not surprising that cells have developed a complex system of chaperone elements, particularly expressed inside the endoplasmic reticulum, that permits correct protein folding in post-translational phase [9–12]. At the same time, incorrectly folded proteins (and thus, incorrectly working proteins) trigger the so-called Unfolded Protein Response, an advanced intracellular pathway that aims to get rid of misfolded elements through activation of processes of auto-phagocytosis or by implementing proteasome-mediated proteolysis [9–11]. As soon as these processes are no longer efficient, because of aging processes [12], or of mutations that either dramatically impair this system or that make proteins themselves more susceptible to incorrect folding [12], misfolded elements become no more controllable and lead to activation of inflammatory and pro-apoptotic pathways culminating in cell loss and local tissue damage [13,14].

In neurodegenerative diseases, single misfolded monomers tend to aggregate to form small aggregates (oligomers) having the ability of spreading through cells via different pathways [15] and to assemble more complex polymeric structures (protofibrils), which eventually go through a process of progressive elongation and consequent fragmentation in smaller elements, thus leading to further expansion and diffusion, and finally forming amyloid fibrils [16–18]. Moreover, some of these aggregates have demonstrated the ability of converting native, correctly folded proteins, to pathological misfolded elements, amplifying exponentially the process, like in an autocatalytic one [16]. In parallel, a cross-seeding phenomenon can be observed: The aggregation process of one protein type may involve a different protein type with a similar tertiary structure, leading to a domino effect (an example is given by Alzheimer's disease, where both Tau and Aβ aggregates coexist) [16,19].

The first deciphering of all these properties can be found in the coherent paradigm of prion

encephalopathies. They are caused by proteins behaving like proper infective pathogens, since they have been demonstrated to spread across tissues and expand their number converting natively folded elements into misfolded toxic elements, in absence of genetic RNA or DNA code responsible for their replication [20]. Their origin can be identified in endogenous events of incorrect protein folding, or also - what is more striking about their nature - in external contamination from other tissues of affected individuals. So far, they are considered the only neurodegenerative diseases in which inter-individual transmission is clearly confirmed [21,22]. A historical example that may be cited is kuru, a fatal cerebellar ataxia with choreoatethoid movements, fatal in 12–23 months from symptoms' onset. Typical of certain areas of Papua-New Guinea, kuru has been documented to transmit during ritual cannibalistic funeral rites, where people got infected by eating cerebral tissue of deceased patients [23].

Human spongiform encephalopathies like kuru are caused by PrPSc, the misfolded variant of human PrPC, a protein whose physiological function is under active investigation. Monomeric PrPSc aggregates to create polymeric structures that elongate and undergo fragmentation and further spreading, involving natively folded PrPC that is converted to the misfolded homologous. Histological alteration and tissue degeneration are the consequence of this pathway [24].

Recently, the model of prion diseases is gaining increasing interest as a useful tool to describe the pathophysiology of several other neurodegenerative diseases. A model which seems to fit well in much more epidemiologically relevant diseases, like the family of synucleinopathies [7,16,25], we are going to deal with in the following paragraph.

3.1.2 Protein misfolding in α-synucleinopathies

PD, LBD and MSA are different disorders with some clinical common features, but distinct phenotypes. However, they share the pathological finding of alpha-synuclein aggregates in the CNS. In these disorders, misfolded alpha-synuclein has recently proved to possess prion-like characteristics [7,24]. Alpha-synuclein is coded by a gene called *SNCA* (chromosome 4q22.1) and its primary structure consists of 140 amino-acids organized in three distinct segments: a N-terminal domain, implied in anchoring to membrane phospholipids and provided of repeated α-helix domains; a central core with repeated aminoacidic sequence KTKEGV, susceptible to formation of β-sheets, and a C-terminal domain that interacts with N-terminus and cell lipidic membranes in order to shield the central region (with some commonalities with Heat Shock Proteins) [7]. Due to its primary structure, an efficient system of chaperone molecular machinery is needed to avoid its incorrect folding; when this becomes inefficient or somehow altered, or in case of particular *SNCA* mutations, this protein meets easily an altered folding [25].

Alpha-synuclein "prion-like" characteristics have been hypothesized since evaluation of cerebral embryonic cell grafts in PD patients. Presence of Lewy Bodies and Lewy Dendrites was demonstrated in graft cells, suggesting an in vivo propagation of endogenous, toxic misfolded alpha-synuclein from host to graft cells [25,26]. Further studies with mutant A53T mice, susceptible to develop α-synucleinopathies, have shown that exogenous administration of brain homogenate from deceased MSA patients within mouse brain tissues was responsible for Lewy Body-like inclusions formation inside host neurons [27–29]. Moreover, systemic administration of misfolded alpha-synuclein led to analogous conclusions, implying a mechanism of misfolded protein spreading from peripheral tissues to the central nervous system [30,31]. The model for PD and AD proposed by Braak et al. itself suggests a spreading of toxic elements across different areas of cerebral tissues, coherently with misfolded proteins converting their native counterpart and transferring cell to cell via endocytic

mechanisms, with a presumably origin located outside the central nervous system [32].

