Sleep Related Movement Disorders

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Disclosures

• Dr Trenkwalder served on a scientific advisory boards of Roche and has received speaker honoraria from UCB.
# Sleep-Related Motor and Behavioral Disorders: Recent Advances and New Entities

David P. Breen, MBChB, PhD, Birgit Högl, MD, Alfonso Fasano, MD, PhD, Claudia Trenkwalder, MD, and Anthony E. Lang, MD

## TABLE 1. ICSD-3 categories and sleep-related motor and behavioral disorders/variants

<table>
<thead>
<tr>
<th>ICSD-3 category</th>
<th>Sleep-related movements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia</strong></td>
<td>Movements associated with sleep arousals(^a)</td>
</tr>
<tr>
<td>Sleep-related breathing disorders</td>
<td>Occasional flailing movements associated with apneic arousals(^b)</td>
</tr>
<tr>
<td>Central disorders of hypersomnolence</td>
<td>Narcolepsy with “negative” and “active” movement abnormalities</td>
</tr>
<tr>
<td>Circadian rhythm sleep-wake disorders</td>
<td>None</td>
</tr>
<tr>
<td>Parasomnias(^c)</td>
<td>REM sleep behavior disorder, NREM parasomnias (somnambulism, confusional arousals, sleep terrors, sexsomnias, sleep-related eating disorder), status dissociatus(^e,f)</td>
</tr>
<tr>
<td><strong>Sleep-related movement disorders</strong></td>
<td>Restless legs syndrome, periodic limb movement disorder, sleep-related leg cramps, sleep-related bruxism, faciometatibular myoclonus, sleep-related rhythmic movement disorder, benign sleep myoclonus of infancy, propriospinal myoclonus at sleep onset</td>
</tr>
<tr>
<td><strong>Sleep-related medical and neurological disorders</strong></td>
<td>Sleep-related hypermotor epilepsy</td>
</tr>
<tr>
<td>Other sleep disorders</td>
<td>Anti-IgLON5 disease, ADCY5-associated disease, benign nocturnal alternating hemiplegia of childhood(^f)</td>
</tr>
<tr>
<td>Isolated symptoms or normal variants</td>
<td>Excessive fragmentary myoclonus, hypnagogic foot tremor, alternating leg muscle activation, high-frequency leg movements, hypnic jerks, neck myoclonus during sleep(^f)</td>
</tr>
</tbody>
</table>

\(^{a,b,c,d,e,f}\)
Parasomnias

– Non-REM-Parasomnias:
  • **Sleep Walking**, sleep terror, **confusional arousals**: occur during deep sleep, 1st half of the night, children and young people
    • Nocturnal eating disorder, seksomnia, nocturnal enuresis, hypnagoge hallucinations

– REM-Parasomnias:
  • **REM Sleep Behavior Disorder (RBD)**
  • Recurrent isolated sleep paralysis,
  • Parasomnia due to medical disorders or substance abuse
Diagnostic Criteria of RBD:
Intern. Class. Sleep Disorders: 2014

• Repeated episodes of sleep related vocalization and/or complex motor behaviors.¹,²
• 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.
• Polysomnographic recording demonstrates REM sleep without atonia (RWA).³
• The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.⁴

ICSD 2014
The bedpartner/caregiver tells you about the patient...

- Shouting, laughing any vocalization in the middle of the night or early morning
- Complex movements, aggressive behavior during sleep
- Violations of the bedpartner or the patient during sleep
- No quiet nights
- Frequent interruptions during sleep
RBD can be violent for the bedpartner
Idiopathic (isolated) RBD, converted to mild Parkinsonian features
„Violent Behaviour“
Normal REM Sleep

- Complete relaxation of all muscles
- no movement
- no vocalization
- some twitches in leg muscles.
Anti-IgLON5 disease: a new sleep and movement disorder

• Clinical Features:
  • sleep disorder with parasomnia and sleep breathing difficulty in 8 (36%) patients;
  • a bulbar syndrome including dysphagia, sialorrhea, stridor, or acute respiratory insufficiency in 6 (27%);
  • a syndrome resembling progressive supranuclear palsy (PSP-like) in 5 (23%);
  • cognitive decline with or without chorea in 3 (14%).
  • All patients eventually developed parasomnia, sleep apnea, insomnia, or excessive daytime sleepiness.

