SOCIETÀ ITALIANA DI NEUROLOGIA

11 Giugno 2019 Milano - Roma - Catania
Giornata dello specializzando in neurologia 2019

Hot Topic

From REM Sleep Behavior Disorder to Neurodegeneration – Clinical spectrum and ethical issues

Luca Baldelli, MD

Medico in Formazione Specialistica - Neurologia

Dipartimento di Scienze Biomediche e Neuromotorie - ALMA MATER STUDIORUM - Università di Bologna

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

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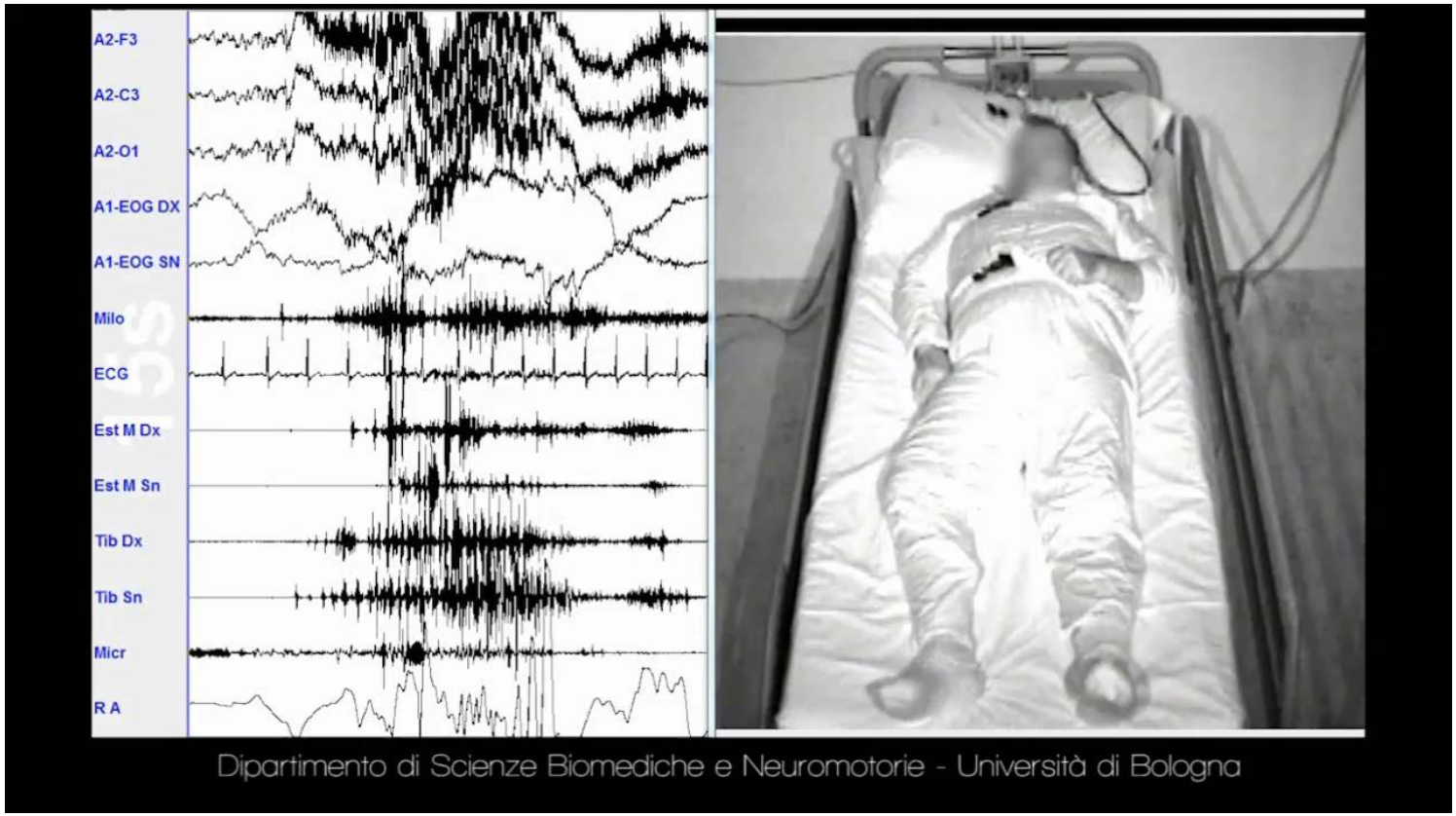
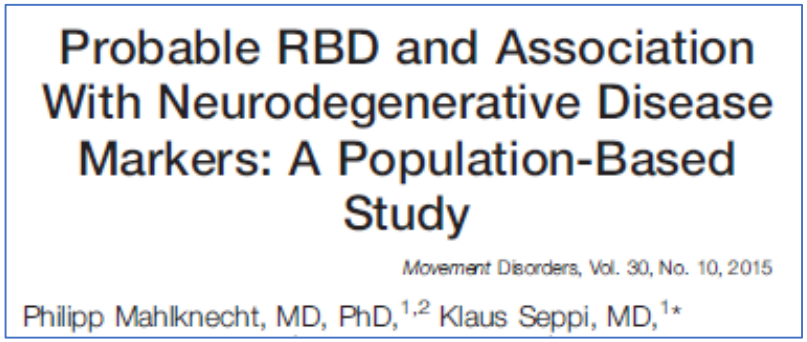
REM Sleep Behaviour Disorder - RBD

RBD is a REM sleep parasomnia characterized by loss of the physiological muscular atonia, associated to the possibility for the patients of «acting out» their dreams.



RBD – Main Features

- RBD can be *idiopathic* or *secondary* (*symptomatic*):
  - *Idiopathic* RBD (iRBD) occurs in absence of signs of neurological diseases → the elderly (~60 y.o.) .
  - *Secondary* RBD is mainly associated to neurological disorders: narcolepsy or neurodegenerative diseases (PD, DLB, MSA), but also to pontine lesions, assumption or abrupt interruption of drugs and substances of abuse, etc…
- RBD is infrequent; exact prevalence in the general population is unknown (0,5-2%?).


Probable RBD and Association With Neurodegenerative Disease Markers: A Population-Based Study

Movement Disorders, Vol. 30, No. 10, 2015

Philipp Mahlknecht, MD, PhD,[1,2] Klaus Seppi, MD,[1*]

- More recently, questionnaire-based studies showed higher prevalence (4,6-7,7%) in ageing population (> 60 y.o.).

iRBD – An Evolving Definition

2009

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Ann. N.Y. Acad. Sci. ISSN 0077-8923

REM sleep behavior disorder

Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions

Bradley F. Boeve

"…RBD occurring in the absence of any other obvious associated neurologic disorder."

2017

Rapid Eye Movement Sleep Behavior Disorder and Other Rapid Eye Movement Sleep Parasomnias

