

Sleep Related Movement Disorders

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CT has received honoraria for educational lectures from UCB (Otsuka), Britannia, Abbvie, STADA, Bial, Advisor for Roche, Ono, Bial, Abbvie. UCB.

Sleep-Related Motor and Behavioral Disorders: Recent Advances and New Entities

David P. Breen, MBChB, PhD,^{1*} Birgit Högl, MD,² Alfonso Fasano, MD, PhD,^{1,3} Claudia Trenkwalder, MD,^{4,5} and Anthony E. Lang, MD^{1,3}

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

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

^aApnoeic arousals with frequent or prolonged sleep-related movements (such as the movements and postures) are seen in patients with obstructive sleep apnea.

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, sexsomnia, nocturnal enuresis, hypnagogic hallucinations

— REM-Parasomnias:

- **REM Sleep Behavior Disorder (RBD)**
- Recurrent isolated sleep paralysis,
- Parasomnia due to medical disorders or substance abuse

Non-REM Parasomnias

Confusional Arousal – Sleep Terror

NonREM Disorders of Arousal and Related Parasomnias: an Updated Review

Table 1 Classification of parasomnias (excluding REM parasomnias)
(1)

NonREM parasomnias

1. Confusional arousal
2. Sleepwalking
3. Sleep terror
4. Sexsomnia
5. Sleep-related eating disorder

Other parasomnias

1. Exploding head syndrome
2. Sleep-related hallucinations
3. Sleep enuresis
4. Parasomnia due to medical disorder
5. Parasomnia due to medication
6. Parasomnia unspecified

Isolated symptoms

1. Sleep talking

Parasomnia overlap disorder

Status dissociatus



Distiguishing various NREM parasomnias

Table 8 Distinguishing clinical features of various NREM parasomnia

	CoA	SW	ST	SRED	Sexsomnia
Sleep state boundary	NREM–wake	NREM–wake	NREM/REM	NREM–wake	NREM/wake
Behavior	Disoriented, simple to complex movements in bed	Disoriented, ambulation out of bed, prolonged wandering	Frightened, agitated, screaming/crying	Consumption of high-caloric and at times bizarre food items	Abnormal sexual behavior from sleep/partial arousal
Duration	minutes	Several minutes—prolonged	several minutes	Several mins to prolonged	Several minutes
Ambulation	–	+	–	+	– (rarely, with sleepwalking)
Autonomic Activity	–	–	+	–	–
Amnesia	+	+	+	–/+	+

NonREM Disorders of Arousal and Related Parasomnias: an Updated Review

Neurotherapeutics 2021

Muna Irfan¹ • Carlos H. Schenck² • Michael J Howell³

**REM-PARASOMNIAS:
REM-SLEEP BEHAVIOR DISORDER**

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

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

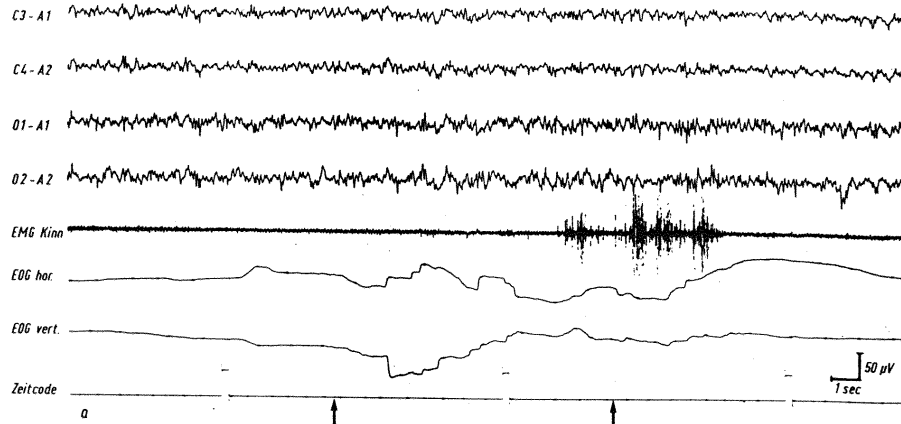
RBD can be violent for the bedpartner



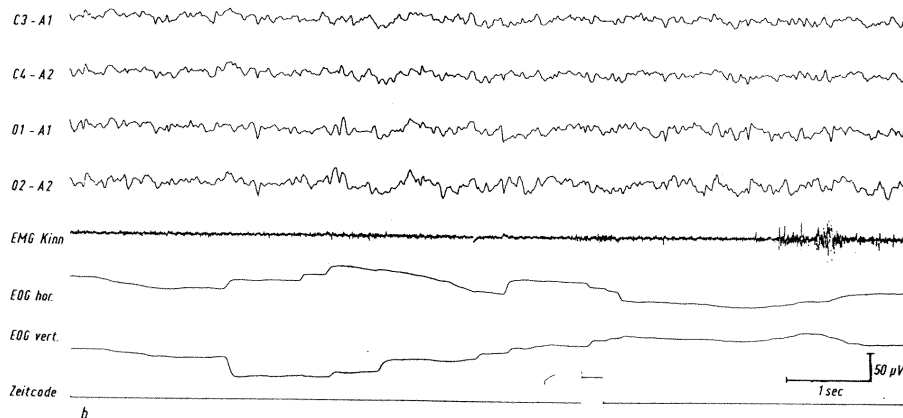
Idiopathic (isolated) RBD, converted to mild Parkinsonian features „Violent Behaviour“



