REM SLEEP, REM PARASOMNIAS, REM SLEEP BEHAVIOUR DISORDER

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We review the literature on REM parasomnias, and their the underlying mechanisms. Several REM parasomnias are consistent with sleep dissociations, where certain elements of the REM sleep pattern emerge in an inadequate time (sleep paralysis, hypnagogic hallucinations and cataplexy) or are absent/partial in their normal REM sleep time (REM sleep without atonia, underlying REM sleep behavior disorder). The rest of REM parasomnias (sleep related painful erection, catathrenia) may have other still unclear mechanisms.
REM parasomnias deserve attention, because in addition to disturbing sleep and causing injuries, they may shed light on REM sleep functions as well as the heterogeneous etiologies of parasomnias. One of them, REM sleep behavior disorder has special importance as a warning sign of evolving neurodegenerative conditions mainly synucleinopathies (some cases synucleinopathies themselves) and it is a model parasomnia revealing that parasomnias may have by autoimmune, iatrogenic and even psychosomatic etiologies.

Keywords: *REM sleep, REM parasomnia, REM sleep behavior disorder, synucleinopathy*

REM-ALVÁS, REM-PARASOMNIÁK, REM-MAGATARTÁSZAVAR
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Áttekintjük a REM-parasomniák irodalmát, és röviden foglalkozunk a hátterükben álló mechanizmussal. A csoport tagjainak egy része alvásdisszociációnak felel meg, ahol a REM-alvás egyes elemei inadekvát fázisban (például alvási paralysis, hypnagog hallucinációk) jelennek meg, vagy fordítva, elmaradnak/töredékesek a REM-alvás alatt, amelynek egyébként fiziológiás részei (REM-alvás izomatónia nélkül, a REM-magatartászavar hátterében álló rendellenesség).
A többi REM-parasomnia (alvásfüggő fájdalmas erectio, catathrenia) hátterében egyéb, egyelőre tisztázatlan mechanizmus állhat. A REM-parasomniák alvászavart és sérüléseket okozhatnak, és tanulmányozásuk megvilágíthatja a REM-alvás funkcióit és a parasomniák hátterében álló sokszínű etiológiát. A REM-magatartászavarnak különleges jelentősége van: neurodegeneratív betegségek, különösen synucleinopathiák előjele (vagy kísérője) lehet, talán maga is az. Egyben modell-rendellenesség, ami autoimmun, iatrogén és pszichoszomatikus zavarok feltárását teheti lehetővé.

Kulcsszavak: *REM-alvás, REM-parasomnia, REM-magatartászavar, synucleinopathia*

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The International Classification of Sleep Disorders (2014) defines parasomnias as unusual movements, behaviors, autonomic phenomena and dreams during sleep. They may co-occur with other sleep disorders e.g. obstructive sleep apnea syndrome, other parasomnias or epilepsy[1]. Based on the hosting sleep stage, NREM-, REM-sleep-related and other parasomnias are distinguished. We overview REM parasomnias focusing on REM sleep behavior disorder (RBD).

Physiology background

Sleep, regulated by intrinsic rhythm-generators and environmental stimuli, is far from homogeneous. It is composed of the cyclic alternation of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages constituting the macrostructure of sleep. Both REM and NREM sleep are under homeostatic control[2]. REM sleep alternates phasic and tonic phases[3, 4] while NREM sleep contains multi-level oscillations as the cyclic alternating pattern (CAP), the alternation of slow wave up- and down states and possibly shorter rhythms[5].

The pattern of REM sleep is made by the combination of striated muscle atonia, rapid eye movements, dreaming, a desynchronized EEG activity, "saw tooth" waves (STW), ponto-geniculo-occipital (PGO) discharges and rhythmic hippocampal slow waves[6].

The GABAergic inhibitory neurons in the dorsomedial medulla (DmM) and the excitatory neurons in the ventral medulla (VM; containing the GABA synthesizing enzyme, glutamate decarboxylase - GAD2) initiate and maintain REM sleep, possibly through their projections to the dorsal and median raphe (DR; MR). During NREM sleep, their activity synchronizes with the infraslow oscillations of the EEG spindle band, modulating the latency of REM sleep episodes. Thus, dorsomedial and ventral medullary neurons promote REM sleep, and their slow activity-changes may coordinate NREM-REM sleep transitions[7].

STW are theta-range transients emerging from the EEG background. They are joined by an increase of variable frequency oscillations over widespread cortical regions, suggesting an involvement in cognitive processes[8].

PGO waves are biphasic field potentials known in several mammalians including humans[9]. Pontine P-waves (parts of PGO waves) couple with hippocampal slow oscillations – theta in mice, delta in humans. Together with the bursts of hippocampal CA1 neurons, they may coordinate brainstem and hippocampal activity and participate in sleep-related neural plasticity[10, 11].