Different clinical phenotypes in α-synucleinopathies have led to consider that different molecular isoforms ("strains") of misfolded alpha-synuclein could be responsible for variable tissue involvement and consequently variable clinical manifestations. Different strains of misfolded alpha-synuclein in vitro have been characterized: A study from Peelaerts et al. has described two types of polymers, ribbons, and fibrils, the former leading in mice model to PD or MSA phenotypes, and the latter causing rapid motor impairment and death [33]. Another possible link between in vitro and in vivo models, and by extension between clinical presentation and molecular strains, derived from the observation of ribbon strain-containing astrocytes in MSA patient cells, and not in PD patients' autoptic samples [14]. A recent work by Shahnawaz et al. (2020) has depicted a clear set of differences in molecular structure and toxicity of different strains of alpha-synuclein from cerebrospinal fluid and cerebral tissues of PD and MSA patients. By using protein misfolding cyclic amplification techniques, they have evaluated their samples through a series of biochemical, biophysical and biological analysis, establishing clear properties that distinguish PD-related versus MSA-related alpha-synuclein strains with an overall specificity of 95,4%, thus paving the way to a more specific and precocious molecular diagnosis of synucleinopathies [34].

3.2. A clinical overview of RBD

3.2.1. Clinical features of RBD

RBD is a REM sleep parasomnia typically affecting middle-aged people. First reports indicated a predominance in men, with male to female ratio up to 9:1 [35]. However, more recent epidemiological data tend not to emphasize significant sex differences in RBD occurrence [36]. Diagnosis usually follows early manifestations by several years, since symptoms tend to develop insidiously and patients rarely notice their problem [37], unless they provoke serious trauma to the patient itself or to the bed partner. RBD is characterized by active enactment of dreams, in absence of REM sleep typical muscular atonia; this can vary from unobtrusive hand gestures, speaking or moaning to episodes of kicking, punching, and falling from bed, with the concrete risk of injuries. During dream enactment, patients with RBD maintain a state of REM sleep. They can be awakened immediately after these episodes with a reminiscence of their dreams [37], which typically consist of being chased or attacked, or arguing with someone; however, they typically do not awaken spontaneously unless they get injured because of their behavior. Episodes can vary in frequency from annually to almost every night and they tend to manifest during the second half of night, when REM sleep is more prominent [38,39]. Aside from nocturnal findings, daytime signs have been described, particularly sleepiness as assessed through Epworth Sleepiness Scale and autonomic dysfunction (orthostatic hypotension, erectile dysfunction, constipation, cardiac and respiratory regulation) [40].

3.2.2 Diagnostic criteria, role of neurophysiology and neuroimaging

RBD is currently diagnosed according to the third edition of the International Classification of Sleep Disorders (ICSD-3), as summarized in Table 1 [39]. Polysomnography plays a key role in the diagnostic workup, as demonstrating the presence of RWA has a confirmatory value. The AASM sleep scoring manual defines RWA including excessive "tonic" (sustained), "phasic" (transient) and "any"

(as percentage, regardless of whether it consisted of tonic, phasic or a combination of both) muscle activity (Table 1). After the scoring process, an RWA index can be calculated as the percentage of stage R epochs that meets AASM criteria [41].

Table 1. AASM diagnostic criteria for RBD and scoring rules for RWA.

AASM diagnostic criteria for "definite" RBD (all required)*	
Repeated episodes of sleep-related vocalization and/or complex motor behaviors	
Behaviors are documented by PSG to occur during REM sleep	
Detection of RWA on PSG	
Absence of epileptiform activity during REM sleep	
No better explanation (other sleep, medical, neurological or mental disorders; drugs or substances)	
AASM scoring rules for RWA (at least one required)	
At least half of the 30-s epoch with excessive tonic activity in the chin EMG	With activity amplitude: ● ≥ 2 times greater than stage R atonia level, or ● greater than the lowest amplitude in NREM sleep (if no stage R atonia is present).
At least half of 3-s mini-epochs with excessive phasic activity in the chin or limb EMG	For the presence of 0.1–5.0 s bursts with amplitude: ● ≥ 2 times greater than stage R atonia level, or ● greater than the lowest amplitude in NREM sleep (if no stage R atonia is present).
At least half of 3-s mini-epochs containing any chin EMG activity	For any duration activity with amplitude: ● ≥ 2 times greater than stage R atonia level, or ● greater than the lowest amplitude in NREM sleep (if no stage R atonia is present).
At least half of 3-s mini-epochs containing EMG limb activity	For the presence of 0.1–5.0 s bursts with amplitude: ● ≥ 2 times greater than stage R atonia level, or ● greater than the lowest amplitude in NREM sleep (if no stage R atonia is present).