Continuum (Minneap Minn) 2017;23(4):1017–1034

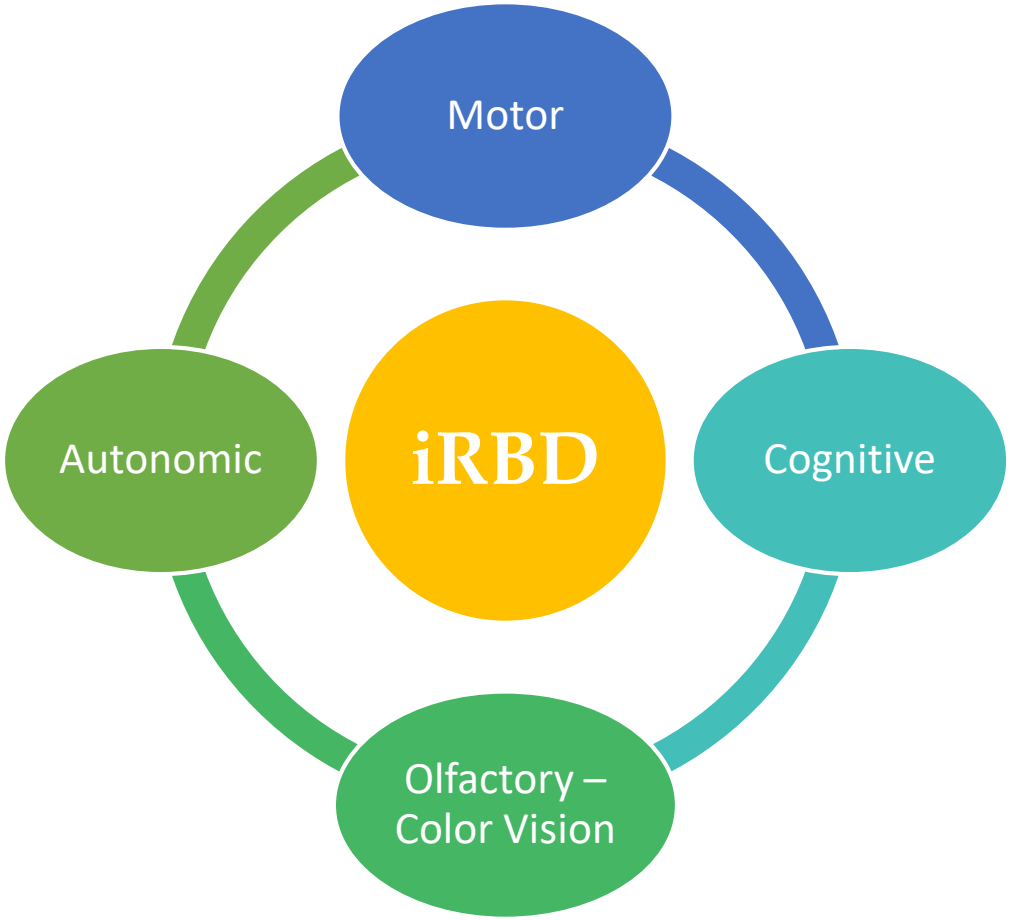
Birgit Högl, MD; Alex Iranzo, MD

"iRBD [can be considered] as an early feature of synucleinopathies."

- The definition of idiopathic RBD is frequently based on the sole clinical observation. *Is that enough?*

iRBD – Not always just a Sleep Disorder

- Patients with idiopathic RBD show often subtle subjective or objective clinical abnormalities.
- These pathological findings are the same found in α-synucleinopathies.
- Healthy ageing alone cannot account for these results.



iRBD – Motor Function

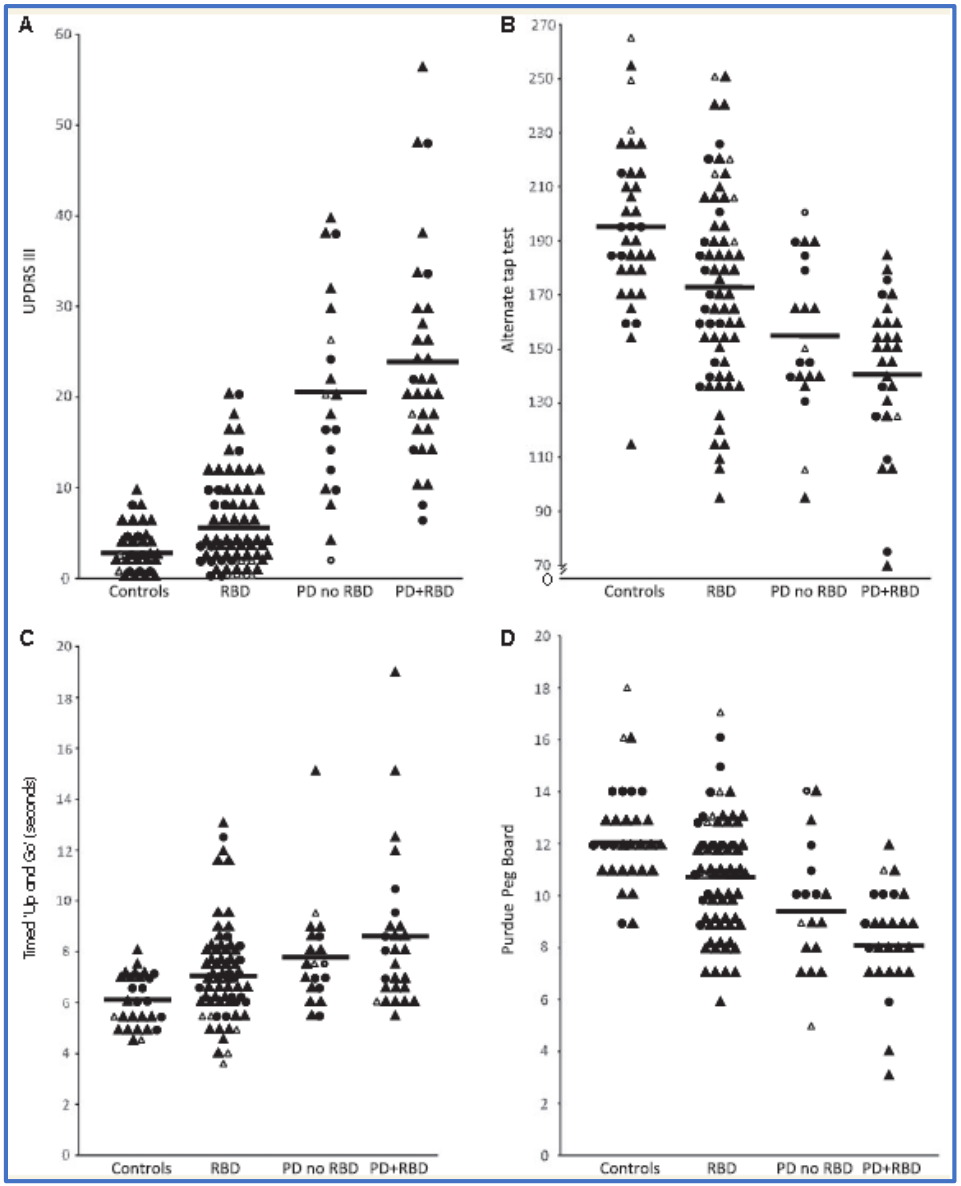
doi:10.1093/brain/awp244 Brain 2009: 132; 3298–3307 | 3298

BRAIN
A JOURNAL OF NEUROLOGY

Markers of neurodegeneration in idiopathic rapid eye movement sleep behaviour disorder and Parkinson's disease

R. B. Postuma,[1,2] J. F. Gagnon,[2,3] M. Vendette[2] and J. Y. Montplaisir[2,3]

	HC	iRBD	PD - RBD	PD + RBD
n°	36	68	21	34
RBD Duration	NA	9,3±1,1 years	NA	NA
Motor Tests	*UPDRS-III, Alternate tap test, Purdue Peg Board, Timed «Up and Go».*			



- iRBD patients show **intermediate results** in motor functions tests between healthy controls and PD patients.
- Subtle parkinsonian signs can be found in some patients.

iRBD – Cognitive Performance

frontiers in NEUROLOGY

MINI REVIEW ARTICLE
published: 17 May 2012
doi: 10.3389/fneur.2012.00082

Cognition in rapid eye movement sleep behavior disorder

Jean-François Gagnon*, Josie-Anne Bertrand and Daphné Génier Marchand

Center for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada

- Cognitive deficits are **more frequent** in iRBD than in healthy controls.