A recent revolutionary discovery has identified Gq-type muscarinic acetylcholine receptors (Chrm) 1 and 3 as 'dream genes'; their knock-out resulted in short-sleeper phenotypes and loss of REM sleep[12, 13].

PHASIC AND TONIC REM

Phasic REM sleep features muscle twitches, rapid eye movements, PGO waves and dreaming. In tonic REM sleep with even EEG activity, the awakening threshold is lower and the evoked responses resemble those in waking[3, 14].

THE REM SLEEP NETWORK

Jouvet's pioneer cat-brain trans-section experiments[15] have shown that the neural circuitry of REM sleep nestles in the brainstem, mainly in the

ABBREVIATIONS

BDNF: brain-derived neurotrophic factor
CA: cornu ammonis
CAP: cyclic alternating pattern
Chrm: muscarinic acetylcholine receptor
CeA: central amygdala
cLDTN: caudal laterodorsal tegmental nucleus
DLB: diffuse Lewy body disease
DmM: dorsomedial medulla
DR: dorsal raphe
DTI: diffusion tensor imaging
EEG: electroencephalography
EMG: electromyography
GABA: γ-aminobutyric acid
HLA: human leucocyte antigen
LC: locus coeruleus
LH: lateral hypothalamic
LDT: laterodorsal tegmental (pontin)
LPT: lateral pontine tegmental
MCH: melanin-concentrating hormone
MN: motoneuron
MR: median raphe
MRI: magnetic resonance imaging
NREM: non-REM
OX: orexin
PC: precoeruleus
PD: Parkinson's disease
PGO: ponto-geniculo-occipital
PPT: pedunculo-pontin-tegmental
RBD: REM sleep behaviour disorder
REM: REM rapid eye movement
RSWA: REM sleep without atonia
SLD: sublaterodorsal
SSRI: selective serotonin reuptake inhibitor
SSNI: selective noradrenaline reuptake inhibitor
STW: saw tooth wave
SVH: spinal ventral horn
TDP-43: transactive response DNA 43 kDA binding protein
vlPAG: ventro-lateral periaqueductal grey
VM: ventral medulla
VmM: ventromedial medulla

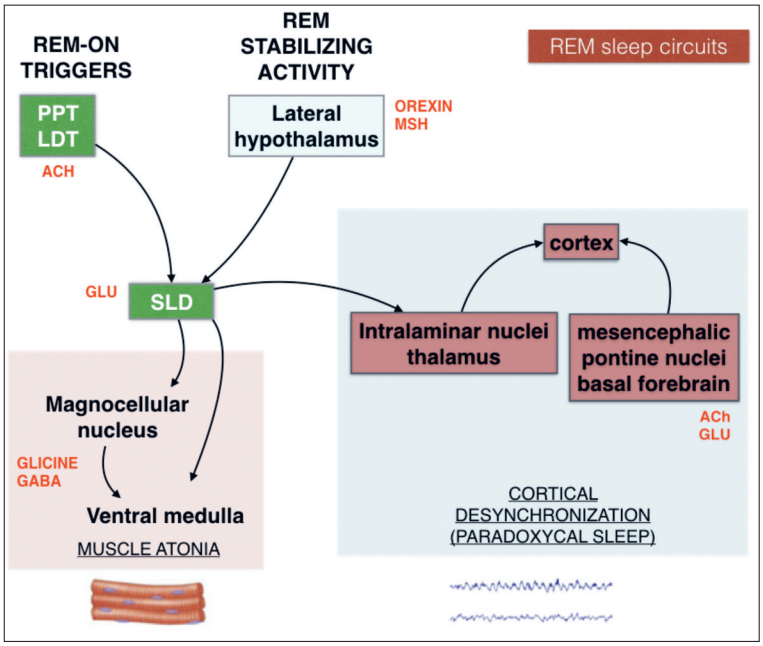

Figure 1. *REM sleep network. The caudal laterodorsal tegmental nucleus (cLDT), the sublaterodorsal (SLD) nucleus and precoeruleus region (PC) comprise an executive pontine circuit element for REM sleep. REM-on glutamatergic neurons of the ventral SLD mediate REM motor atonia through direct synaptic activation of glycinergic interneurons of the spinal ventral horn (SVH) as well as via GABAergic/glycinergic neurons of the ventromedial medulla (VmM). Lateral hypothalamic neurons containing orexin (OX) provide excitatory and stabilizing synaptic control over LPT neurons. Cholinergic laterodorsal tegmental and pedunculopontine tegmental (LDT/PPT) neurons may produce REM sleep through activation of REM-on SLD neurons. Lateral hypothalamic (LH) neurons containing melanin-concentrating hormone (MCH) also regulate REM sleep, possibly through direct inhibition of REM-off vlPAG/LPT neurons*[20]

dorso-rostral pons. A REM on/off system regulates REM through multiple ascending and descending sleep trajectories[16] **(Figure 1)**.