*Note: *In the absence of video-polysomnography or evidence of RWA, a clear-cut clinical history is sufficient for a "probable" diagnosis of RBD.* AASM: American Academy of Sleep Medicine; EMG: electromyography; NREM: Non-Rapid Eye Movement; PSG: polysomnography; RBD: REM sleep Behavior Disorder; R: REM; REM: Rapid Eye Movement; RWA: REM sleep Without Atonia; s: seconds.

As a result of a large systematic prospective analysis of the Sleep Innsbruck Barcelona (SINBAR) group, it is now recommended to quantify "any" EMG activity in the mentalis muscle and "phasic" EMG activity in both upper limbs, particularly in flexor digitorum superficialis muscles. Applying this method, the SINBAR group has defined a 32% cut-off of muscle activity for a 100% specific diagnosis of RBD [42]. Computerized automated systems for RWA scoring and calculation of RWA index have been developed in order to speed up the analysis and reduce the scoring workload [43,44]. However, the reliability of computerized programs is conditioned by the quality of recordings, and manual exclusion of epochs containing EMG artifacts is still needed. Moreover, video examination of REM-related movements and behaviors is part of the diagnostic workup. The typical hallmark of RBD is represented by simple movements and minor jerks, which are far more frequent compared to complex and violent behaviors [45,46]. At present, a dedicated RBD severity scale can be used in clinical

routine to score REM-related movements [47], but computerized video analysis could represent a novel approach to RBD screening in the next future [48].

Brain MRI can be useful in clinical practice to exclude secondary causes of RBD. In addition, MRI studies have found abnormalities in different brain regions of patients with RBD. These alterations mostly involve the brainstem [49,50] and the basal ganglia [51], as can be expected when considering RBD as a frequent prodromal condition in α-synucleinopathies.

Finally, DaTSCAN can help to predict the phenoconversion risk in patients with isolated RBD. In line with the Braak staging model of pathology [32], a reduced striatal DaT uptake has been associated with the development of an overt synucleinopathy within 2.5–3 years of follow-up [52,53].

3.2.3. Clinical management and current treatments

Current treatments for RBD are symptomatic, including behavioral and pharmacological strategies aimed at controlling motor manifestations, which are potentially harmful both for the patient and the bed partner. Treating RBD is also intended to reduce sleep fragmentation and movement-related arousals, then improving sleep and life quality of the patient.

Treatments should be tailored to the extent of the patient's symptoms. Behavioral strategies (level A of recommendation) [54] are focused on making safe the bedroom, preferring lower beds, placing pillows on the floor, using corner protectors and removing ornaments around the bed; in some cases, the patient and the bed partner should be invited to sleep in different beds [55]. Pharmacological therapies include melatonin and clonazepam (level B of recommendation) [54]. Melatonin can be effective on RBD symptoms at dosages of 3–12 mg, with minimal side effects compared to clonazepam [56]. Clonazepam should be used at the lowest effective dosage (0.5–2 mg is usually recommended), with particular caution in patients with dementia, gait disorders, or concomitant obstructive sleep apnea syndrome [54].

Whether or not to inform the patient with iRBD about the risk of phenoconversion to a neurodegenerative disease is still debated [57,58]. On one hand, the negative psychological impact of such communication as well as the clinical and economic burden of prognostic tests [59] have to face with the current lack of disease-modifying treatments. On the other hand, the choice to disclose that risk can help the patient to preventively adopt a healthy lifestyle (with regular physical exercise, moderate caloric intake and antioxidant diets) with a possible protective effect. Also, the patient can be helped to make well-informed decisions in family, working, social and economic contexts. And more importantly, the patient can be trained for early recognition and treatment of initial neurodegenerative symptoms. Those patients will be monitored annually and will have more chances to be included in upcoming pharmacological clinical trials.