• Gaig et al Neurology 2017
RBD: REM-Sleep without atonia
Normative EMG Values during REM Sleep for the Diagnosis of REM Sleep Behavior Disorder

Birgit Frauscher, MD*1; Alex Iranzo, MD*2; Carles Gaig, MD2; Viola Gschliesser, MD1; Marc Guaita, MD2; Verena Raffelseder, MD1; Laura Ehrmann, MD1; Nuria Sola, MD2; Manel Salamero, PhD3; Eduardo Tolosa, MD2; Werner Poewe, MD1; Joan Santamaria, MD2; Birgit Högl, MD1; for the SINBAR (Sleep Innsbruck Barcelona) Group

*Dr. Frauscher and Iranzo contributed equally to this work.

Methods:
15 patients with IRBD, 15 patients with RBD and PD, 30 controls
Polysomnograms with 11 EMG channels;
Evaluation of both phasic and tonic activities during REM

Conclusion:
For the diagnosis of iRBD and RBD associated with PD, we recommend a polysomnographic montage quantifying “any” (any type of EMG activity, irrespective of whether it consisted of tonic, phasic or a combination of both) EMG activity in the mentalis muscle and phasic EMG activity in the right and left flexor digitorum superficialis muscles in the upper limbs with a cutoff of 32%, when using 3-sec miniepochs.

Frauscher B, Iranzo A et al, Sleep 2012
REM-on neurons: glutamatergic (3: SLD) excite GABA and glycinergic neurons (4: GIV) inhibition of spinal motor neurons causing REM atonia

RBD: lack of inhibition to finally spinal motor neurons and thalamocortical neurons

From: Breen et al, Mov Disord 2017
Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study

The overall conversion rate from iRBD to an overt neurodegenerative syndrome was 6.3% per year, with 73.5% converting after 12-year follow-up.

The rate of phenoconversion was significantly increased with abnormal quantitative motor examination, olfactory deficit, mild cognitive impairment, erectile dysfunction, abnormal DAT scan, colour vision abnormalities, constipation, REM atonia loss, and age.

Limitation: heterogenous group of iRBD patients with various observation times.
ABSTRACT

Objective: To investigate the frequency, phenomenology, and associated risk factors of REM sleep behavior disorder (RBD) in Parkinson disease (PD).

Methods: An unselected cohort of sleep-disturbed patients with PD (n = 457) was investigated with video-supported polysomnography. We determined the frequency of RBD and analyzed the influence of age, clinical disease features, disease duration, cognitive and physical impairment, medication, comorbidity, and sleep architecture.

46% of a treated PD population of different stages of the disease with sleep complaints showed PSG confirmed RBD.
PD patients with RBD show older age, higher psychiatry comorbidity
Higher PLMS indices
Increased amount of REM sleep
but
No subjective change of their quality of sleep

Sixel-Döring et al, 2011
Rapid Eye Movement Sleep Behavioral Events: A New Marker for Neurodegeneration in Early Parkinson Disease?

Friederike Sixel-Döring, MD²; Ellen Trautmann, PhD¹; Brit Mollenhauer, MD¹,⁴,⁵; Claudia Trenkwalder, MD¹,⁴

**RBE**: Small movements not yet fulfilling ICSD criteria for RBD
- Visible in video – PSG during REM sleep

- Prodromal RBD: early sign of synucleinopathy?

**Sixel-Döring et al, Sleep 2014, Sleep 2016**

**Muntean et al, J Clin Sleep Med, 2015:**

**REM Sleep Behavioral Events and Dreaming**
Therapy of RBD (idiopathic)

- **Clonazepam:**
  - 0.5mg – 1mg (2mg) at night

  Schenck C, Mahowald M: A polysomnographic, neurologic, psychiatric and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89.5% of 57 treated patients, Clev Clin J Med. 1990;57:10-24.

- **Melatonin:**
  - 2-6mg at night (evening)

- **Avoid SSRI for antidepressive treatment**

  Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep. 2004 Mar 15;27(2):317-21
Clinical Summary RBD

• Mostly small, distal, abrupt movements are combined with vocalisation,
• Falls and violations are less frequent
• Some patients remember nightmares, others do not remember dreams or RBD
• Some patients wake up after RBD (2nd half of the night!), others don ‘t
• RBD is the most specific syndrome of prodromal Parkinsonism due to a synucleinopathy
Sleep-related movement disorders

• **Periodic Limb Movements** (PLM) during sleep and wakefulness (PLMS, PLMW)
• **Restless Legs Syndrome** (RLS)
• **Bruxism**
• **Rhythmic movement disorders** (head rolling, head banging)
• **Propriospinal myoclonus**
PLMS Periodic Limb Movements in Sleep

Nocturnal Myoclonus Symonds 1956
Periodic Leg Movements Lugaresi et al 1968
Coleman 1982