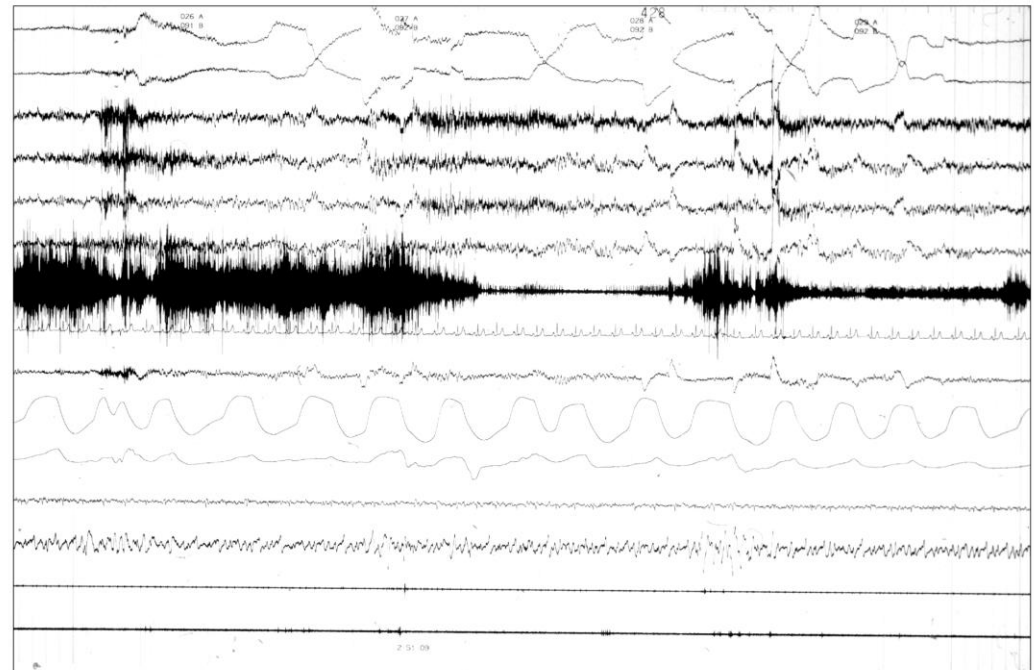
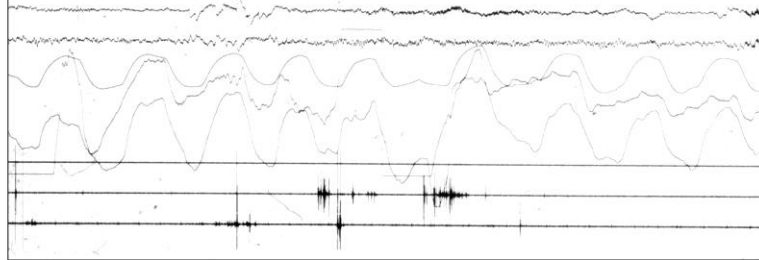
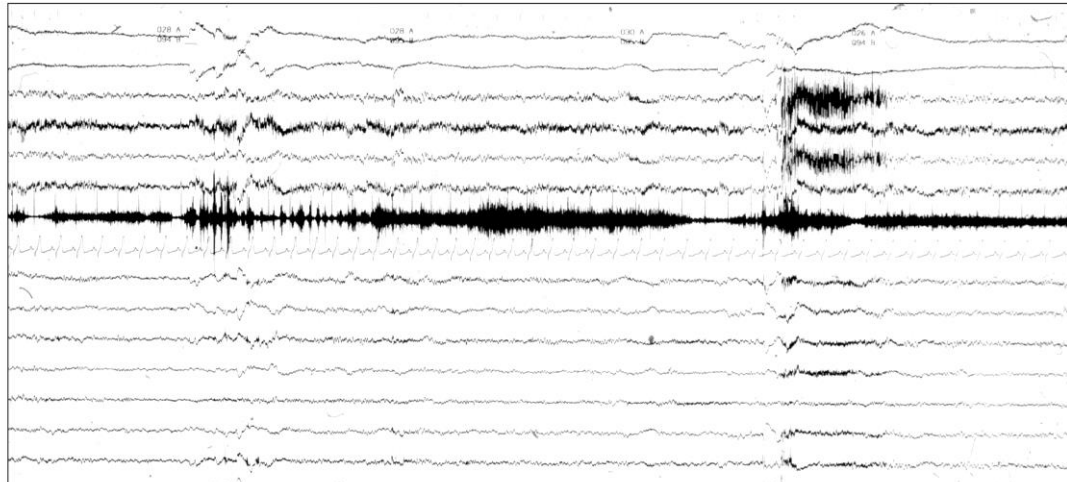
Normal REM Sleep



- Complete relaxation of all muscles
- no movement
- no vocalization
- some twitches in leg muscles.



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 Salameo, PhD³; Eduardo Tolosa, MD²; Werner Poewe, MD¹; Joan Santamaria, MD²; Birgit Högl, MD¹; for the SINBAR (Sleep Innsbruck Barcelona) Group

*Drs. 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:

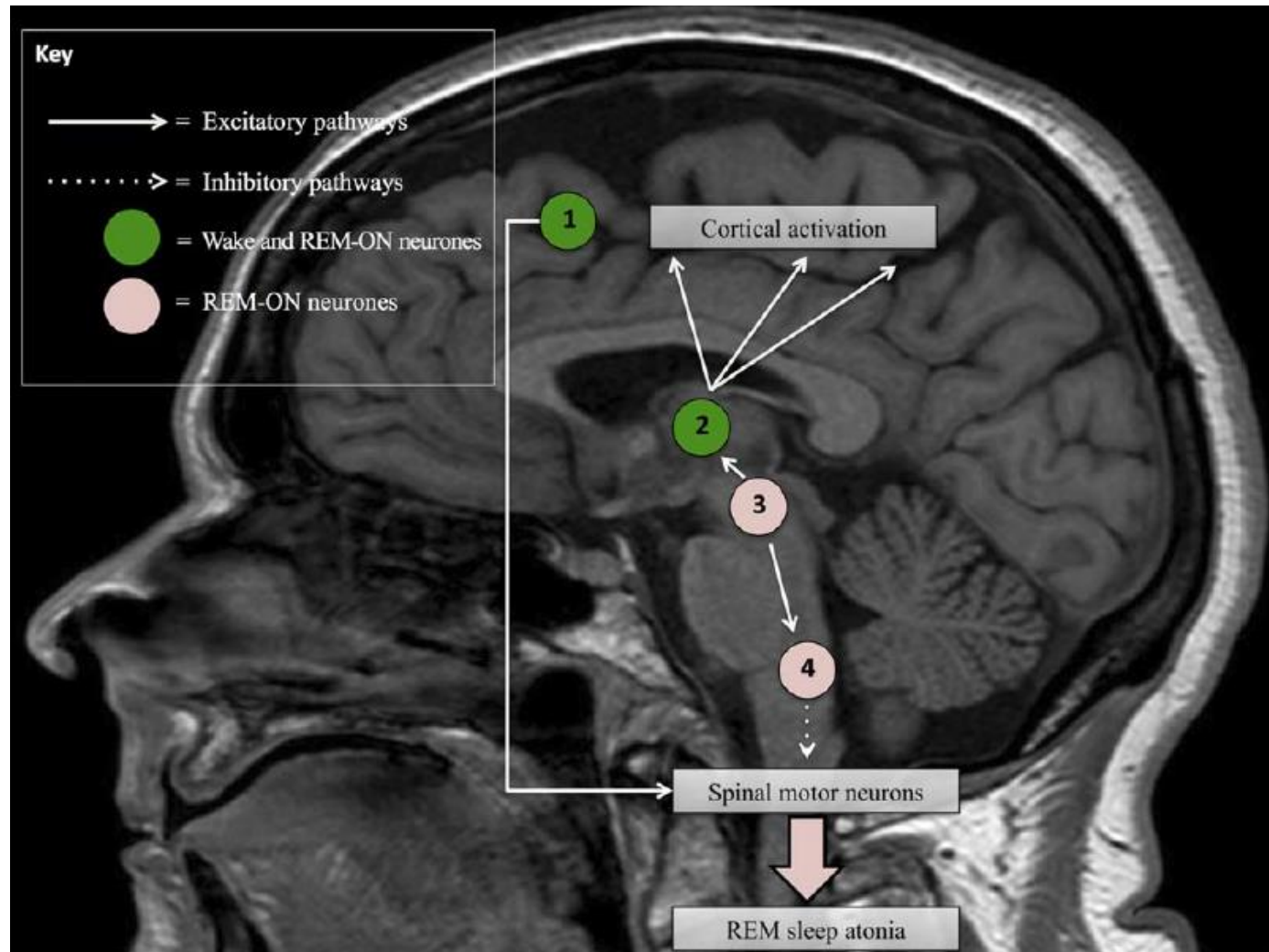
For the diagnosis of iRBD and RBD associated with PD, we recommend a polysomnographic montage quantifying “any” (any type of EMG activity, irrespective of whether it consisted of tonic, phasic or a combination of both) EMG activity in the mentalis muscle and phasic EMG activity in the right and left 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