3.3. Different etiologies for a common pathophysiology

3.3.1. Physiology of REM sleep and pathophysiology of RBD

Brain structures involved in REM sleep and muscle tone modulation, under physiologic and pathological conditions (B) were shown in Figure 1. Normal REM sleep requires the inhibition of tonic and phasic muscle activity, as well as the inhibition of complex movements of dream enactment. The main generator of REM sleep is the sub-coeruleus nucleus (SubC), located in the lateral pontine

tegmentum just below the noradrenergic locus coeruleus [60]. It has glutamatergic projections stimulating the inhibitory neurons located in the ventral horn of the spinal cord and in the ventromedial medulla (VMM). In response, the release of glycine and gamma-aminobutyric acid (GABA) inhibits the spinal motor neurons, resulting in skeletal muscle atonia [61–63]. Moreover, the VMM inhibits the red nucleus in the rostral midbrain, which is involved in the generation of muscular twitches, contributing to muscle atonia during REM sleep. In turn, re-afferent stimuli coming from muscular twitches can activate the sensory and motor cerebral cortex, but they are all inhibited in REM sleep [64]. During wakefulness and slow-wave sleep, GABAergic projections from the periaqueductal gray, mesencephalic and pontine nuclei of the reticular activating system (RAS) inhibit the SubC, but during REM sleep this inhibition is lacking. However, the pedunculopontine nucleus (PPN) of the RAS has descending projections activating the SubC, thus promoting REM sleep; it also regulates ascending projections through the intralaminar thalamus to the cortex, modulating arousal [65]. In patients with RBD, different possible causes may lead to a disruption in SubC circuits directed to the VMM and the spinal ventral horn interneurons. The consequence is a lack of inhibition of the spinal motor neurons and, as a result, the loss of normal muscle atonia during REM sleep [61,62]. However, RBD is not merely the presence of increased tonic and phasic muscular activity during REM sleep; it is also characterized by complex movements performed by patients in enacting generally unpleasant dreams. In view of this, there is likely a more extensive dysfunction throughout the CNS, involving the motor cortex, the amygdala, and a broader spectrum of neurotransmitter pathways including cholinergic, noradrenergic and dopaminergic circuits [58,59].

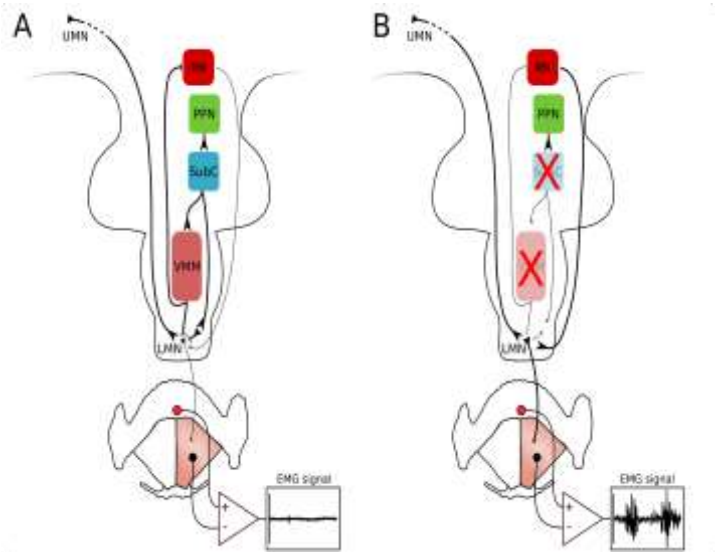

Figure 1. Brain structures involved in REM sleep and muscle tone modulation, under physiologic (A) and pathological conditions (B). UMN: Upper Motor Neuron; LMN: Lower Motor Neuron; RN: Red Nucleus; PPN: pedunculopontine nucleus; SubC: sub-coeruleus nucleus; VMM: ventromedial medulla; EMG: electromyography.

3.3.2. Isolated RBD (iRBD) and secondary causes

Until recently, RBD has been classified as “primary” or “idiopathic” when in absence of other

health complaints or causative agents, and "secondary" when associated with specific provoking factors, such as use of antidepressants, brainstem structural lesions, autoimmune neurological disorders or neurodegenerative diseases [66–68]. This historical view of RBD is progressively declining, in light of the increasing amount of evidence demonstrating the high rate of phenoconversion to a neurodegenerative disorder (particularly synucleinopathies) in patients with formerly idiopathic RBD. Conversion rate can reach 73.5% after 12 years of follow-up [69]. Actually, it is hypothesized that conversion rate could raise up to 100% for longer times of follow-up. As a result, the term "isolated" RBD is currently preferred to indicate what was previously defined "idiopathic", in light of the high risk to develop a neurodegenerative disorder. In the Movement Disorder Society (MDS) criteria for prodromal PD criteria, PSG-proven iRBD is included between the "clinical nonmotor markers", and it is recognized as the most predictive marker of phenoconversion (positive likelihood ratio, LR+: 130), even more than an abnormal DaTSCAN (LR+: 40) [70]. In more recent times, however, iRBD has been properly considered as a motor sleep-related symptom of synucleinopathy [71].

All possible causes of RBD share a dysregulation or a lesional disruption of brainstem structures regulating REM sleep. With particular reference to parkinsonisms, brainstem depositions of different abnormal proteins (including alpha-synuclein, tau, parkin and ataxin) have been associated to the development of RBD; conversely, several lines of evidence have been provided against a supposed role of dopaminergic depletion in RBD pathophysiology [72]. In some cases, however, lesions of supratentorial structures connected with the brainstem nuclei regulating REM sleep have also been described. We summarized the known etiologies of RBD in Table 2.