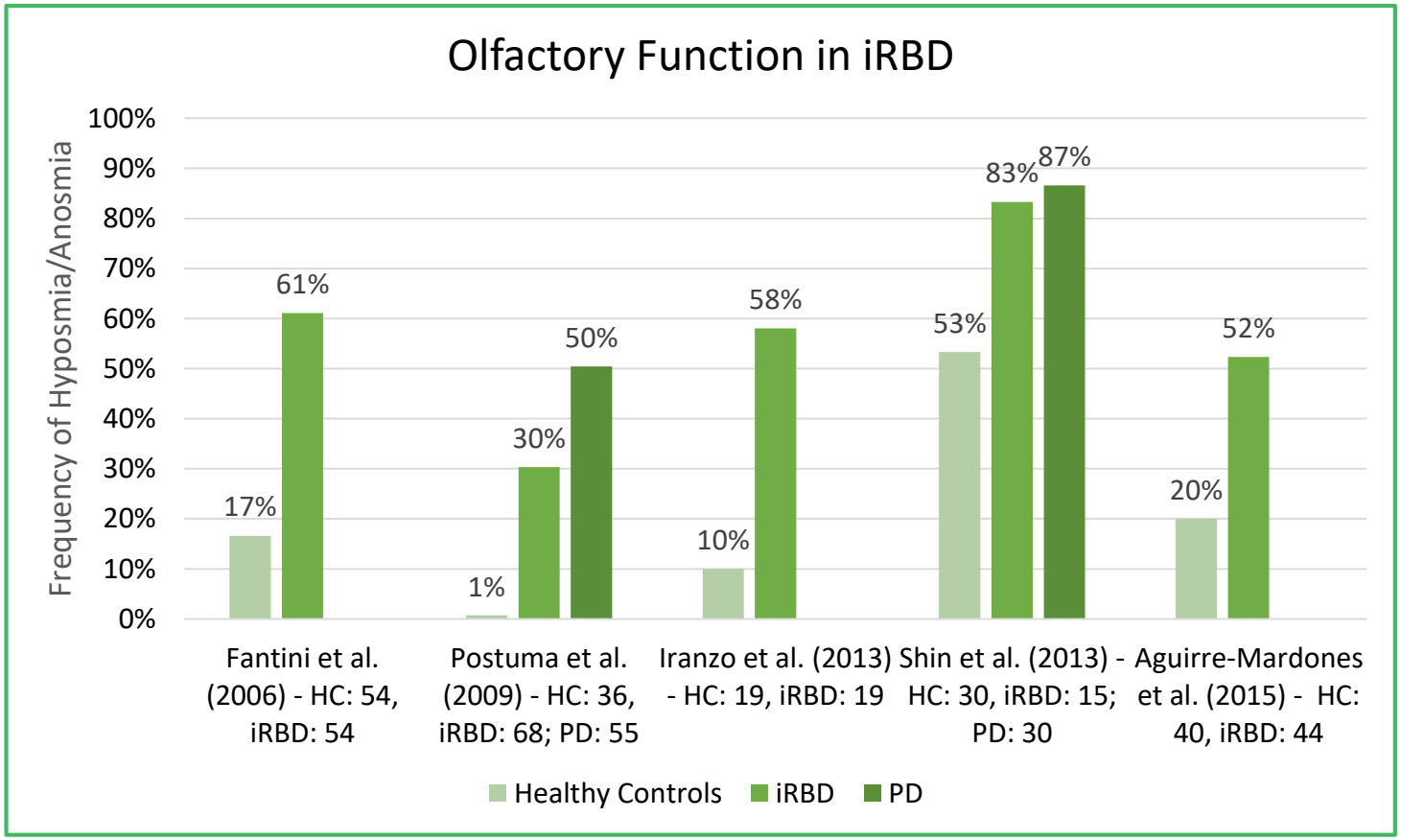
Cognitive domains	Terzaghi et al. (2008)	Massicotte-Marquez et al. (2008)[a]	Gagnon et al. (2009)[a]	Marques et al. (2010)	Ferini-Strambi et al. (2004)[b]	Fantini et al. (2011)[b]
Attention/executive functions	Yes	Yes	Yes	Yes	Yes	No
Verbal episodic memory	Yes	Yes	Yes	Yes	Yes	Yes
Non-verbal memory	Yes	–	–	–	Yes	Yes
Visuospatial abilities	No	No	No	Yes	Yes	Yes

[a,b] Share common participants; Yes = patients show poorer performance than controls ($p < 0.05$); No = similar performance between patients and controls.

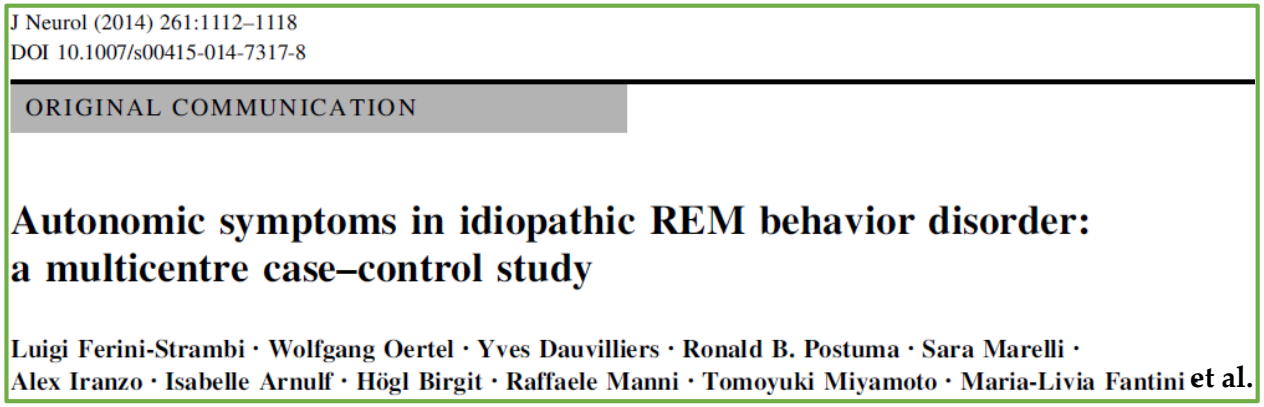
- iRBD patients have worse cognitive performances than PD patients without RBD and intermediate to PD patients with RBD.
- Mild Cognitive Impairment (**MCI**) is present in up to **54%** of iRBDs.

iRBD – Olfaction

- Hyposmia is **more frequent** in iRBD patients than in healthy controls and usually less frequent if compared to PD patients.



iRBD – Autonomic Regulation



J Neurol (2014) 261:1112–1118
DOI 10.1007/s00415-014-7317-8

ORIGINAL COMMUNICATION

Autonomic symptoms in idiopathic REM behavior disorder: a multicentre case–control study

Luigi Ferini-Strambi · Wolfgang Oertel · Yves Dauvilliers · Ronald B. Postuma · Sara Marelli · Alex Iranzo · Isabelle Arnulf · Högl Birgit · Raffaele Manni · Tomoyuki Miyamoto · Maria-Livia Fantini **et al.**

- Autonomic function in isolated RBD has been investigated by means of:
  - **Questionnaire-based studies**: SCOPA-AUT - *Ferini-Strambi et al. (J Neurol, 2014)*; COMPASS – *Frauscher et al. (J Neurol, 2012)*, etc…
  - **Cardiovascular reflex tests**: *Ferini-Strambi et al. (Sleep, 1996)*, *Lee et al. (Mov Disord, 2015)*, etc…
  - **Nighttime heart rate variability (HRV)**: *Ferini-Strambi et al. (Sleep, 1996)*, *Lanfranchi et al. (Sleep, 2007)*, etc...
  - **Cardiac scintigraphy:** *Miyamoto et al. (Sleep, 2008), Kashihara et al. (Parkinsonism Relat Disord, 2010), etc…*
  - **Quantitative sudomotor axon reflex tests (QSART)**: *Lee et al. (Mov Disord, 2015).*

- Autonomic dysfunction is present and predominantly involves the **sympathetic** and **cardiovagal** branches and is **intermediate** between healthy controls and patients with manifest parkinsonism.