Pathways of RBD

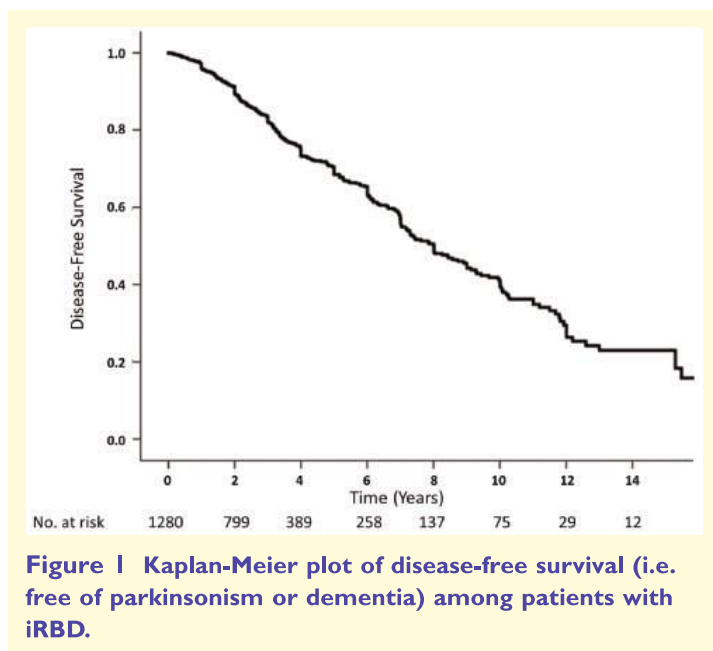
REM-on neurons: are glutamatergic (3: SLD) And excite GABA and glycinergic neurons (4: GIV) with inhibition of spinal motor neurons causing REM atonia

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



Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study

Postuma et al 2019



Limitation: heterogenous group of iRBD patients with various observation times

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 motor examination,
 - olfactory deficit
 - mild cognitive impairment
 - erectile dysfunction, constipation
 - abnormal DAT scan
 - colour vision abnormalities,
- REM atonia loss and age.

Associated factors for REM sleep behavior disorder in Parkinson disease

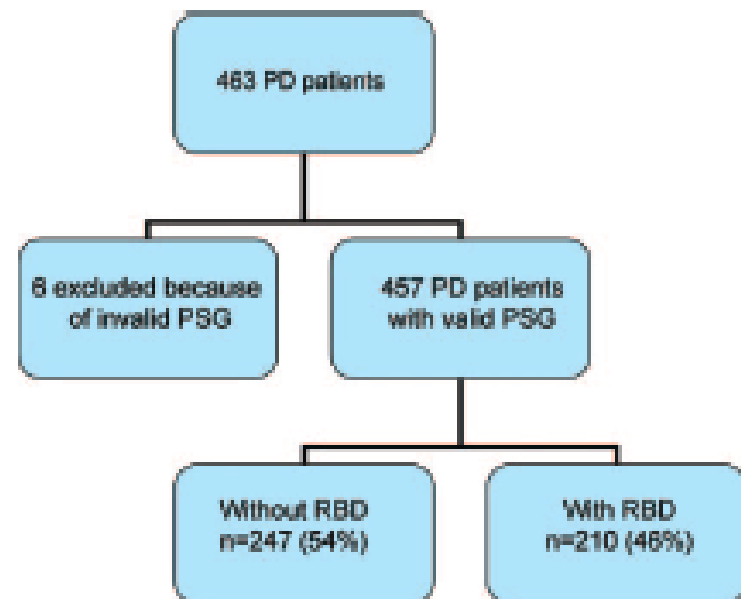
Friederike Sixel-Döring,
MD
Ellen Trautmann, PhD
Brit Mollenhauer, MD
Claudia Trenkwalder,
MD

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



RBD = REM sleep behavior disorder.

Table 2 Polysomnographic measurements of sleep parameters in patients with Parkinson disease (PD) with and without REM sleep behavior disorder (RBD), adjusted for age and gender*

	PD + RBD (n = 210)	PD non-RBD (n = 247)	Significance, p
Sleep latency in minutes	17 ± 19; 12 (0-144)	19 ± 23; 11 (0-147)	NS
Sleep efficiency, %	68 ± 15; 70 (15-96)	65 ± 19; 69 (7-97)	0.007
Sleep stages 1 and 2, %	72 ± 15	76 ± 16	NS
% TST	74 (1-71)	78 (20-100)	
Sleep stages 3 and 4, %	8 ± 11	9 ± 12	NS
% TST	4 (0-51)	5 (0-54)	
Sleep stage REM, %	19 ± 12	14 ± 11	0.000
% TST	18 (2-50)	14 (0-53)	
REM latency in minutes	132 ± 101; 106 (2-392)	130 ± 91; 98 (0-391)	NS
Awakenings total	26 ± 18; 23 (1-115)	28 ± 19; 22 (1-106)	NS
PLM index all	36 ± 40; 21 (0-182)	29 ± 44; 10 (0-187)	NS
PLMS index	35 ± 43; 17 (0-188)	22 ± 40; 4 (0-192)	0.019
PLMW index	24 ± 33; 9 (0-174)	24 ± 37; 10 (0-197)	NS
Patients diagnosed with SDB, n (%)	76 (36)	85 (34)	NS

