

Torino, 10 Novembre 2017

I disturbi del sonno nelle malattie neurodegenerative

RBD significato prognostico e terapie

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GUEST EDITORIAL

The REM sleep behavior disorder odyssey

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Carlos H. Schenck

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Minneapolis, MN, USA*

- 1953 Aserinsky & Kleitman first describe REM sleep
- 1965 Jouvett & Delorme pontine lesions in cats cause “oneiric behaviour”
- 1986 Schenck & Mahowald formally identified RBD in humans
- 1996 Schenck & Mahowald delayed emergence of Parkinsonian disorder

RBD - definition

Rapid eye movement sleep behavior disorder (RBD) is characterized by **dream enactment** and **complex motor behaviors** during rapid eye movement sleep and **rapid eye movement sleep atonia loss** (REM sleep without atonia) during polysomnography.

The **prevalence of RBD** has been estimated to be in the range of **0.5% to 2%**, more common in men

RBD is **5-fold** more likely in patients receiving **antidepressants** and **10-fold** more likely in those with a **psychiatric diagnosis**

Usual **onset** in **fifth or sixth decade**

REM Sleep Behavior Disorder: Clinical, Developmental, and Neuroscience Perspectives 16 Years After its Formal Identification in *SLEEP*

Sleep 2002

Carlos H. Schenck MD¹ and Mark W. Mahowald MD²

- RBD in humans was formally identified in the journal *SLEEP* in 1986, when we reported on a series of five elderly patients.

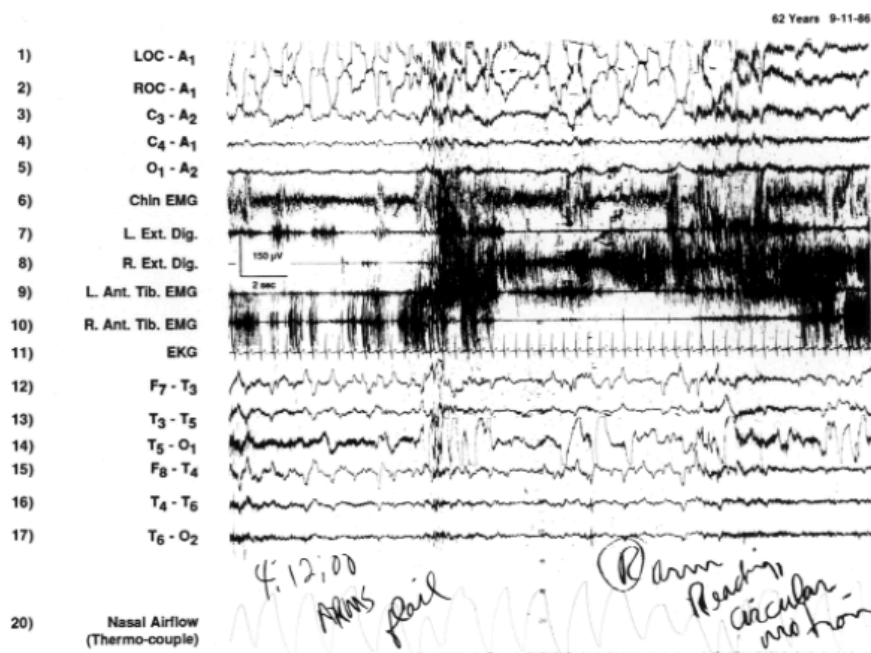


Figure 1—A patient with chronic RBD demonstrates his homemade restraint apparatus that he used every night for five years to prevent himself from leaving the bed and injuring himself during dream-acting episodes.

Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder

Carlos H. Schenck, MD; Scott R. Bundlie, MD; and Mark W. Mahowald, MD

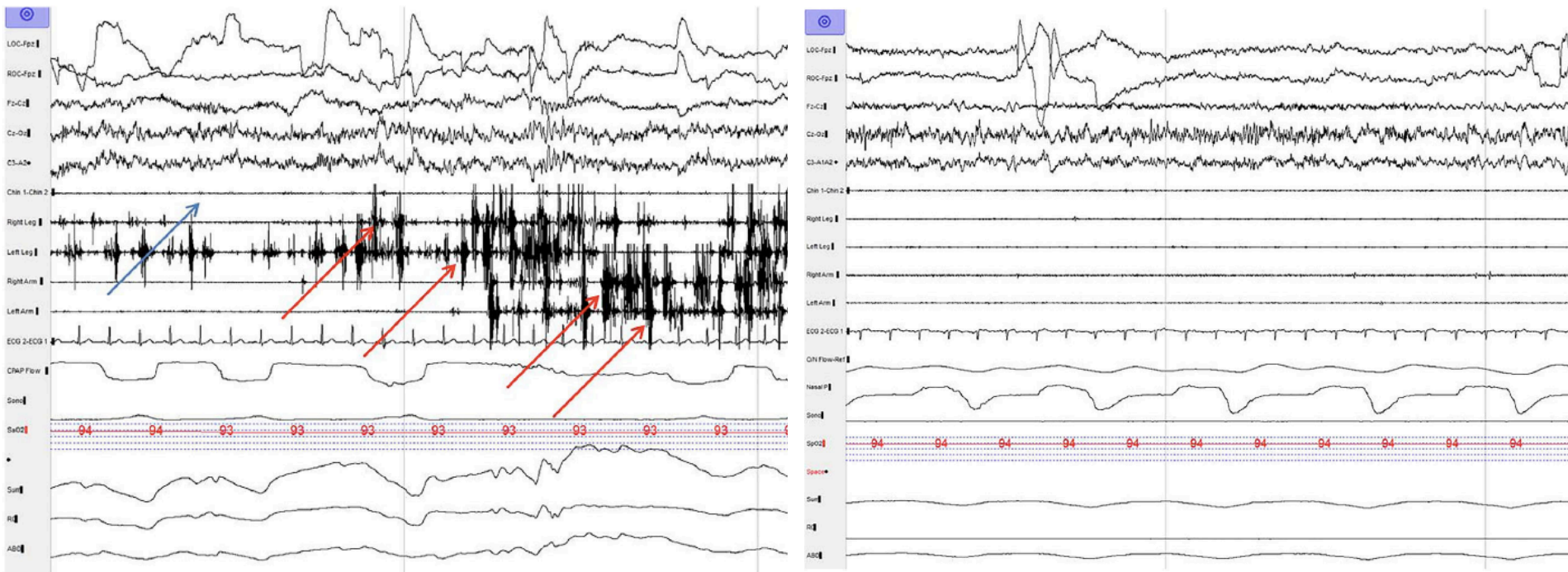
February 1996 NEUROLOGY

We report longitudinal data on a group of **29 male patients 50 years of age or older** who were initially diagnosed as having idiopathic REM sleep behavior disorder (RBD) after extensive polysomnographic and neurologic evaluations. Thirty-eight percent (11/29) were **eventually diagnosed as having a parkinsonian disorder** (presumably Parkinson's disease) at a **mean interval of 3.7 ± 1.4 (SD) years** after the diagnosis of RBD, and at a mean interval of **12.7 ± 7.3 years after the onset of RBD.**

REVIEW

REM Sleep Behavior Disorder in Parkinson's Disease and Other Synucleinopathies

Erik K. St Louis, MD, MS,^{1,2*} Angelica R. Boeve, BA,^{1,2} and Bradley F. Boeve, MD^{1,2}



NEUROLOGY 2005;65:1010–1015

Aggressive dream content without daytime aggressiveness in REM sleep behavior disorder

M.L. Fantini, MD, MSc; A. Corona, MPs; S. Clerici, PhD; and L. Ferini-Strambi, MD

