Sleep and Parkinson Disease and other synuceinopathies

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มหาวิทยาลัยเชียงใหม่

ประชุมสมาคมประสาทการนอนหลับประจำปี **2562**

Outline (20 mins):

- Case demonstrations
- REM behavioral DO
- Sleep Apnea
- Excessive daytime sleepiness
- Insomnia

Synucleinopathies

- Parkinson disease
- MSA (MSA-P, MSA-C) or

  Shy Dragger Syndrome
- Diffuse Lewy body

Case 1

- A 86 yr old man came to neuro clinic 8 yrs ago.
- Presented with short step gait, postural instability, presyncope symptom, hallucination, constipation and acting out dream.
- PE: Bradykinesia, postural hypotension
  (Sitting BP 76/50 mmHg,
  standing BP 60 mmHg)
  No resting tremor.

Case 1

- Motor symptom-good response to L-Dopa plus COMT-inhibitor and DA.
- Hallucination – good response to Quetiapine.
- Constipation- need bulk forming, laxatives, lactulose.
- Postural hypotension - Florinef

Diagnosis

Case 1

- REM behavioral DO
- Good response to melatonin (and add on small dose of clonazepam during later stage).

ICSD III RBD

1. Repeated episodes of behavior or vocalization that are either documented by PSG to arise from REM or are presumed to arise from REM based on reports of dream enactment .
2. Evidence of REM sleep without atonia (RSWA) on PSG

AASM International Classification of Sleep Disorder 3rd ed, 2014

REM behavioral DO

- Loss of physiologic REM atonia
- Causes of RBD:
  - Idiopathic
  - Parkinson's disease
  - Brainstem stroke
  - Multiple sclerosis plaque
  - Alcohol withdrawal

REM behavioral DO

- Middle aged or elderly men
- Abnormal motor activity during sleep
- Violent dream-enacting behavior during REM sleep (often cause self or bed partner injury)
- Often misdiagnosed as psychiatric or complex partial seizure

Case II

- A 51 yr old man presented with snoring, witnessed apnea and excessive daytime sleepiness.
- PE: BMI = 32.
- Full night polysomnography

  (Split night study).