The rise of ACh from laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) neurons promotes REM sleep through the activation of REM-on glutamatergic sublaterodorsal (SLD) neurons[2]. REM-on neurons' activation (and concomitant REM-off circuits' inhibition) is supported by the suspension of the tonic monoaminergic and GABAergic inhibition present in wakefulness and slow-wave sleep. SLD activity builds up the REM sleep pattern throughout descending inhibitory signals generating muscle atonia and ascending activating pathways leading to cortical desynchronization.

The melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus have maximal activity during REM-sleep regulating it by the inhibition of the REM-off GABAergic, histaminergic and mono-aminergic neurons[17, 18]. Also the orexin neurons of the lateral hypothalamus stabilize REM sleep through their receptors on 3/4 of SLD neurons, increasing SLD's downstream output[19].

REM SLEEP PRESSURE AND HOMEOSTASIS

REM homeostasis is at least partially independent from the circadian clock[21]. REM sleep pressure is mediated by a brain-derived neurotrophic factor (BDNF), accumulating after REM sleep deprivation[22]. REM sleep deprivation links with changes in the hypothalamic-pituitary-adrenal axis, metabolic balance, thermoregulation and the concentration of neurotransmitters including steroid hormones and prolactin[23].

REM SLEEP EVOLUTION AND ONTOGENESIS DURING THE LIFE-SPAN

Humans sleep less (~7 hours) than other primates, have a higher ratio of REM/ NREM sleep (~1:3.5) and a higher sleep efficiency. The luxury of excess REM sleep may be related to humans' 'earthbound' sleeping (with no risk of drop-downs due to REM-atonia)[24]. It may contribute to the maturation of networks for innovation, creativity and ideation[25]. Interestingly, REM sleep is reduced in astronauts in weightless environment, suggesting a role of gravity in REM sleep regulation[26].

REM sleep dynamics vary with aging. Neonatal sleep begins with 'active sleep' (continuous mixed fast activity with rapid eye movements and muscle twitches) the precursor of REM sleep, alternating with 'quiet sleep', the precursor of NREM sleep[27]. Its amount declines in the first months/years, when a regular alternation of NREM/REM sleep stages builds up and wakefulness last longer. During school-age, the amount of REM sleep declines further, then it remains stable in adulthood undergoing a slight reduction later[28].

The functions of REM sleep

REM sleep is believed to be strongly linked with mood regulation, creative problem solving and emotional memory consolidation[29, 30].

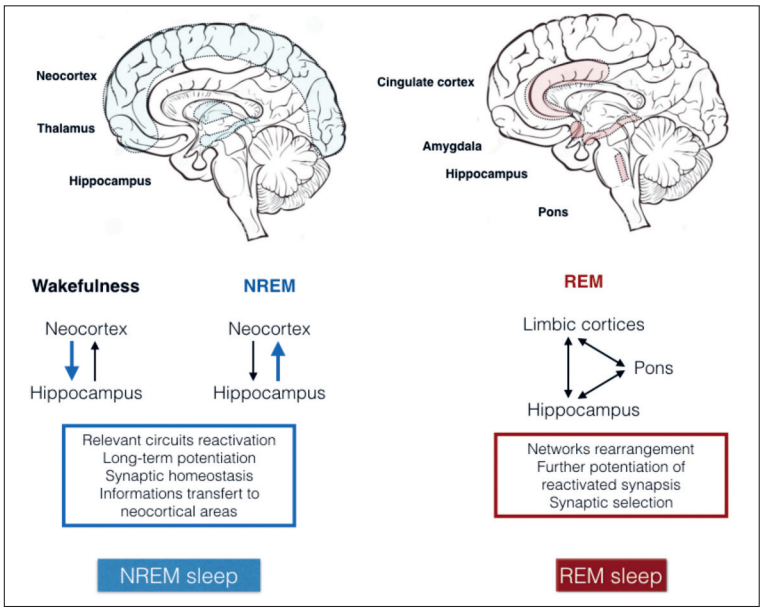

Figure 2. *Schematic representation of NREM and REM sleep dependent memory processes*