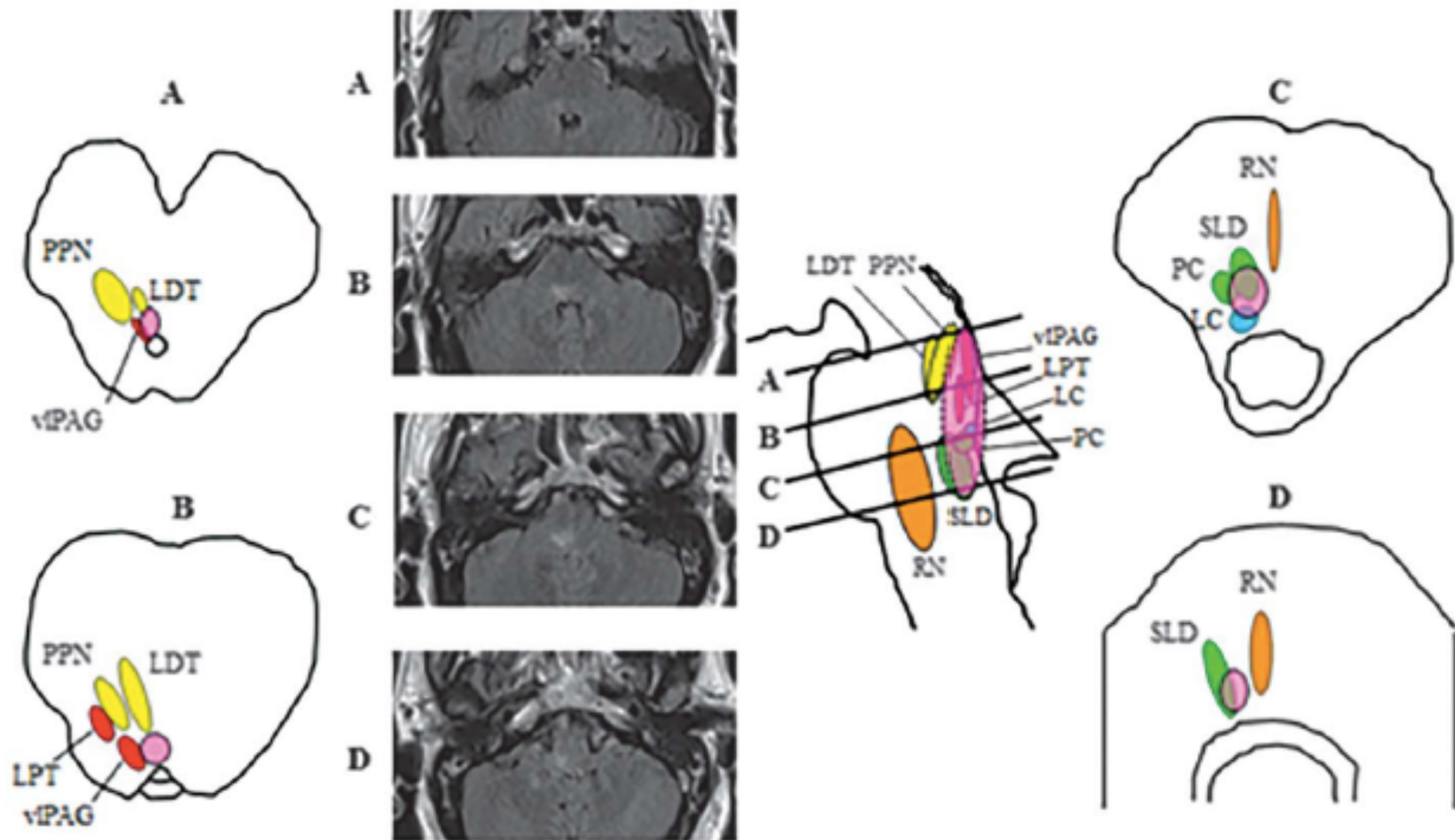


Courtesy of Prof. Cicolin

LESIONAL REM SLEEP BEHAVIOR DISORDER LOCALIZES TO THE DORSOMEDIAL PONS

Neurology 83 November 11, 2014

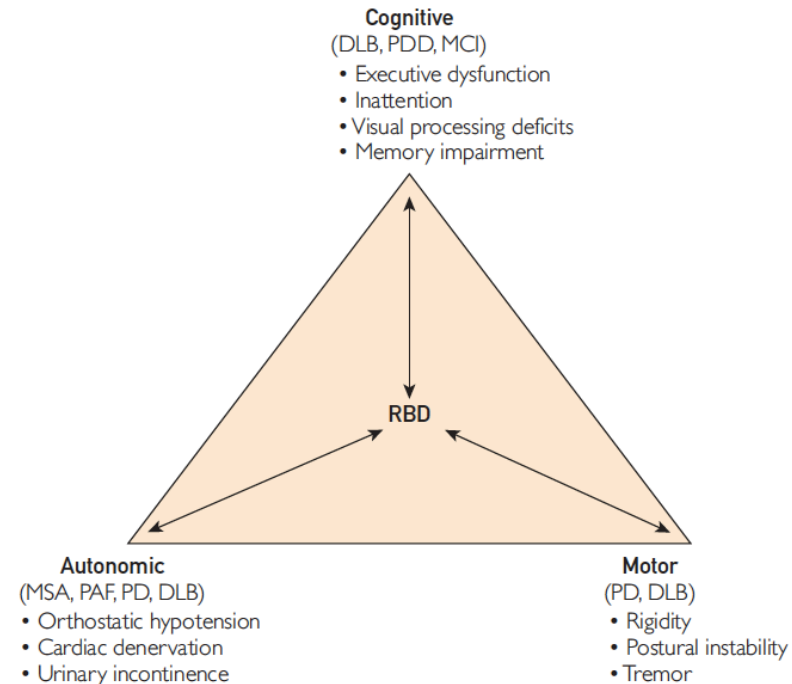
Erik K. St. Louis, MD
Stuart J. McCarter, BA
Bradley F. Boeve, MD