PD patients with RBD show older age, higher psychiatric comorbidity

Higher PLMS indices

Increased amount of REM sleep

but

No subjective change of their quality of sleep

Sixel-Döring et al, 2011

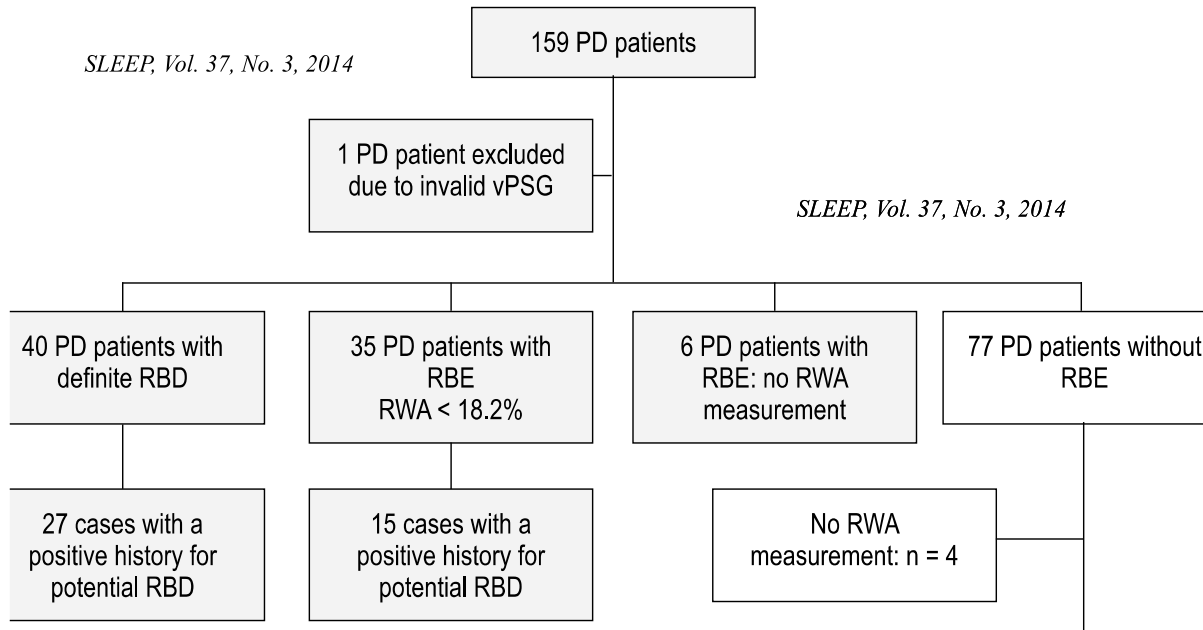
Rapid Eye Movement Sleep Behavioral Events: A New Marker for Neurodegeneration in Early Parkinson Disease?

Friederike Sixel-Döring, MD^{1,2}; Ellen Trautmann, PhD^{1,3}; Brit Mollenhauer, MD^{1,4,5}; Claudia Trenkwalder, MD^{1,4}

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

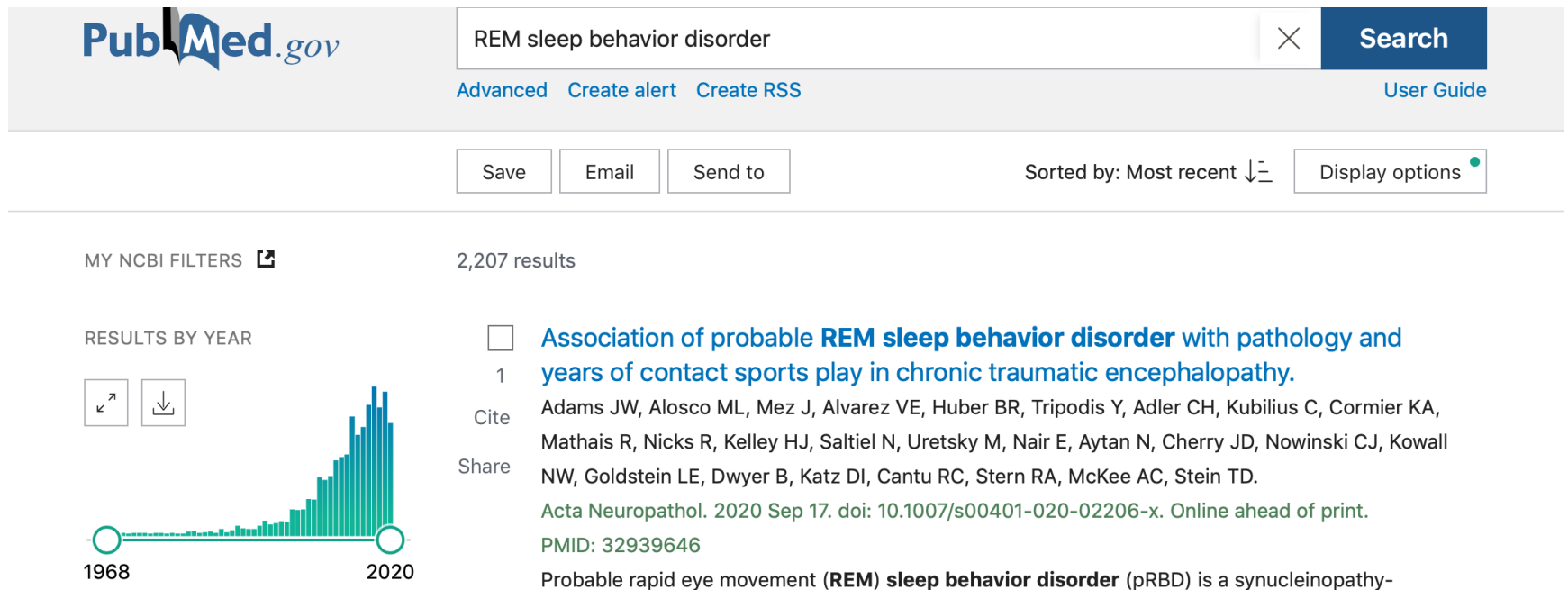
Clinical Summary RBD

- 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
-

Mov Disord. 2020 Sep 15. Online ahead of print.