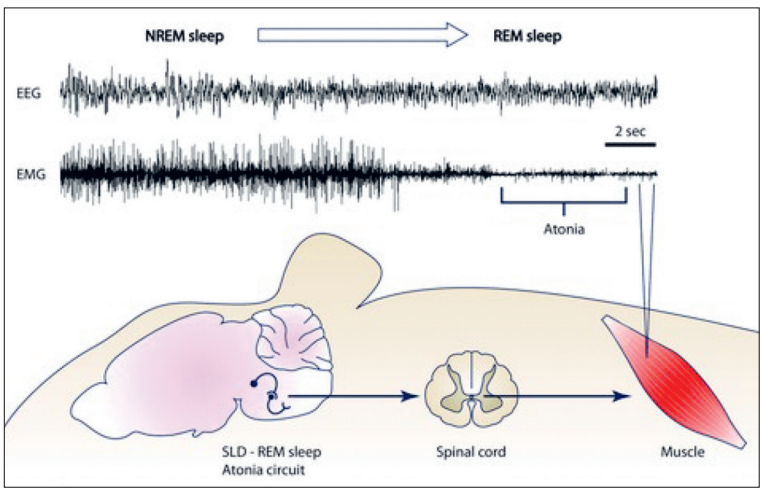

Figure 3. *The sublaterodorsal nucleus (SLD)'s central role in REM sleep atonia*[40]

While the low level of acetylcholine in NREM sleep favors the communication of the dorsolateral prefrontal cortex and the hippocampus sustaining the transfer and consolidation of declarative memory traces[31] , the high level of acetylcholine in REM sleep promotes 'emotion-driven memory-processing' involving the amygdala, the anterior cingulate and medial prefrontal cortices[32] **(Figure 2)**. The consolidation of fear memories during REM sleep possibly contributes to post-traumatic stress disorder (PTSD)[33]. REM sleep allows novel associations based on the information learned in NREM sleep[34]. Synaptic pruning and selection is likely linked to REM sleep, too[35]. Dream reports can be elicited after awakening from any sleep stages, however, REM sleep is considered the "dream-phase" with longer dreams and more bizarre contents compared to NREM sleep[36].

THE FUNCTION OF THE REM SLEEP-RELATED MUSCLE ATONIA

The function of REM sleep-related muscle atonia is mysterious. It certainly protects the sleeper from acting out dreams, and the suppression of motor activities can outweigh certain potentially sleep-disruptive stimuli. In this regard, REM-dependent muscle atonia is a sentinel of sleep resilience[37].

During RBD episodes, the rigid muscle tone of Parkinson's disease (PD) patients normalizes[38], suggesting a correcting function of REM sleep for normal waking muscle-tone. Similarly, PD's muscle rigidity parallels the lack of muscle atonia – REM sleep without atonia (RSWA) –, the basic feature of RBD, which is often a precursor and companion of PD.

THE REGULATION OF REM SLEEP ATONIA

The key members of the atonia network are the SLD and the noradrenergic precoeruleus region (PC); additionally, the caudal laterodorsal tegmental nucleus (cLTDN), the mesencephalic periaqueductal grey, orexin and melanin cells of the lateral hypothalamus, as well as nuclei of the ventromedial medulla (VmM) participate in it[39].

The glutamatergic activation of REM-on neurons in the ventral SLD[40, 41] mediates REM motor atonia through two redundant trajectories: recruiting glycinergic interneurons in the spinal ventral horn (SVH) and GABAergic/glycinergic neurons in the VmM; inhibiting SVH motor neurons in both ways.

Silencing SLD neurons suspends normal REM sleep muscle atonia resulting in RSWA, while its selective activation favors cataplexy and sleep paralysis[42–44]. A direct noradrenergic pathway links the spinal motoneurons with the locus coeruleus (LC), and a serotonergic one with the dorsal raphe (DR) both inhibiting the REM-atonia generation of the SLD[45] **(Figure 3)**.

Table 1. *REM sleep dissociation phenomena*

	Abnormally emerging/ missing element of REM sleep	State of appearance	Duration
Sleep paralysis	REM muscle atonia	Sleep-wake transition	Minutes
Cataplexy	REM muscle atonia	Wakefulness	Seconds -minute; sudden
Hypnagogic hallucination	REM sleep dreaming	Sleep-wake transition, sleep paralysis, cataplexy	Minutes?
Sleep attacks in narcolepsy or Parkinson's disease	REM sleep	Wakefulness	>Minutes
REM sleep without atonia	REM muscle atonia is absent or fragmentary	REM sleep	periods of REM sleep

Parasomnias

SEVERAL REM SLEEP PARASOMNIAS REPRESENT REM DISSOCIATION PHENOMENA

The separated ascending and descending pathways regulating the rostral and caudal components of the REM sleep pattern allow REM dissociation; i.e. REM sleep elements as dreaming or muscle atonia emerging separately in a wrong time or missing in the right time, during REM sleep **(Table 1)**. Cataplexy, sleep paralysis and hypnagogic hallucinations make positive REM sleep dissociation states (REM sleep phenomena emerge in inadequate phases), while RBD represents a negative dissociation, where the normal muscle atonia is absent or fragmentary during REM sleep **(Figure 4)**.