RBD - association

RBD may be idiopathic or symptomatic and in both settings is highly associated with **synucleinopathy neurodegeneration**:

- **PD**
- **DLB**
- **MSA**
- **PAF**

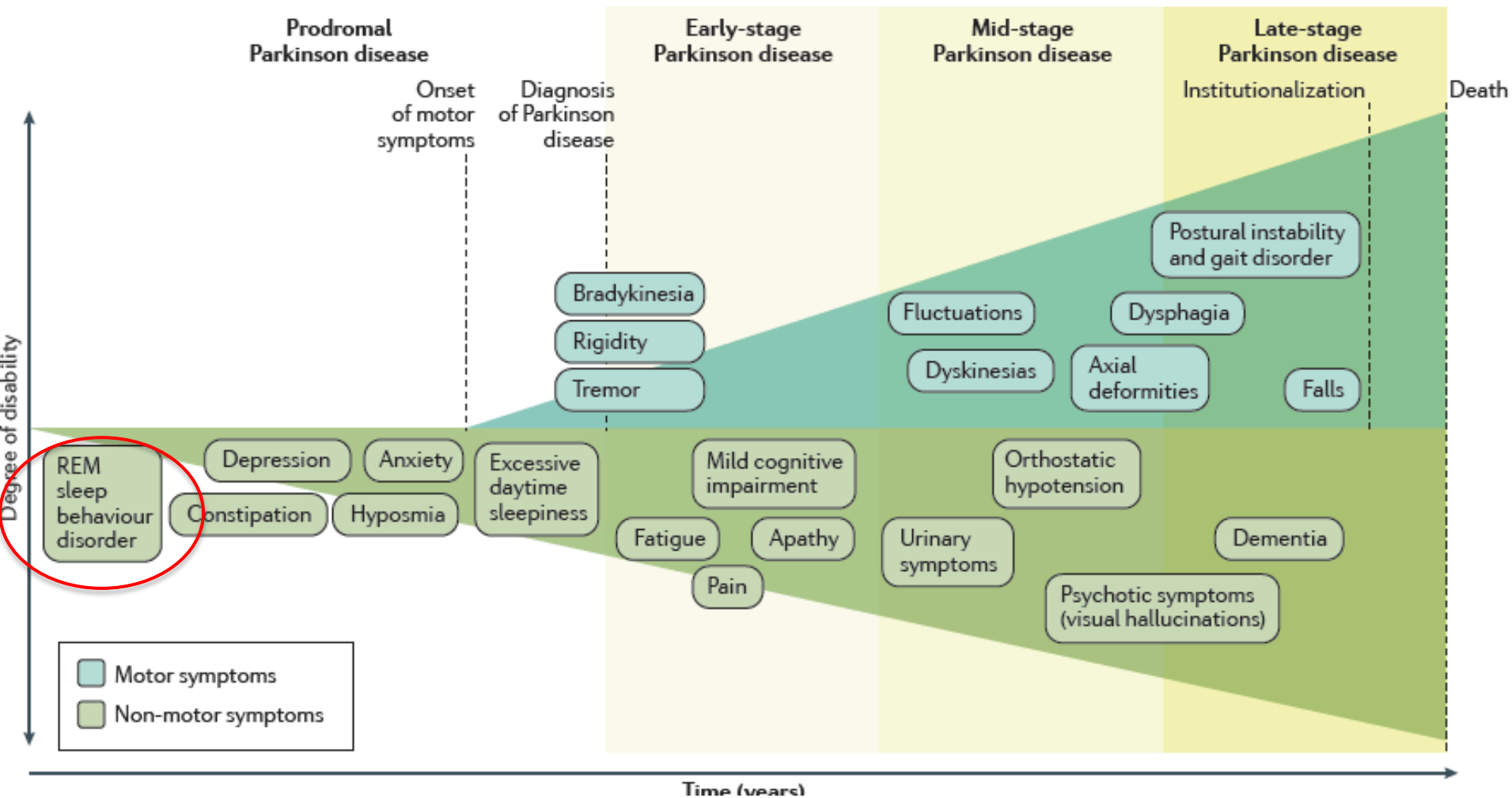


RBD – prodromal

RBD frequently manifests **years to decades prior** to overt motor, cognitive, or autonomic impairments as the presenting manifestation of synucleinopathy, along with other subtler prodromal “soft” signs of **hyposmia, constipation, and orthostatic hypotension.**