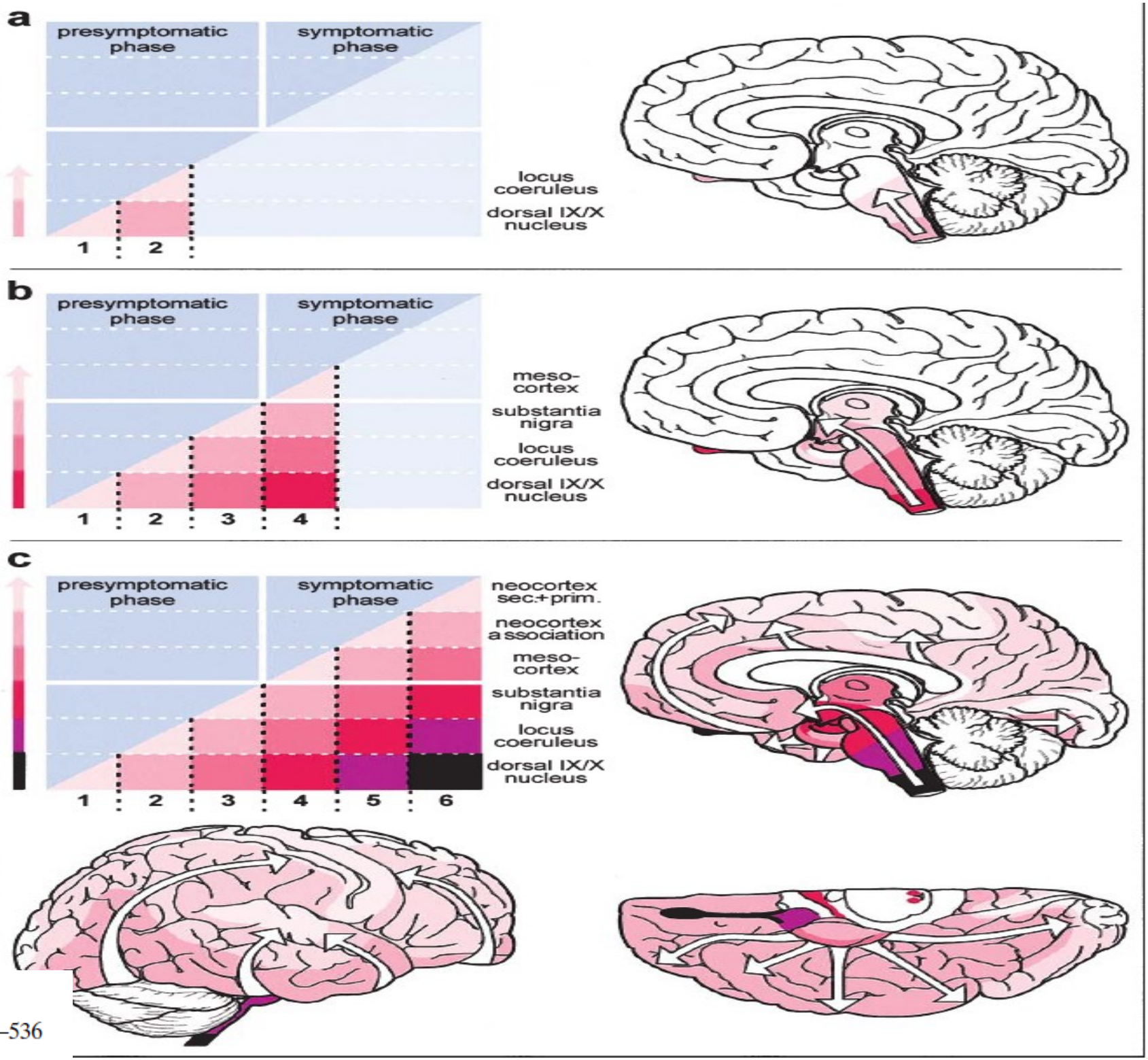
Case II

Diagnosis

Case II

- Severe Sleep Apnea (AHI = 103)
- Idiopathic REM beh DO

Braak's hypothesis



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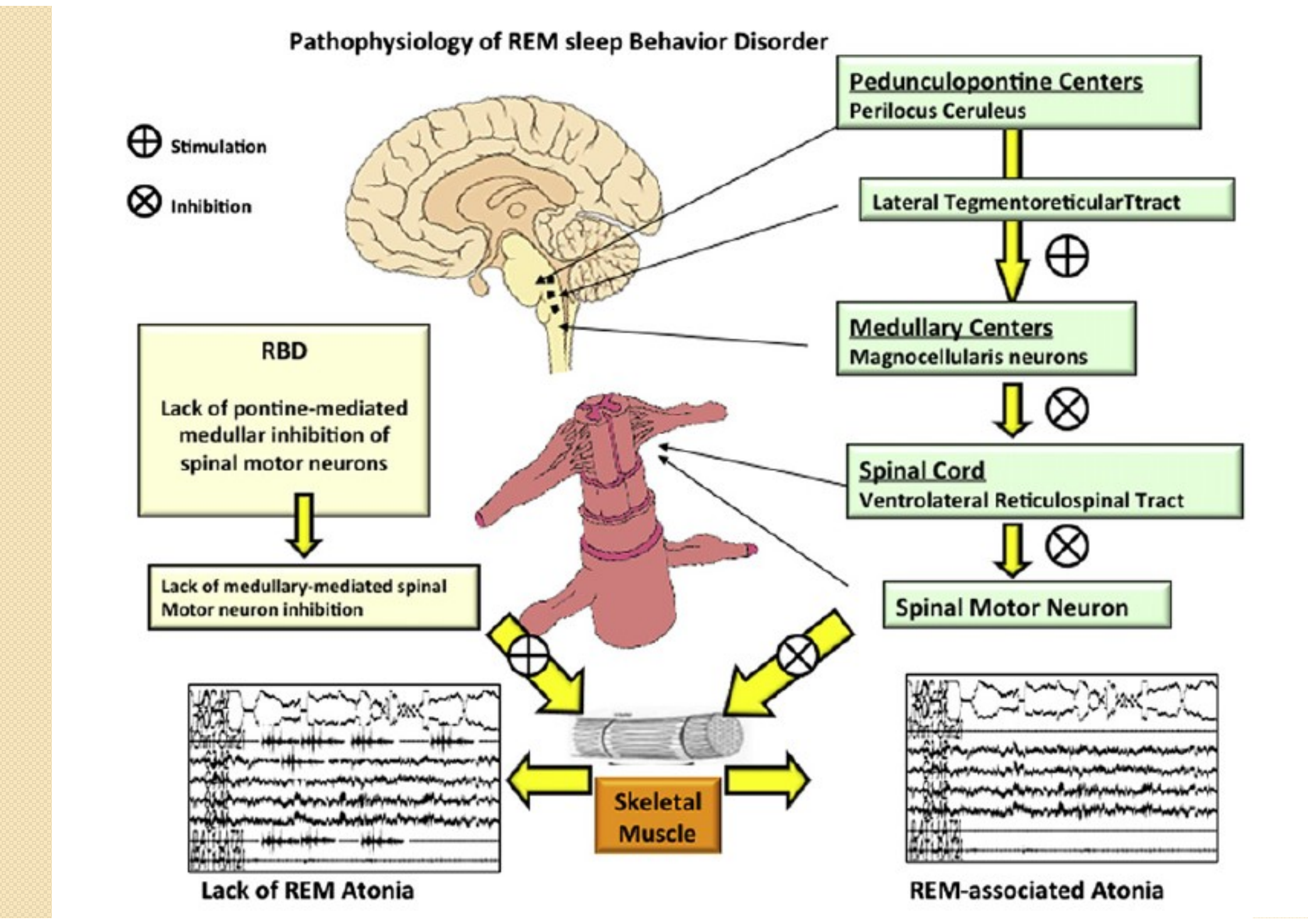
Pathophysiology of REM sleep Behavior Disorder
Stimulation
Inhibition
Pedunculopontine Centers
Perilocus Ceruleus
Lateral TegmentoreticularTtract
Medullary Centers
Magnocellularis neurons
Spinal Cord
Ventrolateral Reticulospinal Tract
Spinal Motor Neuron
RBD
Lack of pontine-mediated medullar inhibition of spinal motor neurons
Lack of medullary-mediated spinal Motor neuron inhibition
Skeletal Muscle
Lack of REM Atonia
REM-associated Atonia