Definition: Sequence of at least 4 leg movements
0.5 - 5 sec duration, 4 - 90 sec intermovement interval
(ASDA criteria, 1990)
Pathological Index > 15/h (new ICSD criteria)

Lugaresi E, Cirignotta F, Coccagna G, Montagna P,
Nocturnal Myoclonus and Restless Legs Syndrome
Adv Neurol, 1986
World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG)

R. Ferri a,*, S. Fulda b, R.P. Allen c, M. Zucconi d, O. Bruni e, S. Chokroverty f, L. Ferini-Strambi d, B. Frauscher g, D. Garcia-Borreguero h, M. Hirshkowitz i, B. Högl j, Y. Inoue k, A. Jahangir l, M. Manconi b, C.L. Marcus m, D.L. Picchietti n, G. Plazzi o, J.W. Winkelman p, R.S. Zak q on behalf of the International and European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG)

New Criteria 2016

PLM: at least four consecutive CLM with an intermovement interval $\geq 10$ and $\leq 90$ s without any PLM preceded by an interval $<10$ s interrupting the PLM series;

Any monolateral or bilateral CLM with 0.5-10s long

CLM: Candidate Leg Movement
Periodic Limb Movements in Sleep (PLMS) with Arousal
PLMS
Periodic Limb Movements in Sleep
Periodic Limb Movements during sleep (PLMS): similar to the Babinski
**RLS Essential Criteria**

- 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
- 2. The urge to move or unpleasant sensations begin or worsen during periods of rest.
- 3. The urge to move or unpleasant sensations are partially or totally relieved by movement.
- 4. The urge to move or unpleasant sensations are worse in the evening or night than during the day.
- 5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

**Specifiers for clinical course of RLS/WED:**
- A. **Chronic-persistent RLS/WED**: symptoms when not treated would occur on average at least twice weekly for the past year.
- B. **Intermittent RLS/WED**: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

*Allen et al Sleep Med 2015*
SIT: Suggested immobilisation test
Periodic Limb Movements during wakefulness (PLMW)
RLS Genetics

- First studies in RLS families: autosomal dominant pattern, segregation analysis shows earlier onset of familial RLS: <30 years, linkage studies identified only RLS associated loci, but no genes
- GWAS by J. Winkelmann identified first genes: MEIS1, BTBD9, currently 19 new loci for RLS

Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions

Juliane Winkelmann1,3, Barbara Schormair1,3, Peter Lichtner1,3, Stephan Ripke2, Lan Xiong4, Shapour Jalilzadeh1,3, Stephany Fulda2, Benno Pütz2, Gertrud Eckstein1,3, Stephanie Hauk1,3, Claudia Trenkwalder2, Alexander Zimprich6, Karin Stiasny-Kolster7, Wolfgang Oertel7, Cornelius G Bachmann8, Walter Paulus4, Ines Peglau8, Ilonka Eisenreich8, Jacques Montplaisir11,12, Gustavo Tureck13, Guy Rouleau5, Christian Gieger14, Thomas Illig14, H-Erich Wichmann14,15, Florian Holsboer2, Bertram Müller-Myhsok2,16 & Thomas Meitinger1,3,16

The results support the hypothesis that cumulative disease burden is more important than the presence of a specific single disease in the pathophysiology of RLS.

<table>
<thead>
<tr>
<th>Single diseases</th>
<th>SHIP Odds ratio (95% CI)</th>
<th>RLS Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.27 (1.45, 3.56)</td>
<td>1.76 (0.90, 3.44)</td>
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<tr>
<td>Obesity</td>
<td>1.32 (0.96, 1.81)</td>
<td>2.12 (1.34, 3.35)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.57 (1.16, 2.13)</td>
<td>1.15 (0.71, 1.87)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.48 (0.06, 3.61)</td>
<td>0.54 (0.16, 1.83)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.05 (1.04, 4.03)</td>
<td>0.66 (0.19, 2.27)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.74 (0.22, 2.43)</td>
<td>0.76 (0.17, 3.41)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>1.57 (0.98, 2.50)</td>
<td>0.38 (0.09, 1.65)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.32 (0.95, 1.83)</td>
<td>1.62 (0.80, 3.31)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1.63 (1.04, 2.58)</td>
<td>0.74 (0.35, 1.56)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>2.16 (1.51, 3.10)</td>
<td>2.21 (1.28, 3.81)</td>
</tr>
<tr>
<td>Migraine</td>
<td>1.52 (1.03, 2.23)</td>
<td>1.97 (1.06, 3.67)</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.59 (1.40, 1.80)</td>
<td>1.47 (1.20, 1.81)</td>
</tr>
</tbody>
</table>
Modulation of Dopamine-D1 and D3-receptors in the spinal cord