iRBD: Harbinger of Neurodegenerative Disease

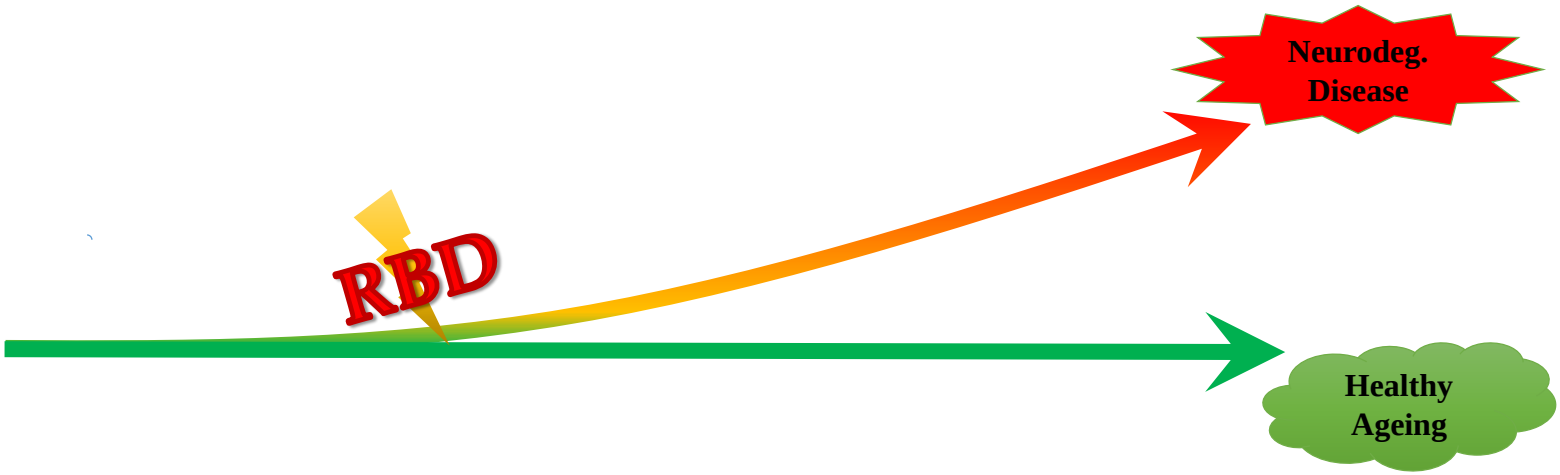
NEUROLOGY 46 **February 1996**

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

- Seen clinically iRBD has become the **prodrome** of an underlying neurodegenerative process.

idiopathic RBD → **cryptogenic/isolated RBD**



Is iRBD a Neurodegenerative Disease?

- How can we demonstrate that iRBD with its concomitant alterations is part of a unique neurodegenerative process?
- What are the implications for clinical practice?

Anatomic Pathology **A**

- Do iRBD and α-syn. share the same pathology?

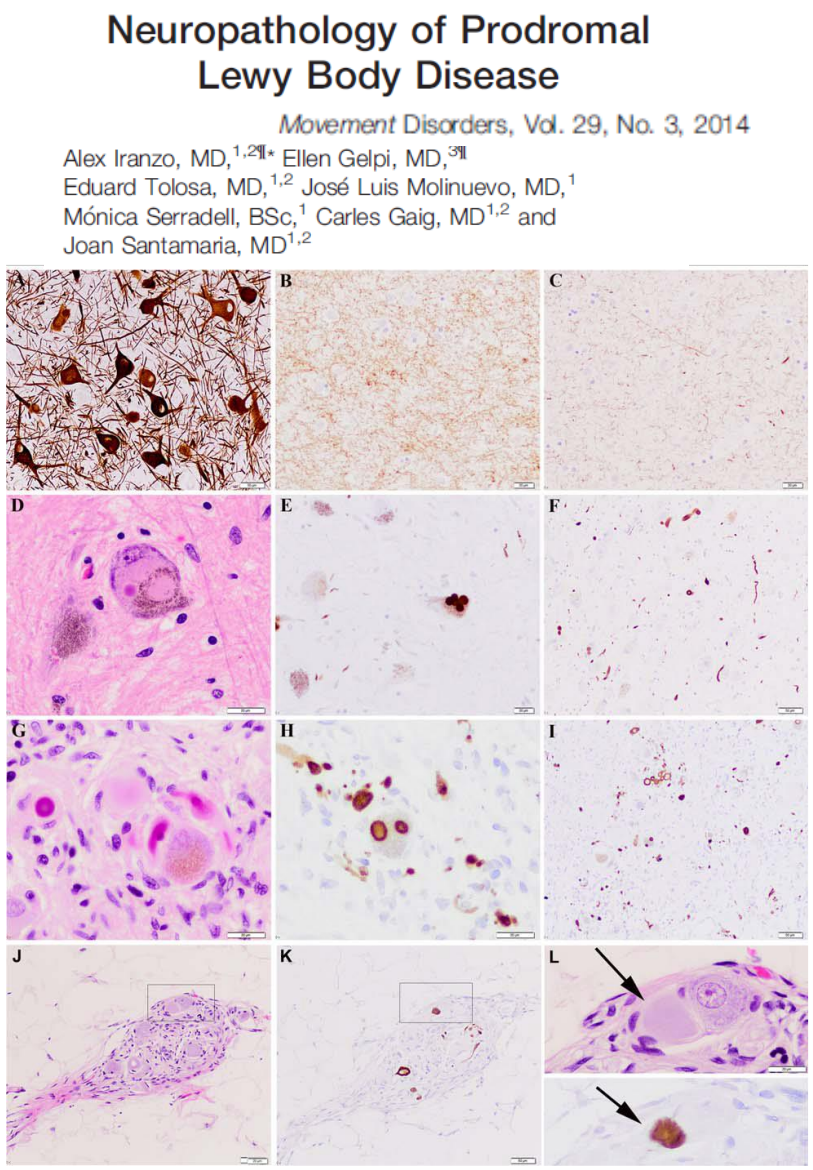
Brain Imaging **B**

- Do iRBD and α-syn. share the same imaging traits?
- Can imaging features predict phenoconversion?

Clinical Follow-up **C**

- Which markers can be considered as real risk factors?
- Are they reliable?

Anatomic Pathology of 3 iRBD –
Incidental Lewy Body Disease



- Only 3 case reports
  - **M. Uchiyama et al** *(Neurology, 1995)*
  - **B.F. Boeve et al**. *(Sleep Med, 2007)*
  - **A. Iranzo et al.** *(Mov Dis, 2014)*

	Uchiyama et al.(1995)	Boeve et al. (2007)	Iranzo et al. (2014)
Age at death	84 y.o.	72 y.o.	78 y.o.
Cause of death	Pneumonia	Cryptog. organized pneumonia	Lung cancer
RBD duration	20 years	15 years	11 years
Comorbidities	Gastric ulcer	//	-Hyposmia (74y) -MCI (76y) -Constip. (78y)

- **Lewy Bodies** and α-synuclein deposits in Locus Ceruleus, Central Raphe Nucleus and Substantia nigra;
  Neuronal loss and **gliosis** in 2 cases.

Brain Imaging of iRBD –

Do iRBD and α-syn. share the same imaging traits?