Ethical Considerations in Screening for Rapid Eye Movement Sleep Behavior Disorder in the General Population

[Lisanne J Dommershuijsen](#) et al



Increase of RBD publications up to 2.207

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)

New Criteria for Research: WASM 2006 (Zucconi et al, Sleep Med)

Pathological Index > 15/h (new ICSD criteria)



Lugaresi E, Cirignotta F, Coccagna G,
Montagna P,
*Nocturnal Myoclonus and Restless Legs
Syndrome*
Adv Neurol, 1986



Coleman et al Sleep 1982; 5 Suppl 2: S191-202
Zucconi et al Sleep Med 2006 Mar; 7(2): 175-83

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)

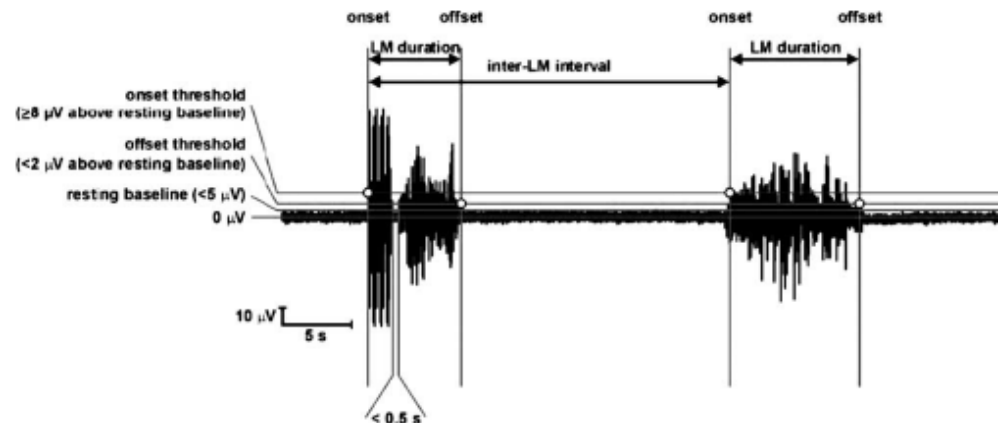
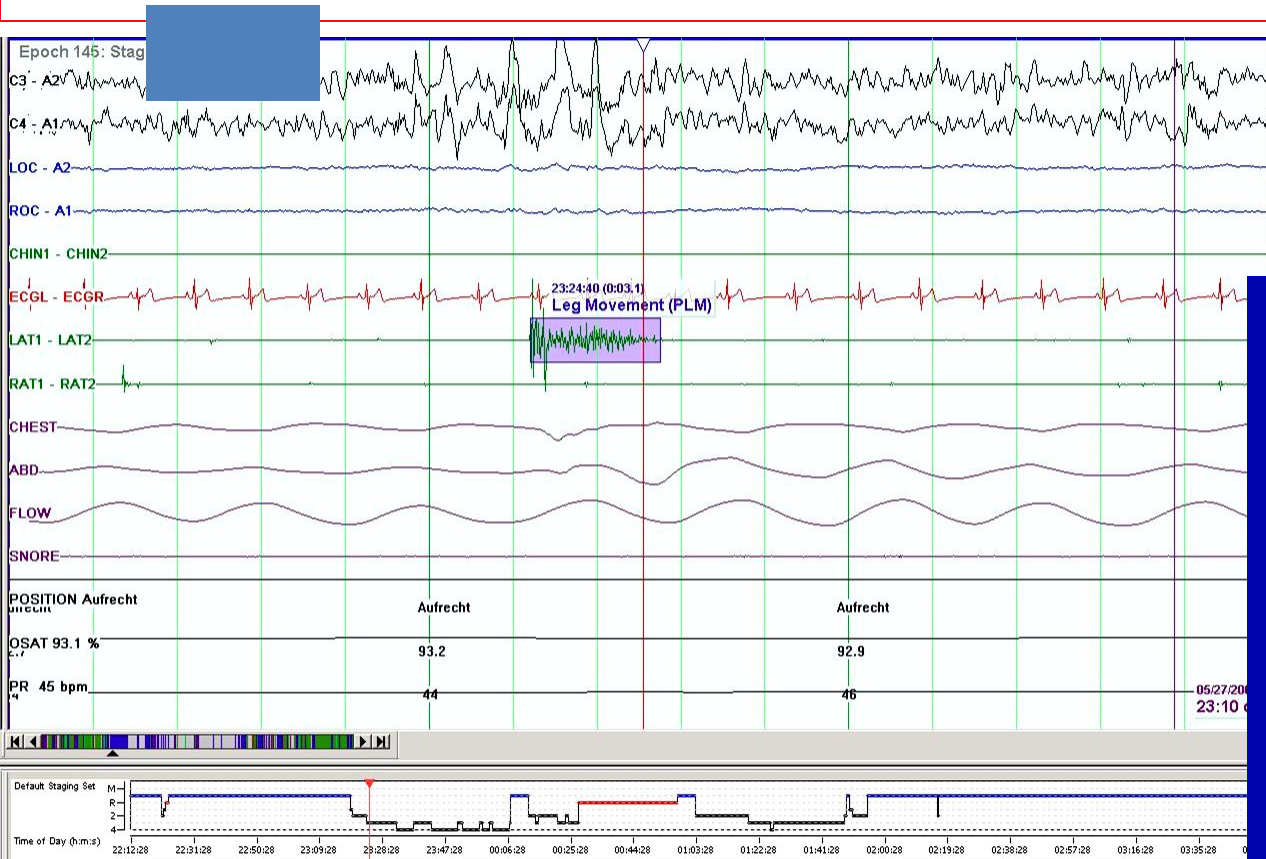


Fig. 4. Overview of the detection parameters for candidate PLM.

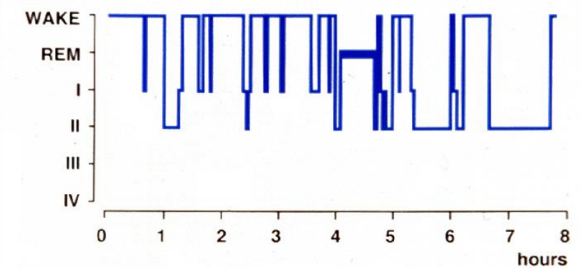
New Criteria 2016

PLM: at least four consecutive CLM with an intermovement interval ≥ 10 and ≤ 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

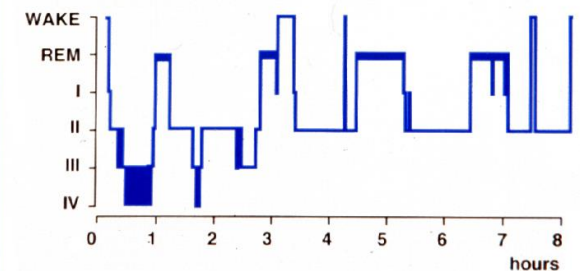
Periodic Limb Movements in Sleep (PLMS) with Arousal