REM behavioral DO

- Can predict PD and other synucleinopathies
- 5-yr cohort of idiopathic REM beh DO → 38% develop PD (Schenck CH, Neurology 1996)
- Equal risk for PD, MSA, DLB

Contents lists available at SciVerse ScienceDirect

Sleep Medicine

2013

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

Original Article

Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series

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Results: 80.8% (21/26) of patients who were initially diagnosed with iRBD eventually developed parkinsonism/dementia (three of the original 29 patients were lost to follow-up). The distribution of diagnoses was as follows: $n = 13$, Parkinson's disease (PD); $n = 3$, dementia with Lewy bodies (DLB); $n = 1$, dementia (unspecified; profound); $n = 2$, multiple system atrophy (MSA); $n = 2$, clinically diagnosed Alzheimer's Disease (AD) with autopsy-confirmed combined AD plus Lewy body disease pathology. Among the 21 iRBD "converters," the mean age (±SD) of iRBD onset was 57.7 ± 7.7 years; mean age (±SD) of parkinsonism/dementia onset was 71.9 ± 6.6 years; and mean interval (±SD) from iRBD onset to parkinsonism/dementia onset was 14.2 ± 6.2 years (range: 5–29 years).

initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series

Carlos H. Schenck [a,*], Bradley F. Boeve [b], Mark W. Mahowald [c]

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Table 1
Eventual parkinsonian disorders/dementia in a series of middle-aged and older males initially diagnosed with idiopathic RBD (iRBD).

N = 13 Parkinson's disease	
N = 3 Dementia with Lewy bodies	
N = 1 Dementia (unspecified; profound)	
N = 2 Multiple system atrophy	
N = 2 Clinically diagnosed Alzheimer's disease with autopsy-confirmed combined Alzheimer's disease plus Lewy body disease pathology	
N = 21 iRBD "converters"	
Mean age (±SD), years, iRBD onset	57.7 ± 7.7
Mean age (±SD), years, parkinsonism/dementia onset	71.9 ± 6.6
Mean interval (±SD), years, iRBD onset to parkinsonism/dementia onset (range: 5–29 years)	14.2 ± 6.2