Brain (2000), **123**, 1155–1160

Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder

Comparison with Parkinson's disease and controls

I. Eisensehr,[1] R. Linke,[2] S. Noachtar,[1] J. Schwarz,[1] F. J. Gildehaus[2] and K. Tatsch[2]

N° iRBD	N° HC	N° PD
5	7	14

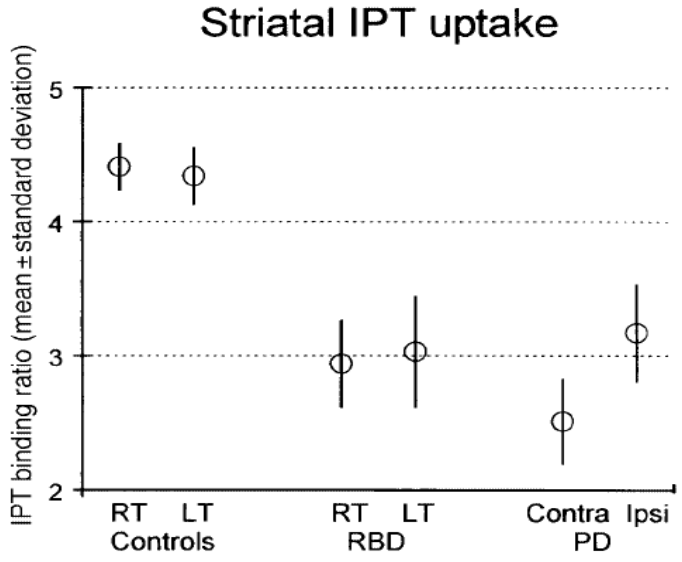


Fig. 1 Striatal presynaptic IPT-binding ratio of patients with RBD and Parkinson's disease (Hoehn and Yahr stage I) and controls. Values are mean ± standard deviation. RT = right; LT = left; Contra = striatal IPT binding contralateral to the symptomatic side of the body; Ipsi = striatal IPT binding corresponding to the asymptomatic side of the body.

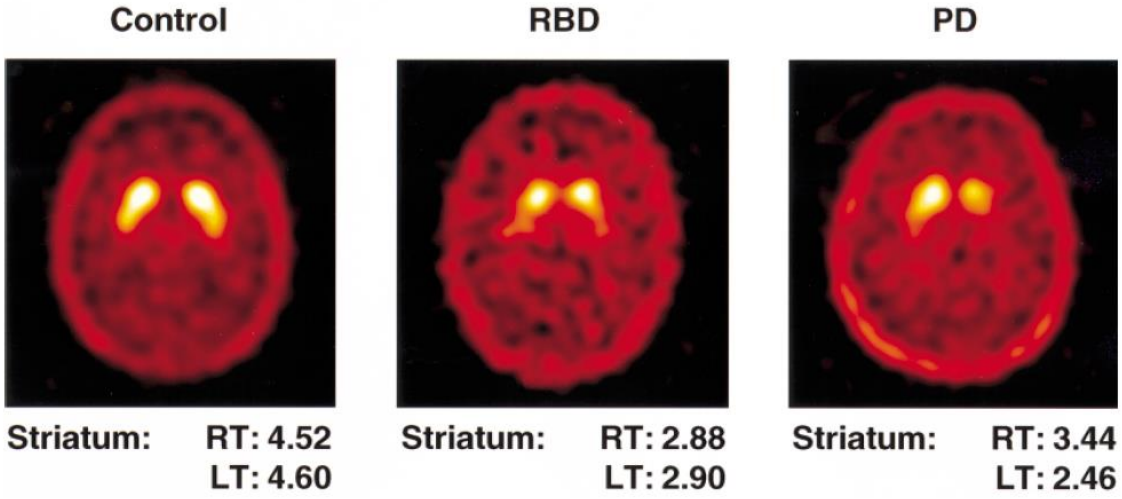


Fig. 2 The [^{123}I]IPT-SPECT of one patient with RBD, one patient with Parkinson's disease (Hoehn and Yahr stage I) and one control subject. Binding ratios are given below the [^{123}I]IPT-SPECTs. Note the bilaterally reduced IPT binding ratio in the RBD patient, whereas in the Parkinson's disease patient the reduction is asymmetrical, being more pronounced contralateral to the symptomatic body side of the patient. RT = right; LT = left.

Brain Imaging of iRBD – DAT-Scan + TCS

Can imaging features predict phenoconversion?

Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study

A. Iranzo et al. / Movement Disorders, Vol. 29, No. 14, 2014

N° iRBD	Conv. 2,5y
39	8

- Combination of TCS with [^{123}I]FP-CIT-SPECT reveals 100% sensitivity and 55% specificity to predict subsequent phenoconversion within 2.5y.

	Age at neuroimaging (years)	RBD duration at neuroimaging (years)	Reduced striatal ^{123}I-FP-CIT uptake	Hyperechogenicity of substantia nigra	Echogenic substantia nigra size (cm^2)		Diagnosis 2·5 years after neuroimaging
					Right	Left	
1	71	21	Yes	Yes	0·24	0·24	Parkinson's disease
2	81	11	Yes	No	0·05	0·13	Parkinson's disease
3	78	10	Yes	No	0·10	0·12	Parkinson's disease
4	78	19	Yes	Yes	0·12	0·25	Parkinson's disease
5	71	11	No	Yes	0·25	0·28	Parkinson's disease
6	70	11	No	Yes	0·34	0·37	Dementia with Lewy bodies
7	77	15	Yes	Yes	0·26	0·35	Dementia with Lewy bodies
8	73	17	Yes	No	0·10	0·09	Multiple system atrophy

- **When** TCS is **associated** with [^{123}I]FP-CIT-SPECT it gains good validity for prognostic monitoring of iRBD.

Clinical Follow-up –
Clinical Markers as Risk Factors for Neurodegeneration

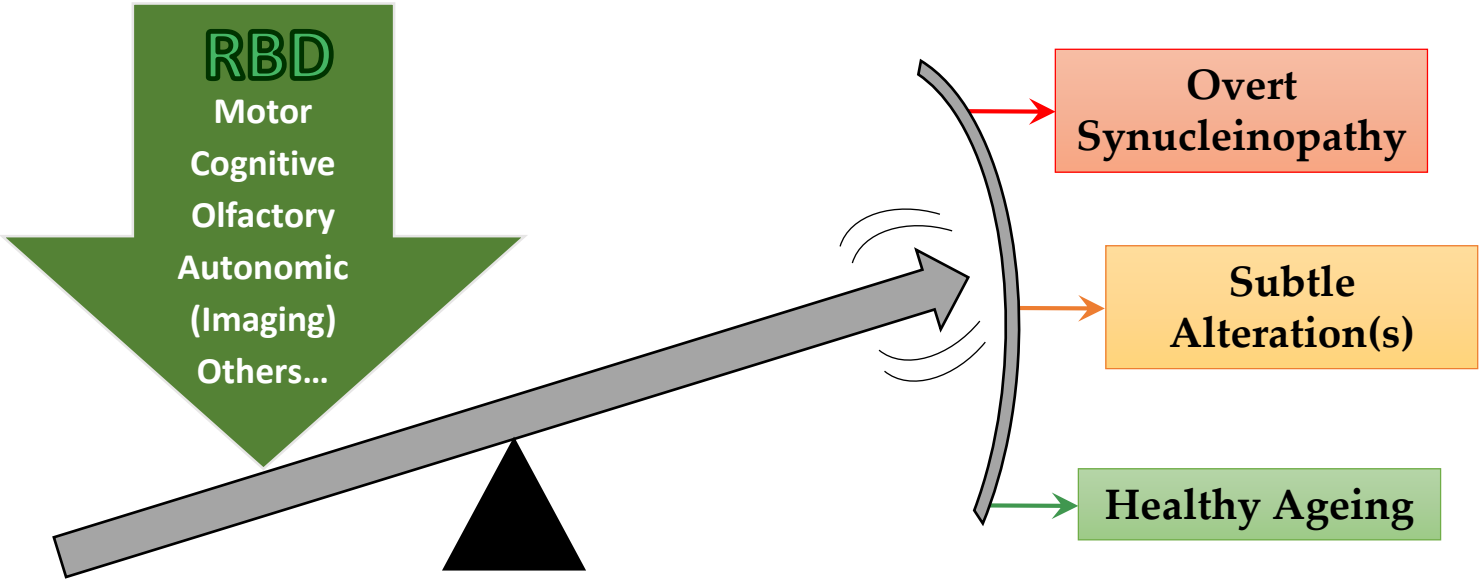
- Concomitant abnormalities in iRBD patients increase the risk of phenoconversion into a neurodegenerative disease.
- Only clinical follow-up of these patients can discriminate their real value.