Parkinson disease

Werner Poewe¹, Klaus Seppi¹, Caroline M. Tanner^{2,3}, Glenda M. Halliday^{4,5}, Patrik Brundin⁶, Jens Volkmann⁷, Anette-Eleonore Schrag⁸ and Anthony E. Lang⁹



REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,^{1†*} Daniela Berg, MD,^{2†*} Matthew Stern, MD,³ Werner Poewe, MD,⁴
C. Warren Olanow, MD, FRCPC,⁵ Wolfgang Oertel, MD,⁶ José Obeso, MD, PhD,⁷ Kenneth Marek, MD,⁸ Irene Litvan, MD,⁹
Anthony E. Lang, OC, MD, FRCPC,¹⁰ Glenda Halliday, PhD,¹² Christopher G. Goetz, MD,¹³ Thomas Gasser, MD,²
Bruno Dubois, MD, PhD,¹⁴ Piu Chan, MD, PhD,¹⁵ Bastiaan R. Bloem, MD, PhD,¹⁶ Charles H. Adler, MD, PhD,¹⁷
and Günther Deuschl, MD¹⁸

REVIEW

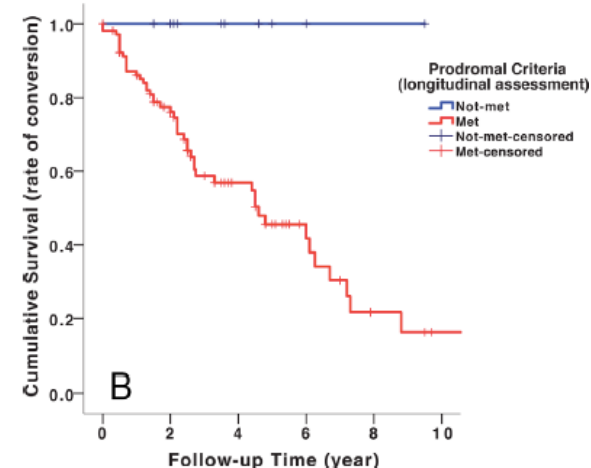
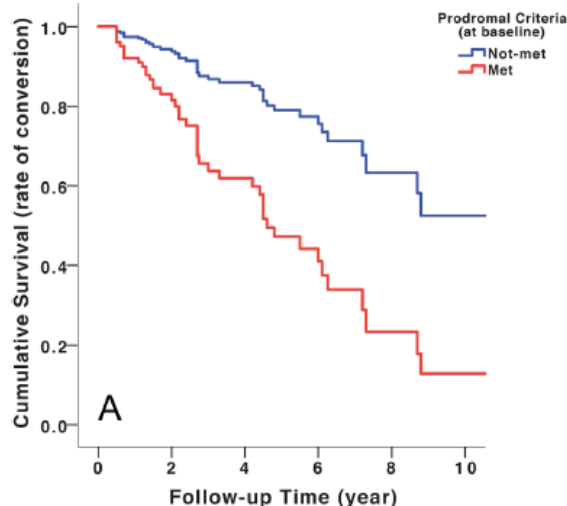
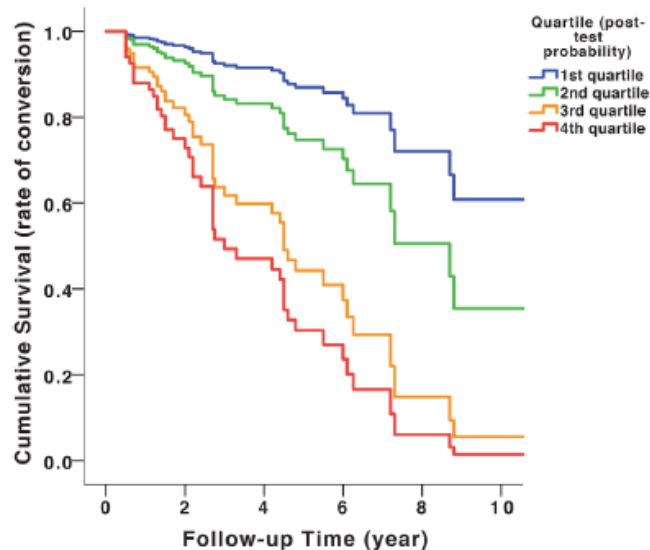
CME

MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,^{1*} Ronald B. Postuma, MD, MSc,^{2*} Charles H. Adler, MD, PhD,³ Bastiaan R. Bloem, MD, PhD,⁴
Piu Chan, MD, PhD,⁵ Bruno Dubois, MD, PhD,⁶ Thomas Gasser, MD,¹ Christopher G. Goetz, MD,⁷ Glenda Halliday, PhD,⁸
Lawrence Joseph, PhD,⁹ Anthony E. Lang, OC, MD, FRCPC,¹⁰ Inga Liepelt-Scarfone, PhD,¹ Irene Litvan, MD,¹¹
Kenneth Marek, MD,¹² José Obeso, MD, PhD,¹³ Wolfgang Oertel, MD,¹⁴ C. Warren Olanow, MD, FRCPC,¹⁵
Werner Poewe, MD,¹⁶ Matthew Stern, MD,¹⁷ and Günther Deuschl, MD¹⁸

Validation of the MDS Research Criteria for Prodromal Parkinson's Disease: Longitudinal Assessment in a REM Sleep Behavior Disorder (RBD) Cohort

Seyed-Mohammad Fereshtehnejad, MD, MPH, PhD,^{1,2} Jacques Y. Montplaisir, MD, PhD,^{3,4} Amelie Pelletier, PhD,⁵ Jean-François Gagnon, PhD,^{3,6} Daniela Berg, MD,^{7,8} and Ronald B. Postuma, MD, MSc^{1,3*}



Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

OPEN

Neurology 89 July 4, 2017

Table 1 Revised^{1,2} criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Essential for a diagnosis of DLB is **dementia**, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, **executive function**, and visuo-perceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.

Recurrent **visual hallucinations** that are typically well formed and detailed.

REM sleep behavior disorder, which may **precede cognitive decline**.

One or more spontaneous cardinal features of **parkinsonism**: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

RBD – prognosis

Between 35% and 91.9% of patients initially diagnosed with idiopathic RBD at a sleep center later develop a defined neurodegenerative disease.

Less is known about the long-term prognosis of community-dwelling younger patients, especially women, and RBD associated with antidepressant medications.

Ethical Considerations in REM Sleep Behavior Disorder

Stephanie Vertrees, MD; Glen P. Greenough, MD, FAASM

ABSTRACT

A patient diagnosed with REM behavior sleep disorder (RBD) has as much as a 65% risk of developing an α -synucleinopathy. Currently, it is not possible to predict whether an individual will develop a disease, or, if so, which disease. The neurologist treating the patient must consider (1) the difference between disclosing a diagnosis and disclosing the risk of a diagnosis; (2) whether to disclose this risk to patients; and (3) if deciding to disclose the risk, the appropriate timing of such a conversation.

Continuum (Minneapolis) 2013;19(1):199–203.

Other Neurodegenerative Disorders and RBD

- RBD has been reported to occur in association with clinically diagnosed **Alzheimer's disease**, yet when RBD is present, concurrent Lewy body pathology should be strongly suspected, as in the largest series of autopsied RBD patients to date, in which synucleinopathy was present in 94% of patients.
- RBD has also been reported in association with **progressive supranuclear palsy (PSP)**, although RBD symptoms appear more likely to parallel motor dysfunction in PSP than in synucleinopathies.
- RBD appears very rare in other primary **tauopathies**, although it has been reported in association with Guadeloupean parkinsonism, a taopathy, and was also recently reported to be strongly associated with the IgLON5 autoimmunity syndrome, which has demonstrated pontine and hypothalamic tau deposition in autopsied patients.

Narcolepsy, Autoimmune Disorders, Brain Lesions, and RBD

- When patients present with RBD at a younger age, **arbitrarily before age 50**, other nondegenerative etiologies should be considered, including narcolepsy, autoimmunity, and antidepressant-associated RBD.
- Of these, narcolepsy type 1 (narcolepsy with cataplexy) has been clearly associated with RBD and altered REM sleep atonia control leading to RSWA.
- In one polysomnography study of narcolepsy patients, **50% were found to have RBD**, and 36% of surveyed narcoleptic patients endorsed possible RBD symptoms.
- In younger and some older patients, RBD may present as a syndromic manifestation of a paraneoplastic and autoimmune neurologic disorder, such as in **Morvan syndrome** (anti-voltage-gated potassium channel antibody syndrome), **IgLON5 autoimmunity**, and brain stem lesions caused by inflammatory, neoplastic, or cerebrovascular disorders.