Sleep Medicine 2013

iRBD

- Iranzo A. PLoS ONE 2014:
- 174 patient with iRBD
- Conversion rate for neurodegen disease
  - 33% in 5 yrs
  - 75% in 10 yrs
  - 91% in 14 yrs

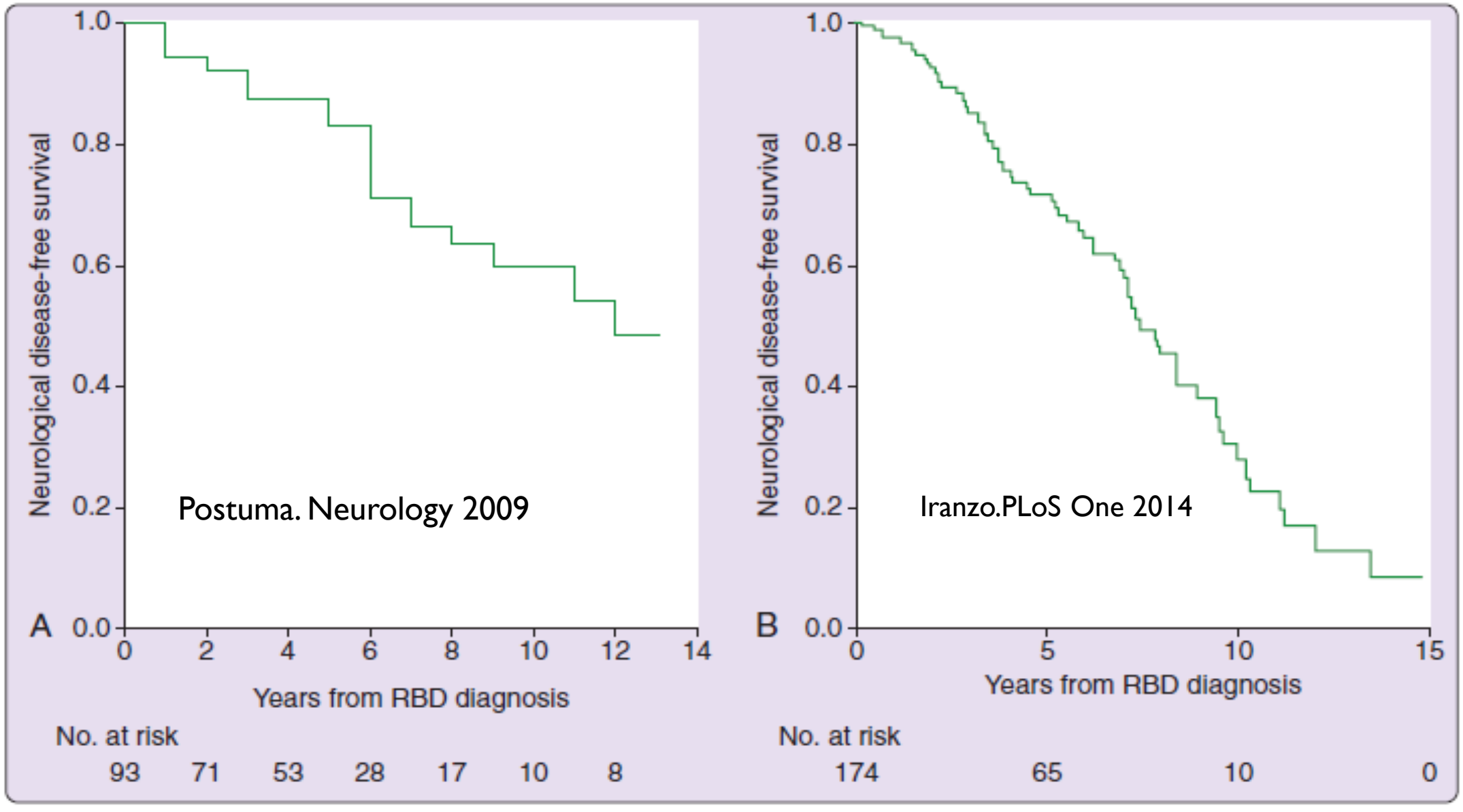

Figure 103-3 Progression from Idiopathic REM Sleep Behavior Disorder (RBD) to Fully Developed Synucleinopathies. Kaplan-Meier curves showing the rate of progression from idiopathic RBD to fully developed synucleinopathies in two studies. (**A,** Modified from Postuma RB, Gagnon JF, Vendette M, et al. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology* 2009;72: 1296–1300, with permission.[72] **B,** Modified from Iranzo A, Fernandez-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One* 2014;9:e89741, with permission.[74])