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

Postuma et al

BRAIN 2019: 0; 1–16

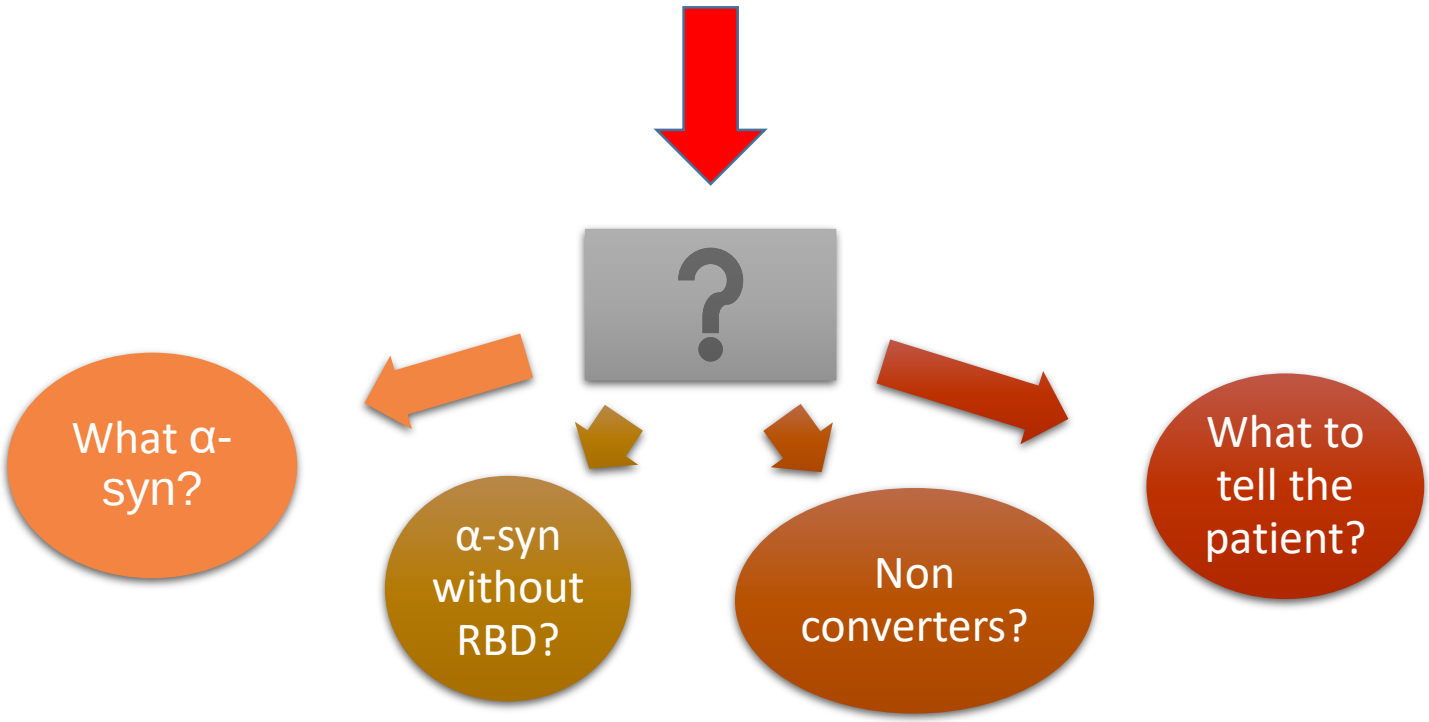
n° iRBD	Conv. Rate	5y Risk	12y Risk
1280	6,25% per year	31,5%	73,5%



Open Issues

- The neurodegenerative nature of "idiopathic" RBD seems to be demonstrated, giving the right tools to discriminate who is at higher risk of phenoconvertion.

However…



Open Issues – What α-synucleinopaty?

- While iRBD conversion into an α-synucleinopathy is well established, there is **unclear evidence** describing towards what **specific disease** will the patients convert and what **markers** should be indicative of that.
- RBD frequency in **MSA** is about **100%**, only **46%** in **PD** and **80%** in **DLB**.

Rapid Eye Movement Sleep Behavior Disorder and Subtypes of Parkinson's Disease

Movement Disorders, Vol. 27, No. 8, 2012

Silvia Rios Romenets, MD,[1] Jean-Francois Gagnon, PhD,[2,3] Véronique Latreille, PhD,[2] Michel Panniset, MD,[2] Sylvain Chouinard, MD,[2] Jacques Montplaisir, MD, PhD,[2,4] and Ronald B. Postuma, MD, MSc[1,2*]

- RBD has been associated with a specific subtype of PD clinically characterized by:
  - Akynetic-rigid syntoms;
  - More severe autonomic disfunction;
  - Worse cognitive deficits;
  - Higher motor fluctuations.

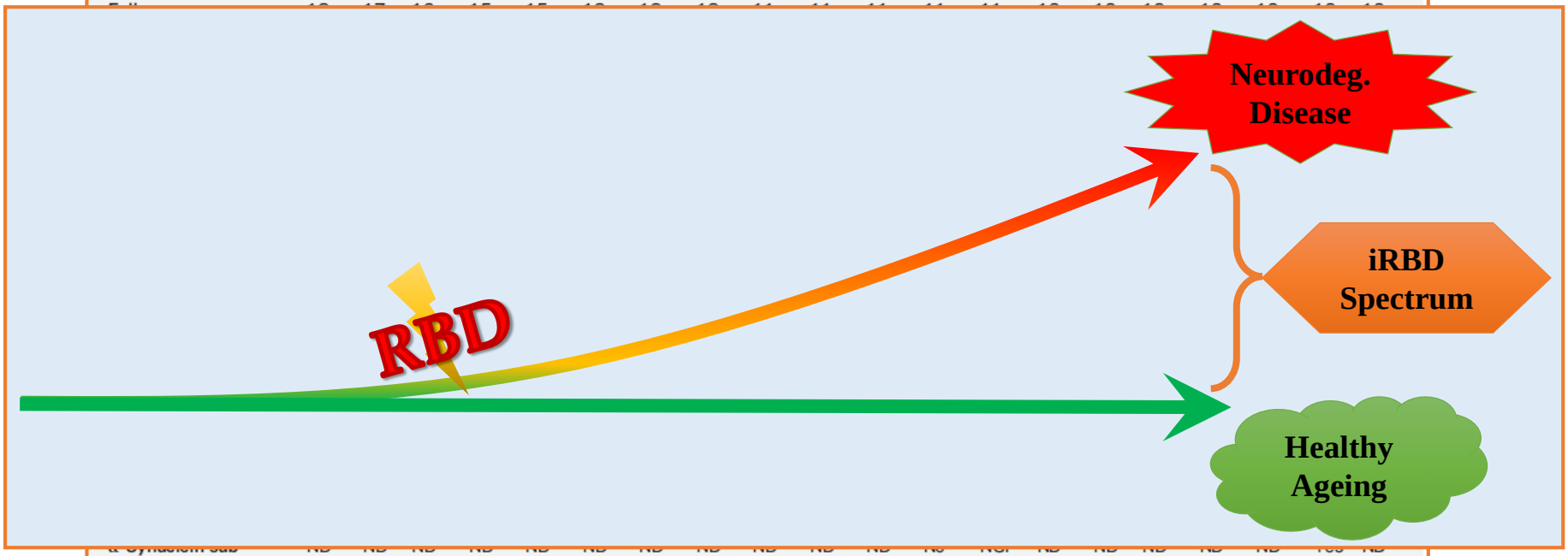
Open Issues – Non Converters?

The «iRBD spectrum»

- Long-term follow-up iRBD patients (>10 y) seem to defy the neurodegenerative nature of iRBD.

Characterization of patients with longstanding idiopathic REM sleep behavior disorder
Alex Iranzo, Ambra Stefani, Monica Serradell, et al.
Neurology 2017;89;242-248 Published Online before print June 14, 2017

	Patient number																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Probability[d]	97.3	9.9	32.7	31.4	99.7	99.6	11.9	30.0	24.4	98.2	59.1	61.7	99.0	99.3	2.1	98.9	99.7	55.0	1.1	93.4



- In-depth evaluation of these patients highlights prodromal PD markers, suggesting and **underlying neurodegenerative process** in absence of an overt disease.