RBD come marcatore di gravità di malattia nella MP

- RBD può rappresentare una “red flag” nella MP?
- Nella MP+RBD le allucinazioni sono 3 volte più frequenti (Pacchetti, 2005)
- Nella MP+RBD vi è maggiore rallentamento EEG (Gagnon 2004)
- MP+RBD si associa a maggior compromissione cognitiva (Vendette, 2007)
- MP+RBD associato alla forma rigido-acinetica, sintomi assiali e maggiori cadute (Postuma, 2008)

RESEARCH PAPER

Sleep and REM sleep behaviour disorder in Parkinson's disease with impulse control disorder

Maria Livia Fantini,^{1,2,3} Michela Figorilli,^{2,4} Isabelle Arnulf,⁵ Maurizio Zibetti,⁶ Bruno Pereira,⁷ Patricia Beudin,¹ Monica Puligheddu,⁴ Florence Cormier-Dequaire,⁸ Lucette Lacomblez,⁸ Eve Benchetrit,⁸ Jean Christophe Corvol,⁸ Alessandro Cicolin,⁹ Leonardo Lopiano,⁶ Ana Marques,^{2,3} Franck Durif^{2,3}

Table 5 Results of univariate and multivariate analysis in PD with and without ICDs

	PD-RBD (n=55)	PD-noRBD (n=25)	Univariate OR (95% CI)	p	Multivariate OR (95% CI) ¹	p
Sex (M,%)	31 (56%)	13 (52%)	0.84 (0.32 to 2.17)	0.72	0.79 (0.25 to 2.47)	0.69
Age at PD onset	55.0±9.0	56.0±10.3	0.99 (0.94 to 1.04)	0.64	1.04 (0.97 to 1.10)	0.30
PD duration	8.7±4.5	6.5±4.0	1.14 (1.00 to 1.29)	0.04	1.47 (0.93 to 2.34)	0.10
UPDRS-III	17.7±10.2	17.2±9.4	1.01 (0.96 to 1.06)	0.84	1.00 (0.95 to 1.06)	0.91
LEDD	898 (654; 1248)	793 (440; 959)	1.01 (1.00 to 1.02)	0.06	1.48 (0.46 to 4.84)	0.51
≥730 mg (n,%) [§]	37 (67.2 %)	13 (52 %)	1.90 (0.72 to 4.98)	0.19		
DA-LEDD	105 [0; 210]	180 (0; 240)	1.00 (0.99 to 1.01)	0.34	0.84 (0.27 to 2.67)	0.77
≥120 mg (n,%) [§]	27 (49.1%)	15 (60%)	0.64 (0.25 to 1.68)	0.36		
Duration of treatment	7.5±4.5	5.9±3.8	1.10 (0.97 to 1.24)	0.13	0.72 (0.46 to 1.14)	0.16
Antidepressant use	16 (29%)	4 (16%)	2.15 (0.64 to 7.28)	0.22	1.74 (0.42 to 7.27)	0.45
ICDs (n,%)	34 (62%)	6 (24%)	5.12 (1.76 to 14.90)	0.003	4.57 (1.27 to 16.53)	0.02*



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Parkinsonism and Related Disorders