Table 2. Currently known causes of RBD.

Cause category	Specific Causes	Possible pathophysiological mechanisms
Drugs	● Antidepressants [73,74] ● Beta-blockers [75,76]	Serotonergic, noradrenergic, cholinergic pathway imbalance
Structural	● Traumatic [77] ● Vascular [78,79] ● Neoplastic [80,81] ● Demyelinating [82,83]	Structural damage of brainstem structures and pathways regulating REM sleep
Immune-mediated	● Autoimmune encephalitis [84,85] ● Narcolepsy [86,87] ● IgLON5 disease [88]	Structural or functional damage of supratentorial regions (e.g., limbic system, hypothalamus, thalamus) connected with brainstem structures and pathways regulating REM sleep
Neurodegenerative	● Alpha-synucleinopathies [72] ● Tauopathies [89,90] ● Prion diseases [91] ● Spinocerebellar ataxias [92] ● Huntington disease [93]	Neuronal/glial loss due to protein aggregates and subsequent cell death of brainstem structures and pathways regulating REM sleep

Note: REM = rapid eye movement.

The genetic background in iRBD needs a separate mention. Some studies tried to test if genes known to be related to parkinsonisms, both dominant and recessive, could explain iRBD occurrence, often with inconclusive results [94]. Among all the mutations so far associated with PD, the ones occurring on *GBA*, *TMEM175*, *SCARB2*, *INPP5F*, *SNCA* proved recently in a large genome-wide association study (GWAS) study to be associated with iRBD but not with PD or LDB without probable RBD [95,96]; other notable GWAS loci for PD and LBD, such as *LRRK2*, *MAPT*, *BIN1*, and *APOE* seem not to play a role in iRBD or RBD associated PD; moreover, some variants in *LRRK2* have been suggested to be even protective towards RBD occurrence [97]. Overall, these findings suggest that iRBD patients could represent a distinct subset of patients among synucleinopathies, with a genetic background that only partially overlaps with PD and LBD. Noteworthy is that all those genes are involved in the so-called autophagy-lysosomal pathway (ALP). It is not clear so far, however, to what extent this pathway is critical for RBD development: in fact, other mutations such as *NPC1* (involved in Niemann-Pick C), have not been linked to RBD development [98].

3.4. Association between RBD and neurodegenerative diseases

An association between RBD and neurodegenerative diseases was already mentioned in the first description of RBD, with two out of five patients being affected by olivo-ponto-cerebellar degeneration and atypical dementia respectively [38]. In the following years, the relationship between RBD and neurodegeneration became clearer: first, a high prevalence of RBD was observed in patients with neurodegeneration. Specifically, 30–60% of patients with Parkinson disease were found to have concomitant RBD [99,100]; the prevalence of RBD was found to be even higher in patients with LBD and MSA, with 50–80% and 80–95% respectively [101–103]. On the other hand, the longitudinal follow-up of patients with iRBD showed that the majority of patients evolved into an overt neurodegenerative disease [104,105]. One of the largest studies showed a phenoconversion rate of 80.8% after a median of 14 years since disease onset, with clinical diagnoses being PD in 62%, dementia in 29% (with clinical and/or pathological evidence of Lewy body disease in the majority) and MSA in 10% [104]. In another large study, an overt neurodegenerative disease was diagnosed in 90.9% of patients after 14 years from diagnosis (median follow-up duration of 4 years); clinical diagnoses were LBD in 45%, PD in 34%, mild cognitive impairment in 18% and MSA in 3% [105]. It appears that RBD is mostly associated with synucleinopathies, that is, neurodegenerative diseases caused by the accumulation of alpha-synuclein either in Lewy bodies (e.g., PD or LBD), or in glial cytoplasmic inclusions (as in MSA). In fact, iRBD is often considered a prodromal synucleinopathy, with neurodegeneration involving the brainstem but no or only minor involvement of the nigrostriatal pathways and the neocortex. The appearance of neurodegeneration in the latter structures determines the phenoconversion from iRBD to an overt synucleinopathy. This spatial-temporal progression reflects the neuropathological staging of PD proposed by Braak [32]. In-vivo multimodal imaging evidence supports this hypothesis: RBD patients and PD patients present the same level of involvement of parasympathetic intestinal neurons (demonstrated with ^{11}C-donepezil positron emission tomography (PET)), postganglionic sympathetic neurons (demonstrated with metaiodobenzylguanidine myocardial scintigraphy) and locus coeruleus (demonstrated with neuromelanin-sensitive magnetic resonance imaging sequences and ^{11}C-2-(α-(2-methoxyphenoxy)benzyl)morpholine PET), but RBD patients present a significantly lower nigrostriatal degeneration (demonstrated with ^{18}F-dihydroxyphenylalanine PET) [59]. However, discordant clinicopathological evidence is also present: it has been noted that