Restless Legs Syndrome

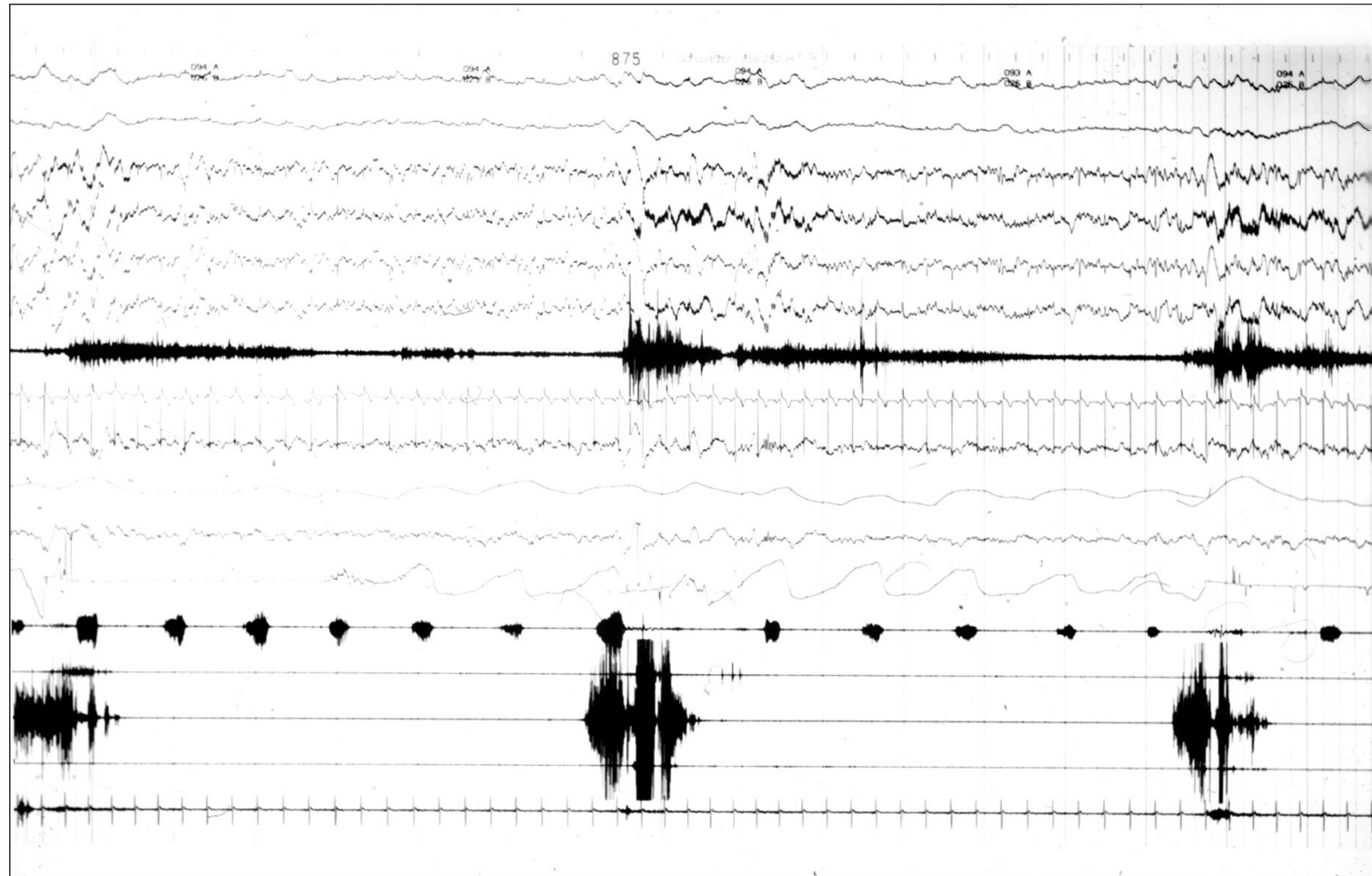


Healthy Control



PLMS

Periodic Limb Movements in Sleep



Periodic Limb Movements during sleep (PLMS): similar to the Babinsky



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.

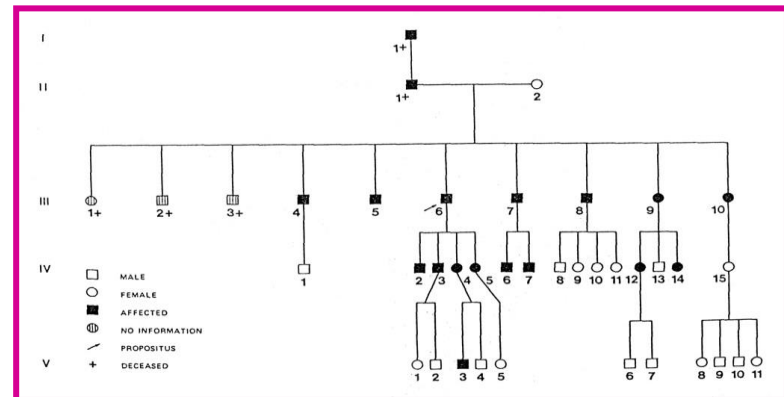
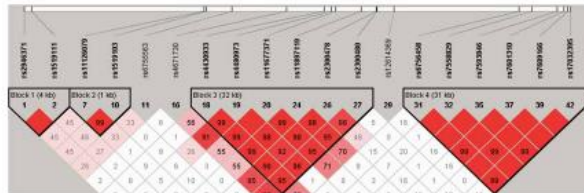
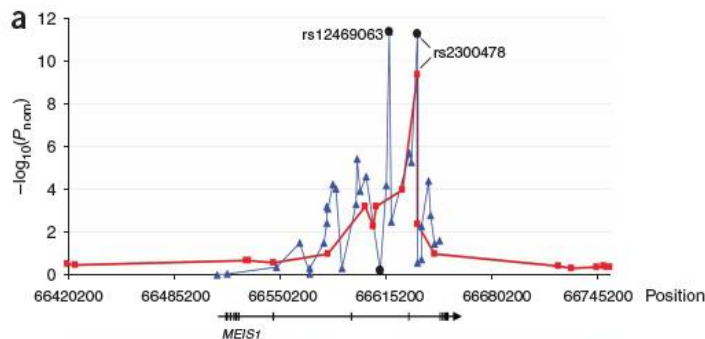
SIT: Suggested immobilisation test