Table 92-1 Prevalence of REM Sleep Behavior Disorder in Neurodegenerative Diseases

Disease	Prevalence (%)
Synucleinopathies	
Parkinson disease[32,36,132,133]	15–60
Multiple system atrophy[34,134]	88–90
Dementia with Lewy bodies[16,17]	76–86
Tauopathies	
Progressive supranuclear palsy[55,56]	10–11
Alzheimer disease[135]	4.5–7
Corticobasal degeneration[17]	Case reports
Frontotemporal dementia[17]	0
Pallidopontonigral degeneration[136]	0
Guadeloupean parkinsonism[137]	78
Genetic Diseases	
Huntington disease[138]	8
Spinocerebellar ataxia type 3[139]	56
Parkin mutation[140,141]	9–60

Claudia Trenkwalder, Chapter in Kryger text book of sleep medicine 2017

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Sleep Medicine 2013

Editorial

Is rapid eye movement sleep behavior disorder in Parkinson disease a specific disease subtype?

98% autopsy of RBD: patho -> synucleinopathy

RBD – potential early biomarker of synucleinopathy

PD-RBD: Higher incidence of dementia
More severe akinetic
Poorer response to dopa med
Higher Hoehn-Yahr score

Potential target for future neuroprotective Rx

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Original Article

Clinicopathologic correlations in 172 cases of rapid eye movement sleep behavior disorder with or without a coexisting neurologic disorder

B.F. Boeve [a,b,*], M.H. Silber [a,b], T.J. Ferman [g], S.C. Lin [d,g], E.E. Benarroch [a], A.M. Schmeichel [a], J.E. Ahlskog [a], R.J. Caselli [h], S. Jacobson [i], M. Sabbagh [i], C. Adler [h], B. Woodruff [h], T.G. Beach [i], A. Iranzo [l], E. Gelpi [l], J. Santamaria [l], E. Tolosa [l], C. Singer [k], D.C. Mash [k], C. Luca [k], I. Arnulf [m], C. Duyckaerts [m], C.H. Schenck [j], M.W. Mahowald [j], Y. Dauvilliers [n], N.R. Graff-Radford [c], Z.K. Wszolek [c], J.E. Parisi [a,e], B. Dugger [i], M.E. Murray [f], D.W. Dickson [f]

- Multicenter, North America & Europe
- Jan 1990-March 2012
- PSG proven RBD vs probable RBD (by clinical)
- RBD precede cog impairment, parkinsonian symptom, autonomic dysfunction 51% (range 10+/-12 yr)
- Neuro degenerative DO with RBD:
  94% synucleinopathy

Sleep Med 2013

Olfaction and Color Vision Identify Impending Neurodegeneration in Rapid Eye Movement Sleep Behavior Disorder

Ronald B. Postuma, MD, MSc,[1,2] Jean-François Gagnon, PhD,[2,3] Mélanie Vendette, BSc,[2]
Catherine Desjardins, MSc,[2,3] and Jacques Y. Montplaisir, MD, PhD[2,3]