autopsy cases that are classified as stage I, IIa or IIb of the current Unified Staging System for Lewy Body Disorders (olfactory bulb, brainstem or limbic involvement) did not manifest RBD, whereas most of those with a higher staging did, thus potentially challenging this spatial-temporal correlation [106]. Despite these controversial findings, the strong association between RBD and synucleinopathies has been consistently confirmed by neuropathological studies [105,107–110]. However, some rare cases of RBD in association with other pathologically proven neurodegenerative diseases have been described [107,110]; this aspect is further discussed in the following paragraphs.

Interestingly, recent evidence suggests that the association between iRBD and increased risk of overt neurodegenerative disease is not dichotomous, but may be a continuum. The increased awareness of this entity and its relationship with neurodegeneration, together with an improvement in the diagnostic process, have brought to clinical attention some patients with episodes of RBD but without video-polysomnographic evidence of RWA. These cases have been defined as "prodromal RBD" [71,111]. Longitudinal studies have shown that prodromal RBD often evolves to RBD and it is associated with an increased risk of developing a neurodegenerative disease [112]. Furthermore, a detailed analysis of EMG activity during REM sleep in patients with RBD reveals that an increased amount of EMG activity (i.e., a stronger loss of REM sleep atonia) is associated with a stronger risk of phenoconversion to an overt neurodegenerative disease [113,114]. Overall, a picture of a spectrum or continuum from prodromal RBD, through RBD to neurodegeneration is gradually emerging from the latest scientific advances [71], with a clear impact on the future perspective of neuroprotective treatments.

3.5. RBD as a clinical biomarker of protein misfolding

The antemortem clinical diagnosis of a specific neurodegenerative disease does not always correspond to the actual autopsy-proven pathology; moreover, the strive for a pathology-specific and possibly disease-modifying treatment requires an in-vivo biological diagnosis of neurodegenerative disease. These hurdles have been pushing the researchers to look for biomarkers of neurodegeneration that are both pathology-specific, or at least "misfolded protein-specific", and easily obtained in-vivo. In the following paragraphs we will discuss the current evidence showing the potential strengths and weaknesses of using RBD as a clinical biomarker of protein misfolding, especially of alpha-synuclein misfolding.

3.5.1. Evidence in favor

As already stated above, there is abundant evidence of a correlation between RBD and neurodegenerative diseases: about 80–90% of iRBD patients develop a neurodegenerative disease within 14–16 years from diagnosis [38,99] and iRBD cases show structural and functional imaging features that are similar to those in patients with overt synucleinopathies [100]. Compelling evidence of a potential role of RBD as a clinical biomarker of neurodegeneration derives from pathological studies: in a large cohort of 170 subjects with RBD, either isolated or associated with a neurodegenerative disease, autopsy documented a synucleinopathy in 94% [101]. In some cases, multiple pathologies were present; 10 patients showed a non-synucleinopathy neurodegenerative disease. It has been observed that the clinicopathological association between RBD and synucleinopathy is stronger in cases with RBD symptoms preceding the appearance of other neurological symptoms. It is noteworthy that in 11 cases with RBD and a suspect non-synucleinopathy,

autopsy actually showed a synucleinopathy [101]. In another large longitudinal study [99], six patients with iRBD that evolved into an overt neurodegenerative disease had pathological evidence of Lewy bodies, Lewy neurites and neurodegeneration in multiple brainstem nuclei. The antemortem clinical diagnosis was diffuse Lewy Body Disease in three, Parkinson disease in two and mild cognitive impairment in one [99]. Finally, autopsy-proven Lewy body pathology has also been reported in two iRBD cases [102,103].

Multiple study groups have used a variety of in-vivo pathological or laboratory biomarkers of protein misfolding, known to be sufficiently accurate in diagnosing specific neurodegenerative diseases, and tested them on iRBD patients. It has thus been shown that the presence of phosphorylated alpha-synuclein can be demonstrated on skin and/or labial salivary gland biopsy in 50–90% of subjects with iRBD [115–118]. Another promising approach is represented by real-time quaking induced conversion (RT-QuIC), a laboratory technique that was created to detect the presence of misfolded prion protein [119], and subsequently applied with success to various other misfolded proteins [120–122], especially alpha-synuclein [34,123,124], both on cerebrospinal fluid and on brushing of the olfactory mucosa [125]. Specifically, RT-QuIC for alpha-synuclein was positive in 44.4% of olfactory mucosa brushing samples from 63 iRBD patients, and the sensitivity was higher in those with concomitant hyposmia [126]. Sensitivity appears to be higher on CSF samples, with most studies indicating around 90% sensitivity [127–129], although the performance may be lower in some specific cohorts that may include patients in an earlier stage [129]. Interestingly, two out of four patients with a negative alpha-synuclein RT-QuIC on CSF at baseline resulted positive on follow-up samples, suggesting that the sensitivity of the test may be lower at an earlier stage [129]. However, Kaplan-Meier curves for phenoconversion did not differ between alpha-synuclein-positive and -negative iRBD patients, indicating that alpha-synuclein RT-QuIC cannot currently be considered a reliable predictor of timing of phenoconversion [129].