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 Winkelmann^{1,3}, Barbara Schormair^{1,3}, Peter Lichtner^{1,3}, Stephan Ripke², Lan Xiong⁴, Shapour Jalilzadeh^{1,3}, Stephany Fulda², Benno Pütz², Gertrud Eckstein^{1,3}, Stephanie Hauk^{1,3}, Claudia Trenkwalder⁵, Alexander Zimprich⁶, Karin Stiasny-Kolster⁷, Wolfgang Oertel⁷, Cornelius G Bachmann⁸, Walter Paulus⁸, Ines Peglau⁹, Ilonka Eisensehr¹⁰, Jacques Montplaisir^{11,12}, Gustavo Turecki¹³, Guy Rouleau⁴, Christian Gieger¹⁴, Thomas Illig¹⁴, H-Erich Wichmann^{14,15}, Florian Holsboer², Bertram Müller-Myhsok^{2,16} & Thomas Meitinger^{1,3,16}

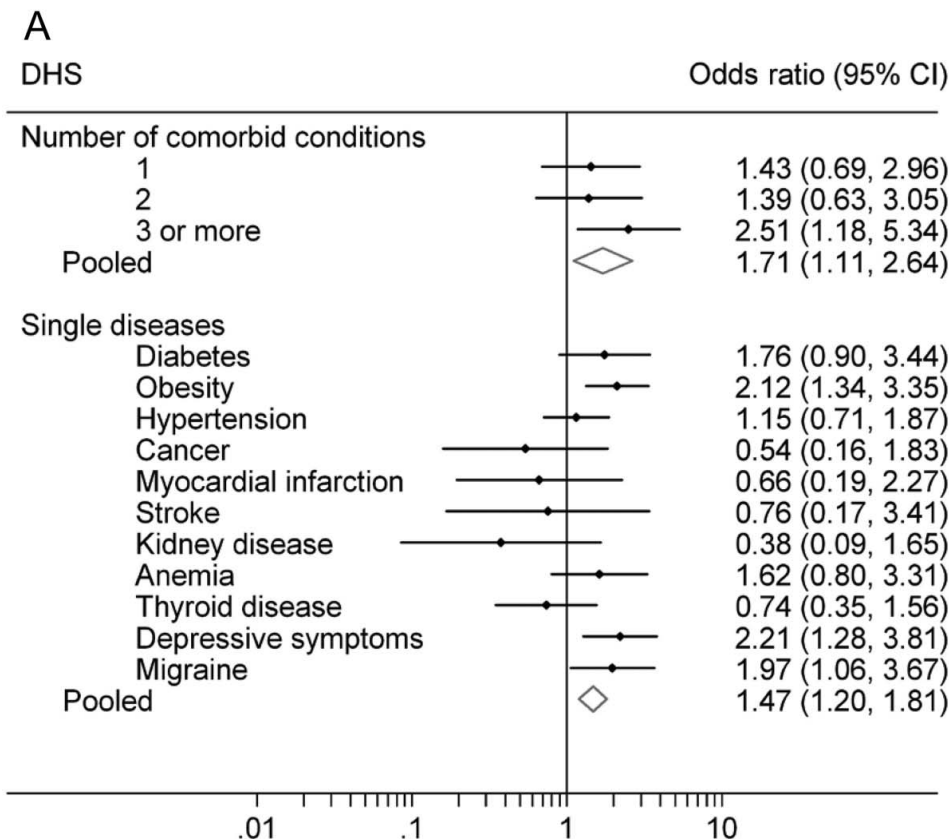
Trenkwalder et al, *Mov Disord* 1996, Winkelmann et al, *Ann Neurol* 2002, Winkelmann et al *Nat Genet* 2007; Johansson/Rye et al *New Engl J Med* 2007; Schormair et al *Lancet Neurol* 2017

András Szentkirályi, MD,
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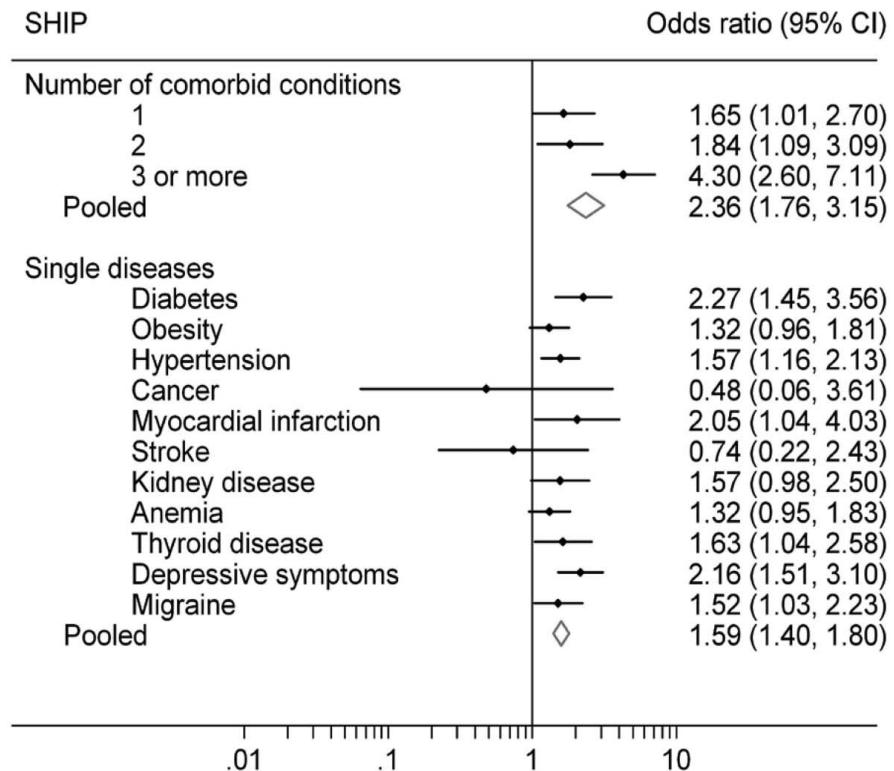
Multimorbidity and the risk of restless legs syndrome in 2 prospective cohort studies

Neurology 82 June 3, 2014

Figure 1 Odds ratios for incident restless legs syndrome associated with each comorbid category and single chronic diseases