Open Issues – Management of the iRBD Patient

To tell or not to tell? – Disclosing the RISK of a diagnosis

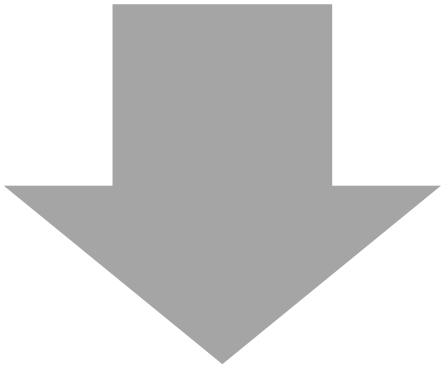
- Treated patients with iRBD feel well: no motor or cognitive impairment.
- No disease modifying therapies.
- Risk for conversion neither absolute nor imminent.

Disclosing a Diagnosis

Disclosing the RISK of a Diagnosis

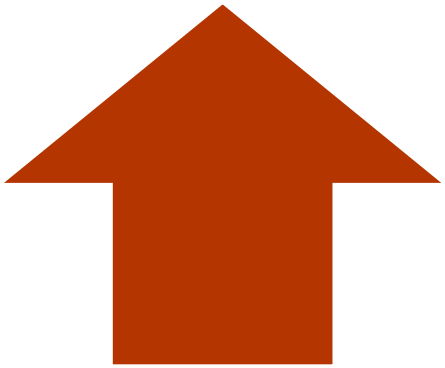
iRBD and Ethical Issues – Disclosure

Is it Right to inform the patient?



Shield the patient from excessive worrying

Principle of Autonomy



iRBD and Ethical Issues – Disclosure

Who will inform the patient?

LA STAMPA

SEZIONI

Lo zucchero di canna è più dietetico di quello bianco?

Disturbi d
malattia n

Un tipo di problem
essere il segnale cl
demenza o la mala

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Disturbo del sonno potrebbe essere la 'spia' di malattie al cervello

CRONACA

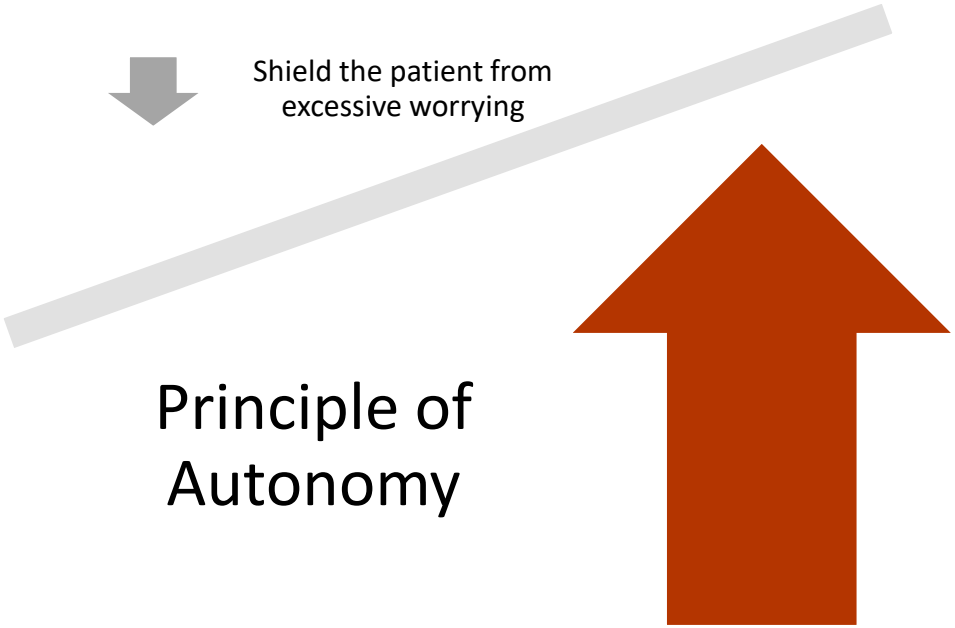
Pubblicato il: 22/04/2014 18:32

Roma, 22 apr. (Adnkronos Salute) - Sonno difficile uguale possibili problemi neurologici. I ricercatori dell'Università di Toronto (Canada) sono convinti che un particolare disturbo del riposo, che avviene in particolare durante la fase Rem, possa essere considerato addirittura il miglior segnale predittivo di malattie cerebrali come il Parkinson e l'Alzheimer. Lo scrivono sulla rivista 'Trends in Neuroscience'.

Il disturbo comportamentale in sonno Rem (Rbd), così si chiama scientificamente questo problema, "non è solo un precursore, ma un segnale di avvertimento della neurodegenerazione che può portare a malattie del cervello, che si verificano infatti nell'80-90% delle persone con Rbd".

iRBD and Ethical Issues – Disclosure

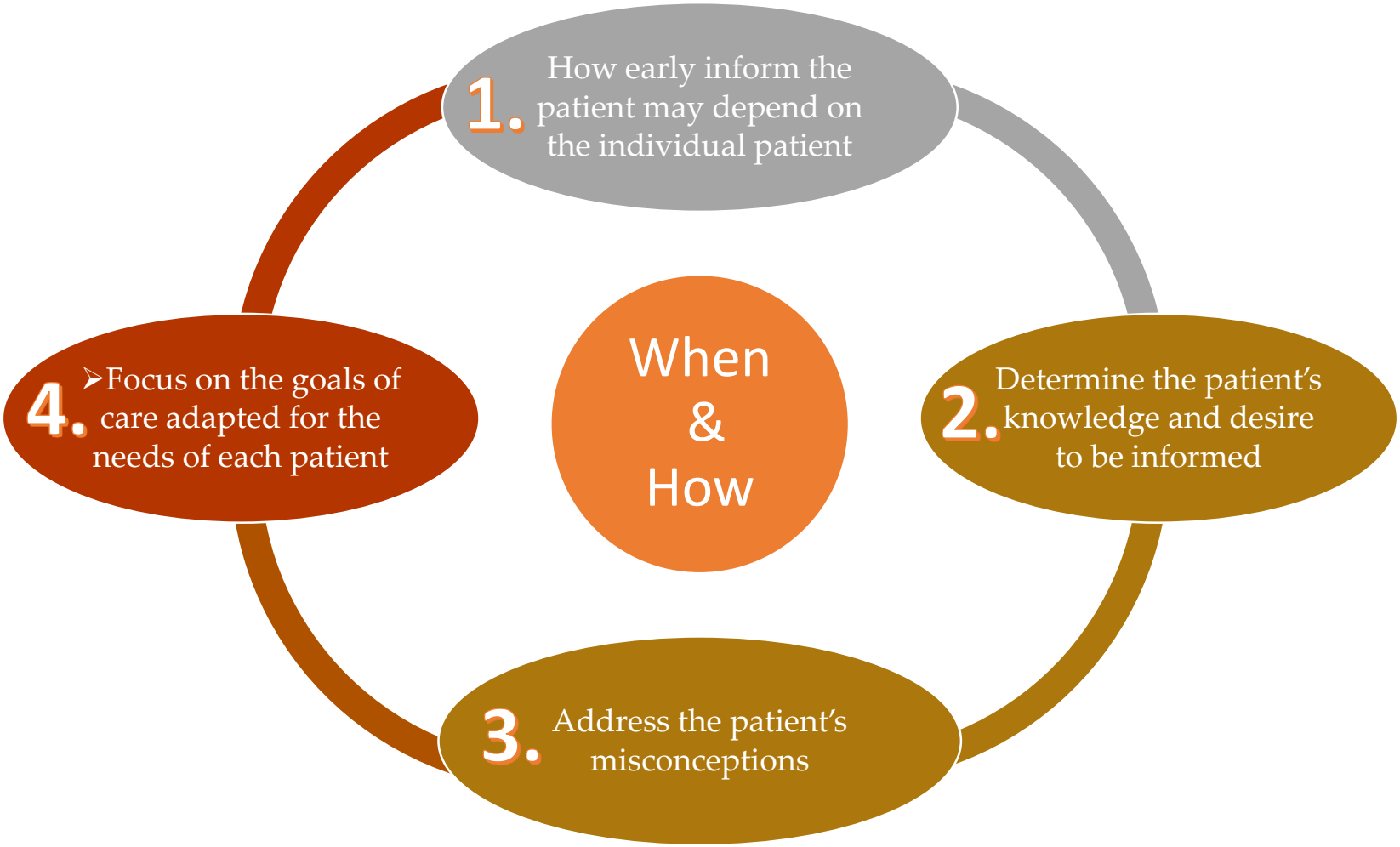
It is Right to inform the patient



Potential frustration from uncertainty is an inadequate justification for withholding information: the patient needs to make an informed decision.