The role of RBD as a clinical biomarker of alpha-synuclein misfolding is so strong that it is currently recognized as a diagnostic criterion for some synucleinopathies. Specifically, its absence despite five years of disease duration is considered a red flag for the clinical diagnosis of PD [130]. Moreover, a diagnosis of RBD with polysomnographic evidence is considered the strongest biomarker for prodromal PD, even stronger than an abnormal dopaminergic nuclear imaging test [2]. RBD plays a fundamental role in the diagnosis of LBD, being considered one of the five core clinical features required for the diagnosis [131]. On the other hand, RBD is recognized as a frequent feature of multiple system atrophy, but it was not included among the diagnostic criteria because it is also a common feature of other diseases [132].

3.5.2. Evidence against

A clinically useful biomarker is required to be both sensitive and specific. Unfortunately, the sensitivity of RBD as a biomarker of synucleinopathy is suboptimal, and it shows a wide range of prevalence among different diseases: from as low as 30% in PD, to as high as 95% in MSA [133].

On the other hand, the specificity may also be less than ideal: RBD is usually considered a manifestation of synucleinopathy [69], but neuropathological evidence shows that this is not universally the case [107,134]. In fact, in the largest series of RBD patients who underwent a post-mortem neuropathologic examination, 10/170 cases with neurodegenerative disease showed no signs of synucleinopathy: diagnoses were AD (6 cases), progressive supranuclear palsy (2 cases),

Creutzfeldt-Jakob disease and amyotrophic lateral sclerosis (one case) and indeterminate neurodegenerative disease (one case). RBD may still be considered a strong predictor of synucleinopathy, since 94% of pathologically proven neurodegenerative diseases showed signs of synucleinopathy most commonly of the Lewy body type, but it seems unable to predict if, when and what kind of neurodegenerative disease iRBD will evolve into. In fact, contrary to what one may expect, a population-based study on 44 iRBD patients showed that over 3.8 years 32% developed mild cognitive impairment, whereas only 2% developed PD [135].

Occasionally, RBD is associated with non-degenerative neurological diseases. In the clinicopathological series by Boeve et al, two cases showed no neurodegeneration, but hypothalamic lesions [107]. Moreover, some cases of RBD due to non-degenerative structural lesions have been reported, with etiologies ranging from pontine stroke [78] to multiple sclerosis [82,83,136,137], to extra-axial compression due to meningiomas, schwannomas, aneurysms and surgery [80,138,139]. RBD associated with narcolepsy deserves a special mention, because it is a relatively common feature of narcolepsy type 1 [140], although it may show some specific clinical features compared to other forms of RBD [118]. Moreover, RBD may accompany NREM sleep parasomnias in the clinical syndrome of anti-IgLON5 disease: this autoimmune disease is particularly intriguing because it is characterized by a primary autoimmune process that induces a neurodegenerative process with accumulation of hyperphosphorylated tau [141], thus linking autoimmunity and neurodegeneration. All these instances underline the fact that RBD cannot be considered an infallible marker of synucleinopathy.

3.6. The emerging role of intestinal microbiota in the association between RBD and neurodegeneration

An early diagnosis of alpha-synuclein misfolding (and, possibly, of neurodegenerative disease) is a target that can be probably achieved by shifting our focus to the gut. Since Braak's model has been described in an attempt to explain Lewy bodies pathology diffusion throughout the brain [32], gastrointestinal tract has gained more and more interest as a responsible of fundamental neuroinflammation processes [142]. Aggregation of alpha-synuclein in the gastrointestinal tract in animal models of advanced and, more interestingly, early PD has been widely described [143–148]. Moreover, growing evidence is showing that PD patients also suffer from a state of colon inflammation [149], characterized by production of pro-inflammatory cytokines by mucosal leukocytes, accounting at least for the non-motor symptoms of constipation and nausea that affect PD patients [150,151]. The local gut microbiome, the vast community of microbial organisms that inhabits our digestive tract and that lives in balance with host cells, is considered a main actor for the production of these inflammatory mediators, especially when a change in its composition or in its relationship with mucosal cells happens [152]. Causes of such changes have not been completely understood, but a probable causal factor can be traced in particular types of diet: Western diet (high in saturated fat and refined carbohydrates) might result in dysbiotic microbiota (e.g., lower bifidobacteria, higher firmicutes, and proteobacteria), triggering an activation of local immune cells [153–156]. Specifically, this inflammatory state is characterized by production of mediators that induce a state of oxidative stress in neurons belonging to the Enteric Nervous System [157–162], thus leading to molecular damages, including misfolding processes. At the same time, such mediators reach the blood-brain barrier through the systemic circulation increasing its permeability and leading to activation of