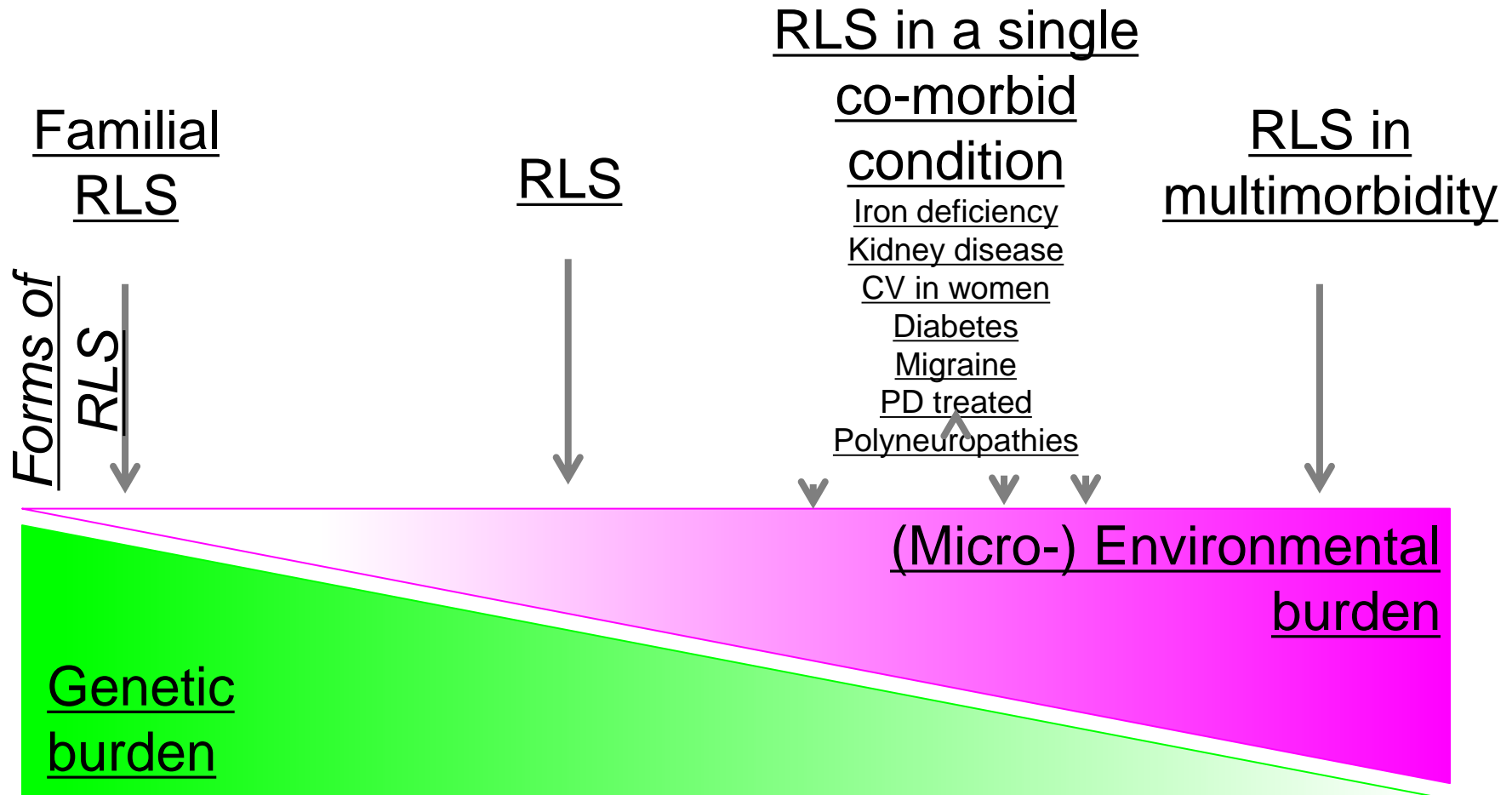
The results support the hypothesis that cumulative disease burden is more important than the presence of a specific single disease in the pathophysiology of BLS



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, Schormair et al 2017*

Gene-(micro) environment interaction in RLS



Medications approved for RLS Therapy

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)

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

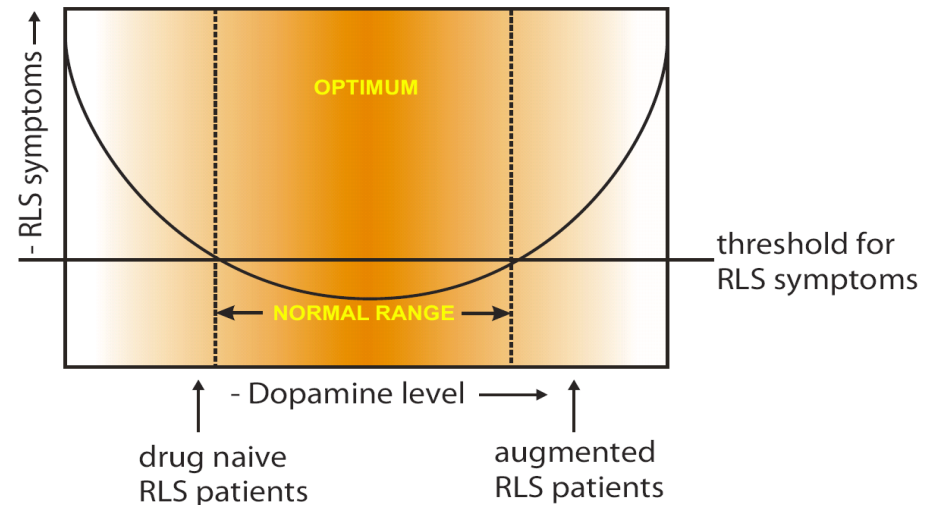
Wolfgang Oertel, Claudia Trenkwalder, Heike Beneš, Luigi Ferini-Strambi, Birgit Högl, Werner Poewe, Karin Stiasny-Kolster, Andreas Fichtner, Erwin Schollmayer, Ralf Kohnen, Diego García-Borreguero, on behalf of the SP710 study group*

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



INCREASED SYNAPTIC DOPAMINE IN THE PUTAMEN IN RESTLESS LEGS SYNDROME

<http://dx.doi.org/10.5665/sleep.2300>

Increased Synaptic Dopamine in the Putamen in Restless Legs Syndrome

Christopher J. Earley, MB, BCh, PhD¹; Hiroto Kuwabara, PhD²; Dean F. Wong, MD, PhD^{2,3,4}; Charlene Gamaldo, MD¹; Rachel E. Salas, MD¹; James R. Brašić, MD, MPH²; Hayden T. Ravert, PhD²; Robert F. Dannals, PhD²; Richard P. Allen, PhD¹

Oertel, Trenkwalder et al, Lancet Neurol 2010, *Paulus and Trenkwalder, Lancet Neurol* 2006; *Earley et al, Sleep* 2013

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



Anti-IgLON5 disease: a new sleep and movement disorder

- Clinical Features:
- sleep disorder with parasomnia and sleep breathing difficulty in 8 (36%) patients;
- **Stridor at night** almost mandatory
- 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*

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