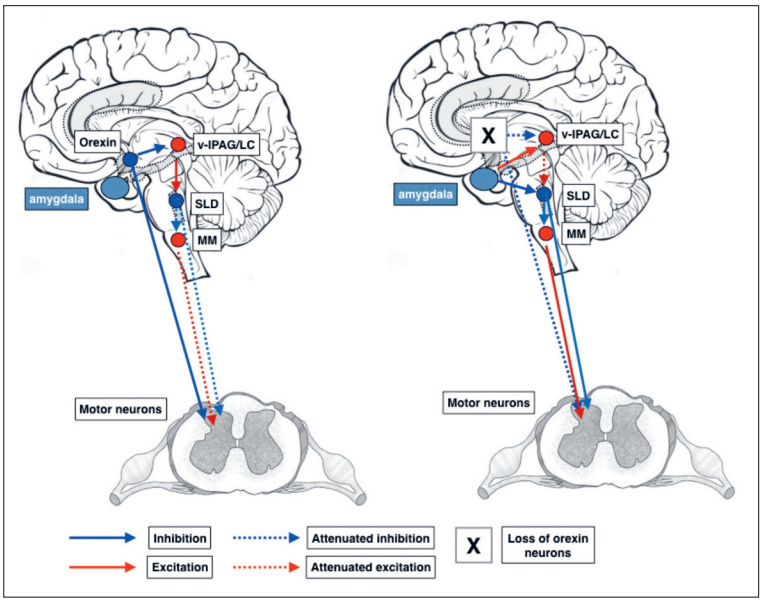

Figure 4. *Inappropriate activation of the REM sleep atonia circuitry during wakefulness is thought to produce cataplexy. Glutamatergic REM-active SLD neurons trigger the paralysis of REM sleep via stimulation of the GABAergic/glycinergic cells in the VmM. These VmM neurons send inhibitory projections to skeletal motor neurons. Under normal conditions, strong positive emotions are processed via GABAergic neurons of the CeA, which then inhibit cells in the LC and vlPAG. However, in the absence of the LH hypocretinergic neurons in cataplexy, this inhibition fails, so the REM sleep atonia circuit is released from inhibition and triggers muscle paralysis while the individual remains conscious. The inhibition of LC neurons during cataplexy removes noradrenergic inputs to motoneurons, thereby enhancing the muscle paralysis of cataplexy*

CeA: central nucleus of the amygdala, GABA: γ-aminobutyric acid, LC: locus coeruleus, LH: lateral hypothalamus, VmM: ventral medial medulla, SubC: subcoeruleus, vlPAG: ventrolateral periaqueductal gray, MN: motoneuron

SLEEP PARALYSIS WITH HALLUCINATIONS: REM SLEEP ATONIA AND DREAMING EMERGE IN WAKEFULNESS OR DROWSINESS

Sleep paralysis has been described in as early as 1664[46]. Over the centuries, it has often been attributed to the presence of evil: demons, the old hag in Shakespeare's Romeo and Juliet. In the frightening paralyzed state occurring during sleep-wake transitions (instead of REM sleep), the affected person cannot move or speak for a few minutes, experiences chest pressure, unable to call, suffocating – "something is sitting on the chest" – or feeling outside own body. It resolves spontaneously or on called by name. Sleep paralysis occurs solely or as a member of the narcoleptic tetrad. Its family accumulation suggests a genetic background[47]. Polymorphisms in the PER2 (Period Circadian Regulator 2) gene, a component

of the circadian clock mechanism, have been associated with a predisposition to sleep paralysis[48].

Multimodal hallucinations and lucid dreaming co-occur in 75% of cases[49, 50] Intruder (someone in the room) and incubus type (someone carrying out aggressive/sexual acts) hallucinations occur. Since those hallucinations are perceived as real by the individual, they may lead to even legal consequences. Due to hallucinations with "demonic significance", the condition has been sometimes linked to schizophrenia. Antidepressants (Escitalopam, Venlafaxine) have been suggested for treating the most disturbing cases, reassurance and tailored psychotherapy (meditation-relaxation therapy) may help.

REM SLEEP BEHAVIOR DISORDER: MISSING OR FRAGMENTED REM MUSCLE ATONIA ALLOWS DREAM ENACTMENT

RBD has emerged out of the big bunch of nighttime confusional states and violent behaviors, the latter reported by 1.7% of the population[51]. First described in 1986[52], RBD is a parasomnia, in that the individual "effects" his/her dreams due to RSWA, because the normal loss of muscle tone (a transient global paralysis) of REM sleep, is absent.