iRBD and Ethical Issues – Disclosure

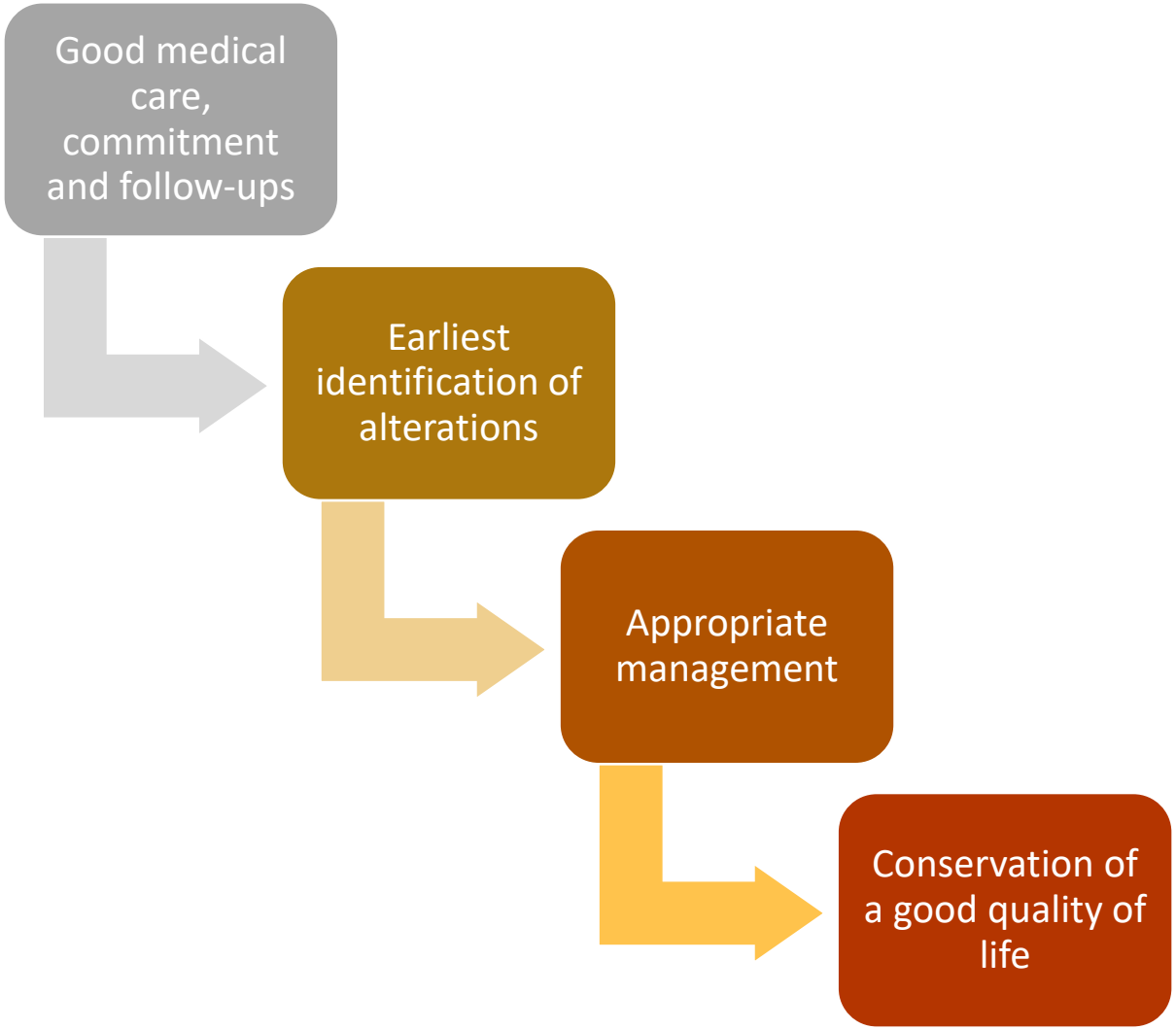
Identify the «when» and «how» for each patient



- Provide tailored information at each subsequent follow-up step, depending on each individual patient.

iRBD and Ethical Issues – Contents

Stress a positive approach and Keep an eye on emerging alterations



iRBD and Ethical Issues – A content example

Early Rehabilitation?

Link Between Parkinson Disease and Rapid Eye Movement Sleep Behavior Disorder With Dream Enactment: Possible Implications for Early Rehabilitation

Brian P. Johnson, OTR/L, Kelly P. Westlake, PT, PhD

Archives of Physical Medicine and Rehabilitation 2018;99:411-5

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Physical Therapy

- Strengthening and stretching of **postural** muscles
  → Limit rigidity and flexed posture of PD;
- Practice of large **range of motion** movements
  → Limit reduction in movement amplitude and speed;
- Dynamic **balance** reactive training → Fall prevention;
- **Agility** training in challenging environmental and dual task conditions
  → Limit potential cognitive-motor deficits;
- Assessment and treatment of subtle **gait** deviations.

Occupational Therapy

- Education on signs and symptoms of **orthostatic hypotension** and compensatory strategies and/or adaptive equipment.
- Adaptations and **cognitive rehabilitation** for memory and cognition affections.
- Behavioral **compensatory strategies** related to mild and subtle deficits (e.g. hyposmia, impaired color vision, constipation, etc.)

Tailored Home & Group Exercise

iRBD and Ethical Issues – Take Home Message

The RISK approach

Disclosing information is the **R**ight choice

Identify the «when» and «how» for each patient

Stress a positive approach

Keep an eye on emerging alterations

Telling the truth about the future risk of neurodegenerative disease with RBD while being honest about the uncertainty of the risk promotes patients' autonomy, is beneficent, and engenders their trust in the physician.

Special thanks to:

Prof. Marco Zucconi

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

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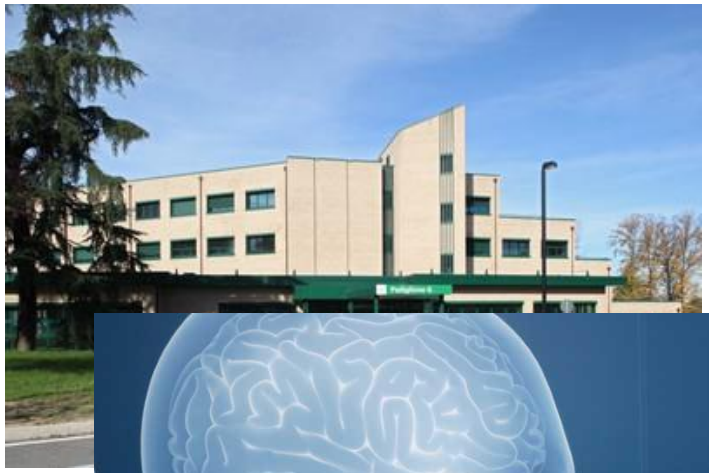

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