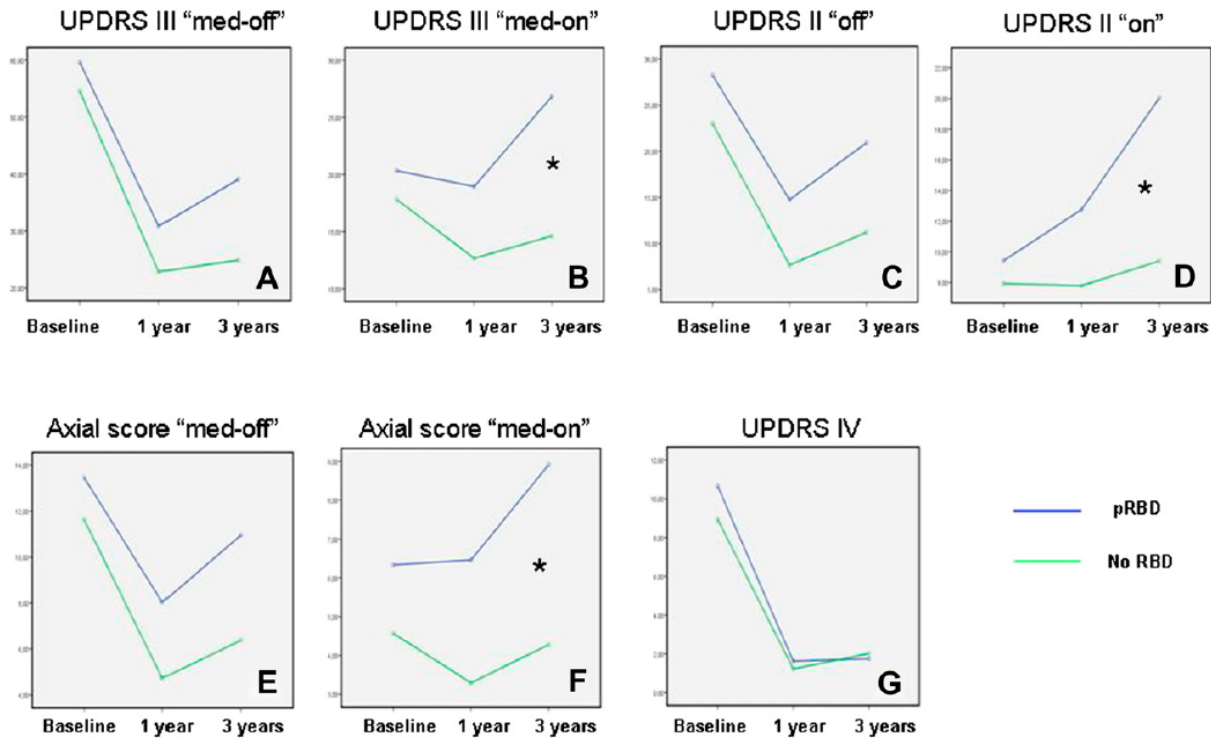
journal homepage: www.elsevier.com/locate/parkreldis



Probable REM sleep behaviour disorder and STN-DBS outcome in Parkinson's Disease[☆]

M. Zibetti*, L. Rizzi, L. Colloca, A. Cinquepalmi, S. Angrisano, L. Castelli, M. Lanotte, L. Lopiano

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RBD – therapy

Patients with RBD are frequently prone to sleep-related injuries and should be treated to prevent injury:

- Bedroom safety principles (Bed alarm)
- Melatonin 3-12 mg
- Clonazepam 0.5-2.0 mg
- Avoid SSRI, SNRI, TCA (->Bupropion)



RBD – conclusions

Further evidence-based studies about RBD are greatly needed, both to enable accurate **prognostic prediction** of end synucleinopathy phenotypes for **individual patients** and to support the application of symptomatic and neuroprotective therapies.

RBD as a prodromal synucleinopathy represents a **defined time point** at which neuroprotective therapies could potentially be applied for the prevention of PD, DLB, MSA and PAF.

Sleep Disorders and RBD: What Would James Parkinson Think?

Ronald B. Postuma*

Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada

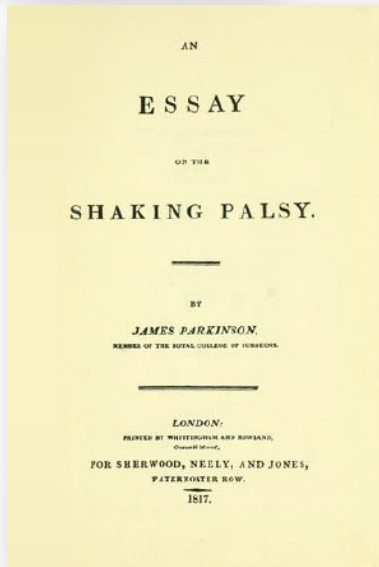


James Parkinson actually did make one mention of sleep, when he wrote:

In this stage the sleep becomes much disturbed. The tremulous motion of the limbs occur during sleep, and augment until they awaken the patient, and frequently with much agitation and alarm.

Parkinson himself would have been especially interested in rapid eye movement sleep behavior disorder (RBD). In the monograph, he wrote:

It is obvious, that the chance of obtaining relief will depend in a great measure on the period at which the means are employed. As in every other disease, so here, the earlier the remedies are resorted to, the greater will be the probability of success.





Grazie dell'attenzione