_Clemens et al. 2018, Trenkwalder et al, Lancet Neurol 2018_
Pathophysiological Concepts of RLS

- The role of the dopamine system: deficiency or overload? *Connor et al 2003, Earley et al 2006 and 2014*

- The role of the spinal system and the periodicity of PLM *Clemens et al 2006, Ferri et al 2013*

- The iron depletion hypothesis: brain iron deficiency by transport mechanisms? *Allen et al 2013, Connor et al 2011*

- The role of peripheral hypoxia? *Salminen et al 2014*

- The role of genetics: 6 genetic risk loci including *MEIS1* and *BTBD9* have been published and identified pathways related to neurodevelopment changes, further risk loci will be defined and direct to new disease mechanisms. *Winkelmann et al 2007, Stefansson, Rye et al 2007, Schormaier et al 2017*
Gene-(micro) environment interaction in RLS

Forms of RLS

- Familial RLS
- RLS
- RLS in a single co-morbid condition
  - Iron deficiency
  - Kidney disease
  - CV in women
  - Diabetes
  - Migraine
  - PD treated
  - Polyneuropathies
- RLS in multimorbidity

(Micro-) Environmental burden

Genetic burden
Medications approved for RLS Therapy (2018)

L-DOPA/Benserazid: 100-200mg standard / sustain. release (parts of EU)
Dopamine Agonists: (EU, USA, Japan, other parts of the world)
    Pramipexol stand. 0.18-0.52mg (0.25-0.75mg)
    Ropinirole stand. 0.5-4mg (mean : 2mg)
    Rotigotine (transderm. patch): 1-3mg
Opioids: (EU) Oxycodone/Nal. Prolonged rel: 2x5-2x20mg
Alpha-2-delta-ligands: (USA, Japan)
    Gabapentin/Enacarbil: 600mg

Off-label Therapy with proven efficacy in RLS
Gabapentine: 300-1800mg (efficacy: 1800mg)
Gabapentine-enacarbil (> 600mg)
Pregabalin: 150-300mg once daily
Iron preparations: i.e. Ferro –carboxymaltose, FCM (500-1000mg)

Winkelmann et al Mov Disord 2018
Augmentation in long-term therapy

**Long-term safety and efficacy of rotigotine transdermal patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study**

Wolfgang Oertel, Claudia Trenkwalder, Heide Remel, Luigi Ferrini-Stromboli, Birgit Hög, Werner Poeue, Karin Stiassny-Kohster, Andreas Fichtner, Erwin Schollmayer, Ralf Kohnen, Diego Garcia-Borreguero, on behalf of the 3P710 study group

First Long-term study for 5-year duration
Augmentation rate for rotigotine
3mg: 5%, 4mg: 8%

Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome

Walter Paulus, Claudia Trenkwalder

Lancet Neurol 2006; 5: 878-86

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**INCREASED SYNAPTIC DOPAMINE IN THE PUTAMEN IN RESTLESS LEGS SYNDROME**

Increased Synaptic Dopamine in the Putamen in Restless Legs Syndrome

Christopher J. Earley, MD, BCh, PhD¹; Hiroto Kuwabara, PhD²; Dean F. Wong, MD, PhD³,⁴; Charlene Gamaldo, MD¹; Rachel E. Salas, MD¹; James R. Brašić, MD, MPH²; Hayden T. Ravert, PhD²; Robert F. Dannahs, PhD²; Richard P. Allen, PhD²

RLS with augmentation:
Coping Strategies
1. Increase of severity
2. Involving other body parts (arms, body)
3. Occurrence during the day and night
Summary: RLS/PLMS

• Restless legs syndrome (RLS) and Periodic limb movements in sleep (PLMS) are two distinctive syndromes
• RLS is a clinical diagnosis
• PLMS is a frequent phenomenon that occurs in more than 80% of patients with RLS, neurodegeneration, elderly people, narcolepsy, many other disorders
Movements during sleep:
Body rolling: since youth
Bruxism: frequent in young people
Stridor in a patient with MSA
Key Message

• Movement disorders in sleep need a careful history of the patient and if possible the bedpartner.
• Polysomnography is needed to detect specific sleep disorders such as parasomnias (i.e. REM-Sleep Behavior Disorder (RBD)), periodic limb movements (PLM) as part of RLS or narcolepsy, bruxism, propriospinal myoclonus or sleep related respiratory disease.
• Diagnosis of RBD is crucial for possible development of neurodegenerative diseases
• RLS should be correctly diagnosed and treated to avoid augmentation and severe RLS conditions