The International Classification of Sleep Disorders (2014) suggested the following diagnostic criteria for RBD: (1) repeated episodes of sleep-related vocalization and/or complex motor behaviors; (2) these behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep; (3) polysomnographic recording demonstrates RSWA; (4) the disturbance is not better explained by another sleep or mental disorder, medication or substance abuse[53].

RSWA is defined as sustained or intermittent elevation of chin electromyographic (EMG) tone or phasic chin or limb EMG twitching[54, 55], during at least one third of the REM sleep period. Since the persisting upper airway muscle tone may prevent some apneic episodes, RSWA can be protective against obstructive sleep apneas.

Despite the fact that RBD is a REM sleep disorder, it seems to affect sleep globally. Based on a cohort study[56], NREM micro-sleep instability reflected by the rate of CAP was lower (sleep was more stable) in idiopathic RBD patients compared to controls. The reduction of CAP rate was even more marked in the converter RBD-group (progressing to a Parkinsonian condition). Thus a lower CAP rate signalized a higher risk for conversion into a syncleinopathy.

RBD is categorized as idiopathic, or rather isolated when standing alone; and symptomatic or rather combined when associated with other disorders or states. The combined forms can be iatrogenic related to medication and other substances. They often associate to neurodegenerative diseases especially α-synucleinopathies, as well as to tauopathies, TDP-43-pathies (transactive response DNA 43 kDA binding proteinopathies), to narcolepsy and to any causes affecting the REM sleep network[57].

Prevalence

The prevalence of isolated RBD is ~ 0.38%-2% in the population >60 years-old and 5-13% in older community-dwellers doubly affecting men[58, 59]. An equal gender ratio has been reported in younger age groups[60], often in combination with narcolepsy and other conditions. There is a high rate of autoimmune comorbidity in women[61]. The disorder is tenfold more frequent in patients with mental health conditions. Additional risk factors include antidepressant use, low educational level, historic head trauma, pesticide exposure, smoking, ischemic heart disease, and inhaled corticosteroids[62].

Clinical features

RBD is characterized by sudden, vehement and fragmentary movements and speech or shouts out of sleep. There are frequent injuries caused by the patient falling out of bed or the bed partner being attacked by the half-sleeping patient enacting often horrifying dreams[61]. RBD episodes favor the second half of the night - the period of REM sleep dominance; contrasting NREM parasomnia episodes emerging in the early hours of night sleep. The patients remember their dreams often involving elements of aggression or animals[63, 64].

Melatonin 3-12 mg or clonazepam 0.5-2.0 mg usually help. Clonazepam may aggravate obstructive respiratory events and cognitive symptoms; melatonin is usually well-tolerated. Donepezil and Vortioxetine are additional treatment options. Second-line therapies include temazepam, lorazepam, zolpidem, zopiclone, pramipexole, ramelteon, agomelatine, cannabinoids, and sodium oxybate. A bed-alarm system may protect patients leaving their bed during episodes, and counselling or hypnosis might help suppressing nightmares[65, 66].

Aetiologies of RBD

Any etiology impairing the complex REM atonia network may cause RSWA/RBD. The duration

(transitory or chronic) and associated features depend on the origin of the brainstem dysfunction (drug, hypoxia in obstructive sleep apnea) or lesion (neurodegenerative, inflammatory etc.)

RBD may be an early sign of neurodegeneration offering an opportunity to understand, and - most importantly - prevent or delay subsequent neurologic impairment. In a seminal study on elderly patients with isolated RBD, 80.8% developed a parkinsonian disorder/dementia during 16 years follow up, with a mean delay of 14 years from RBD onset[67]. This high conversion-rate to neuro-degeneration was confirmed later by many additional studies.

There is a striking specificity of RBD converting to a synucleinopathy as PD, diffuse Lewy body disease (DLB), multisystem aptrophy (MS), spinocerebellar atrophy type 2, Tourette syndrome, Möbius syndrome or Smith-Magenis syndrome. The disorder also links to tauopathies and TDP 43-pathies as Alzheimer's disease, amyotrophic lateral sclerosis and Huntington's disease, Guadalopean Parkinsonism and progressive supranuclear palsy[57, 58, 62, 68]. In a systematic review on 237 adult RBD patients with a non-synucleinopathy neurology conditions 19% had brain lesions, typically in the brainstem. Pontine ischemic lesions were the most frequent, but other types of structural lesions and conditions (including inflammatory, demyelinating and autoimmune, 22%) occurred too. Alzheimer's disease developed in 12% of RBD cases and other tauopathies in 9%. The high prevalence (12%) of Arnold-Chiari malformation highlighted the importance of brainstem involvement; suggesting the pathogenic role of the affected network rather than the type of lesion[69]. Based on clinical experiences, these features of RBD appearing with narcolepsy, do not progress to a neurodegenerative condition; narcolepsy seems to be protective in that respect.