local glial cells, triggering a local state of inflammation far from the gut [163,164]. Another important role of enteric nervous system in pathophysiology of neurodegenerative disease has been found in the misfolded alpha-synuclein capability of using vagal nerve fibers to co-localize in central nervous system through a centripetal axonal transport [165,166], thus giving another evidence of the strict dependence of cerebral inflammatory processes by peripheral (and, particularly, intestinal) triggers.

In a sample of healthy elderly from the prospective Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND) study, possible RBD was associated with a decrease in Lactobacillus, Faecalicoccus and Victivallis and an increase in Haemophilus [167]. These changes do not correspond to the usual changes observed in PD patients [167]. In a study on the gut microbiome in PD and iRBD patients, it was shown that 75% of the deviations between patients with PD or iRBD versus healthy controls were qualitatively similar [168]. Quantitative data were less convergent, and some significant differences were also noted: for example, samples from iRBD patients showed a decrease in Prevotellaceae compared to the PD group from the same study, which had been previously described in a different cohort of newly diagnosed PD patients [169]. On the other hand, in the same study, the analysis of nasal microbiota only showed mild differences between PD patients and healthy controls, probably attributable to the influence of pharmacological treatment [168]. A recent study confirmed similar alterations of the gut microbiome between iRBD and PD patients, and even identified some mild alterations (increase of pro-inflammatory Collinsella and decrease of butyrate-producing [Eubacterium]_ventriosum_group) in first-degree relatives of iRBD patients, which became increasingly more marked in iRBD and in PD patients [170].

It is more and more evident that precocious intestinal impairment in neurodegenerative diseases is a mainstay of their pathophysiology. RBD, aside from being a clinical prodromal of neurodegenerative disorders, could be a witness of microbiome disequilibrium as well, both events tied together by local and systemic inflammation and by protein misfolding as its consequence. Overall, alterations of the gut microbiota can be identified even in patients in the earliest phases of prodromal synucleinopathies such as iRBD. It is reasonable to hypothesize that these changes may not simply represent an epiphenomenon or a marker, but may actually be involved in the induction of neurodegeneration. Moreover, the data presented above suggest that there is not a static microbiome "fingerprint" of synucleinopathies, but that the modifications in the composition of the gut microbiota dynamically evolve throughout the natural history of the disease from iRBD to de novo PD to established PD. Further longitudinal studies on the evolution of the gut microbiome from healthy to prodromal to clinically overt synucleinopathies may shed more light on this dynamic process.

4. Conclusions

RBD is nowadays a well characterized REM sleep parasomnia. However, its prevalence is still probably underestimated, due to cases with very mild clinical manifestations that may not come to clinical attention. Multiple etiologies have been so far described: vascular, immunological, tumoral lesions, and above all neurodegenerative processes of the CNS.

Although it is widely considered the most powerful biomarker of prodromal and overt alpha-synucleinopathy, some uncertainties are still present on its clinical value in predicting phenoconversion to a specific neurodegenerative disease. Furthermore, it cannot be excluded that, in an unknown proportion of patients, coexisting multiple neurodegenerative pathologies might be

responsible of clinical phenotypes of RBD and diseases other than alpha-synucleinopathies; and that unrecognized immunological processes within the brainstem could have led to REM parasomnia without necessarily inducing misfolding events typical of neurodegenerative disorders. Also, the extent of brain pathology at the time of RBD diagnosis and during its follow-up is not completely known, a point that will become relevant in the selection of patients for future disease-modifying treatments. Noteworthy, the relevant inductors of the misfolding process, early in the development of neurodegeneration, are still largely unknown, as well as we lack evidence if those inductors might be "protein specific" or not. The emerging field of gut-brain axis research will hopefully shed lights and will open new perspectives in neurodegenerative disorders' primers.

For all those reasons we believe that RBD needs a more widespread awareness, both in patients and clinicians, in order to diagnose also very mild cases, to implement a more extensive diagnostic workup, and to characterize patients longitudinally. Moreover, a special effort should be made to consider the possibility of multiple neurodegenerative pathologies and to study intestinal microbiota in those patients. This will in turn allow preclinical disease-modifying treatment of several underlying disorders.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare that they have no conflict of interest.

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