Imaging features of RBD may mark the risk for Parkinson's disease

RBD-related brain changes were detected *in vivo* with structural MRI and diffusion tensor imaging (DTI): microstructural changes in the white matter of the brainstem, the right substantia nigra, the olfactory region, the left temporal lobe, the fornix, the internal capsule, the corona radiata, and the right visual stream[70]. The progression of RBD linked with parieto-occipital and orbitofrontal thinning as well as visuospatial loss, while the cognitive decline associated with parietal degeneration[71]. Isolated RBD patients' decreased striatal DAT binding[72], the loss of nigral hyperintensity on 3.0-T MRI and transcranial echo may predict short-term progress of RBD to synucleinopathy[73]. Multimodal MRI, neuro-melanin-sensitive volume-, and signal intensity measures discriminated RBD patients from controls and predict a Parkinsonian progress[74].

RBD caused by autoimmunity: anti-IgLON5 disease

Growing number of diseases have been recognized to have unexpected inflammatory or autoimmune etiologies e.g. PD[75] , Alzheimer's disease[76] and narcolepsy[77] as well as paraneoplastic limbic encephalitis and Morvan syndrome. A human leucocyte antigen (HLA) association is usually considered a hint to autoimmunity e.g. in narcolepsy, which is another REM sleep dysregulation syndrome sometimes overlapping with RBD and carrying the strongest HLA Class II association among all diseases[78]. Also RBD link with HLA class II genes: 84% of 25 RBD patients carried the DQw1 (DQB1*05,06) alleles and 28% were DR2 positive[79].

The possibility of RBD with an autoimmune background is revealed by the recognition of a novel autoimmune-neurodegenerative disease-spectrum anti-IgLON5 disease, manifesting combinations of parasomnias, obstructive sleep apnea syndrome with stridor, bulbar and limb movement disorders, axonal neuropathy and cognitive loss[80]. As an autoimmune tauopathy[81], anti-IgLON5 disease models the link between autoimmunity and neurodegeneration[82]. The hallmark of the disease is the presence of antibodies against IgLON5, a neural cell adhesion protein of unknown function. The effect of immunotherapy is not yet clear. About 80% of anti-IgLON5 patients present with sleep-related vocalizations, movements and behaviors as well as sleep-disordered breathing at age> 60, with an equal male/female ratio. Neuropathology examination shows an atypical neuronal tauopathy with neuronal loss and gliosis in the hypothalamus and brainstem tegmentum[83–85]. Video-polysomnography may reveal a NREM parasomnia with sleep-talking, simple or finalistic movements, poorly structured N2 sleep, obstructive sleep apnea with stridor and RSWA. A lymphocytic pleocytosis was found in one patient. Four syndrome combinations have been delineated: (1) insomnia, parasomnia and disordered breathing; (2) a bulbar syndrome + salivation, stridor, even acute respiratory failure; (3) a supranuclear palsy-like syndrome; and (4) cognitive decline with figural and working memory impairment, with or without chorea. Most patients carry the HLA-DRB1*10:01 and HLA-DQB1* 05:01 haplotypes (the same as isolated RBD patients) and have IgLON5 antibodies both in serum and cerebrospinal fluid. Anti-IgG1 and -IgG4 antibodies are found[86].

RBD variants and the differential diagnosis of RBD

In overlap parasomnias, status dissociatus and agrypnia excitata, fragments of partial wakefulness, NREM and REM sleep amalgamate in irregular combinations, sometimes underlined by brainstem disorders, encephalopathies, neurodegeneration or autoimmune encephalitis.

Sleep-related epileptic seizures, obstructive sleep apneas with pseudo-RBD, confusional arousals as well as nocturnal panic attacks may raise differential diagnostic issues solved by careful analysis of symptoms, clinical history video-polysomnography.

RBD and post-traumatic stress disorder

There is a peculiar link of RBD with PTSD. A motor dysfunction with increased muscle twitches during REM sleep has been early noticed in relation to stress and PTSD[87], and several case studies and war-veteran cohort studies found higher rate of RBD in PTSD patients compared even to trauma-survivors without PTSD[88]. The frequent co-occurrence of RBD and PTSD generated a distinct term - trauma-associated sleep disorder (TASD) - sharing the features of PTSD and RBD[89].

In PTSD patients, the rate of stress-related norepinephrine turn-over might have changed in the LC, leading to norepinephrine depletion and even cell death. LC's fine structural changes in relation to stress could be shown by neuroimaging in humans[90]. In rats, a single acute stressor could precipitate long-lasting changes in LC function contributing to stress-related disease[91]. Due to the persistent decrease of LC noradrenergic output to the REM atonia network, RSWA and RBD may evolve[92]. Another important mechanism potentially leading to the loss of muscle atonia in PTSD might involve stress-related changes of the Papez circuit and serotonergic pathways related to the DR nucleus[93].

RBD in PTSD might be a good example of a deep psychological impact turning to an organic condition. In addition, the specific link of RBD with PTSD justifies the diagnosis of PTSD as a distinct entity: just experiencing distress might be qualitatively different compared to experiencing distress + having PTDS (intrusion symptoms, avoidance of trauma related stimuli, mood and cognitive changes, insomnia or hypersomnia, reckless self-neglecting behavior, irritability and concentration disturbances (DSM-5)[94]. Whether RBD associated with PTSD carries the long-term risk for neurodegeneration, is unknown.

RSWA but no RBD with antidepressants?

The association of RBD/RSWA with the use of antidepressants – selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) – has been early described[95]. A large study found an association of SSRI and SNRI use with RSWA only, curiously not accompanied by an increase of the frequency of RBD[96]. Another study found similar results: RSWA but no RBD had occurred in 8.8% of young psychiatry inpatients treated with fluoxetine, venlafaxine, mirtazapine, paroxetine, clomipramine or sertraline as well as quetiapine; thus, an association of antidepressants with a florid/hypermotor RBD has remained dubious[97]. A large study on 318 patients evidenced the association of comorbid depression and SSRI use with RBD, but a clear cause-and-effect relation between antidepressants and RBD has neither been confirmed[98].

Because antidepressants increase REM sleep muscle tone, they are routinely used in the treatment of cataplexy[99]. On the other hand, since around one third of RSWA cases of variable etiologies manifest RBD[54], the antidepressant-related increase of RSWA-rate without concomitant increase of RBD-rate needs an explanation. One may speculate that the iatrogenic increase in muscle tone is mild, sufficient just to cause RSWA, but it is insufficient to manifest RBD. Another hypothesis is that since the body-site of atonia involved by RSWA determines the clinical manifestation of RBD, RSWA affecting facial muscles only, as may be the case with antidepressants, would not lead to spectacular RBD episodes, while RSWA in limb muscles would[100].

SLEEP RELATED PAINFUL ERECTION: THE NORMAL REM-RELATED ERECTION GOES WRONG

Sleep related painful erection is a rare parasomnia, occurring in 1% of men presenting with sexual problems. It differs from the normal REM-related penile tumescence only by the associated pain awakening the individual from sleep; the patient may have normal penile erection and sexual life when awake[101]. Local origins, a vagal dysfunction and central, especially antero-lateral hypothalamic etiologies have been raised.

Baclofen has been found a good treatment option. Beta blockers, benzodiazepines and antidepressants were transitorily effective in some cases, and several additional treatments have also been used.

Summary and future challenges

REM parasomnias make an interesting and informative group of sleep disorders, rooting in the changes of the wide brainstem REM sleep network. Most of them are REM dissociation phenomena, where one or more elements of the REM sleep pattern occur in a wrong sleep state (cataplexy, sleep paralysis, hypnagogic hallucinations in wakefulness); some are absent or emerge insufficiently in their normal time (RBD). Evidencing the multilateral link with the REM atonia network, RBD, cataplexy and sleep paralysis may co-occur e.g. in narcolepsy, highlighting the dysfunctions of the atonia network with opposite-side effects.

Neurodegenerative diseases including tauopathies, TDP-43-pathies, autoimmune/inflammatory or stroke-related conditions, as well as brainstem compression syndromes as Arnold-Chiari malformation, may damage the REM atonia network. Chemical effects e.g. antidepressants or hypoxia may transitorily or permanently change the atonia network's functioning. These „functional" RBD syndromes may manifest specific symptom-localizations offering a future discrimination tool.

RBD, as an early sign of synucleinopathy (or rather a synucleinopathy itself), may carry a prognostic value, predicting or accompanying an overt neurodegenerative condition and providing opportunity of preventing or delaying it when such tools will be at hand. The special link of RBD with autoimmunity seems more than pure chance, given the important and shared HLA association of RBD and anti-IgLON5 disease, an autoimmune tauopathy. The overlap with narcolepsy, another REM sleep-related and autoimmune condition with HLA Class II association and REM sleep disturbance, needs further scrutiny.

The association of RBD with PTSD, forming together the new entity trauma-related sleep disorder, provides an example of a psychology impact turning to brain-organic. Is RBD in such cases a psychosomatic disease?

Further scrutiny of REM parasomnias may provide data for understanding the role of antidepressants in sleep regulation, the link of depressions (characterized with short REM latency) with other REM disorders, and finally, help clarifying the functions of REM sleep.

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