ANN NEUROL 2011;69:811–818

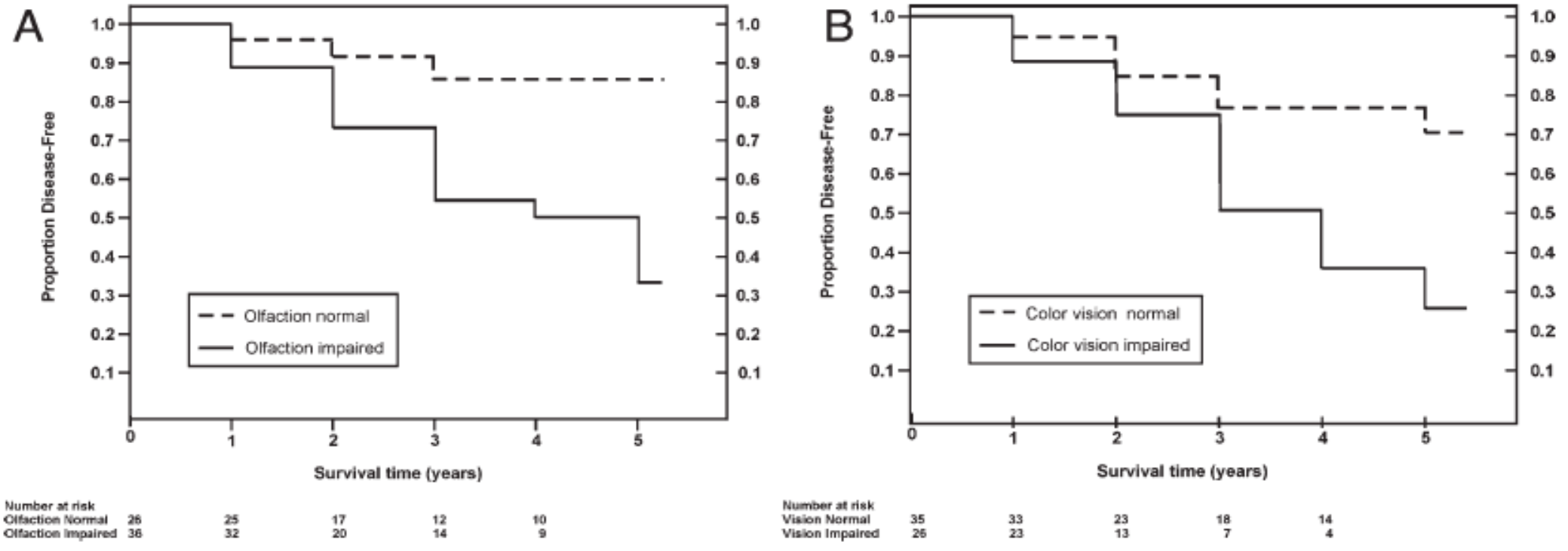

FIGURE 2: Kaplan-Meier plot of disease risk according to (A) baseline olfaction and (B) color vision testing. For illustration, values are dichotomized: olfaction is defined as abnormal if UPSIT scores are <80% expected for age and sex, and color vision is abnormal if total error score is >125% expected. For statistical analysis, baseline olfaction and color vision were tested as linear variables; olfaction and color vision scores were both significantly associated with risk of developing neurodegenerative disease (olfaction: $p = 0.029$; vision: $p = 0.009$; Cox regression).

Impaired color vision

Pathology:

- Degeneration of dopaminergic retinal neuron?
- Abnormal visual association cortex?

Recently observed in LBD

REM behavioral DO

- Secure bed environment
- Discontinue antidepressant
- Melatonin
- Clonazepam (beware of side effects eg. Worsened OSA, reduced cognition, sedation, dizziness, sexual dysfunction).

Sleep attack

- Fall asleep unexpectedly
- Etiology:
  - Dopamine agonist
  - Possible sleep apnea

Movement Disorders
CLINICAL PRACTICE
REVIEW

Sleep Attacks in Patients With Parkinson's Disease on Dopaminergic Medications: A Systematic Review

Eugene Y.H. Yeung, BSc(Pharm), MSc,[1] Andrea E. Cavanna, MD, PhD[1,2,3,4,]*

- Systematic literature review 5 studies
- 10,084 patient
- Occur in13% of PD on dopaminergic medication

Excessive daytime sleepiness

Excessive daytime sleepiness in PD

- Dopamine agonist
- Sleep apnea
- Abnormal circadian rhythm
- Disrupted sleep due to causes as insomnia

OSA: Clinical presentation

- Snoring
- Witnessed apnea
- Excessive daytime sleepiness
- Fatigue, poor memory
- Morning headache
- Cognitive impairment

Parkinson's disease

- Impairment of breathing control
- Obstructive, central, mixed
- Impaired respiratory muscle function
  - Rigidity
  - Faulty autonomic control
  - Fluctuating of muscle functioning
  - Laryngeal spasm during off state
  - Upper airway dysfunction with tremor-like oscillations

OSA Treatment

- Avoid alcohol
- Avoid hypnotics
- Avoid smoking
- Head elevation
- Lateral position
- Relieve nasal congestion
- Weight reduction
- CPAP, BiPAP

Treatment of Central apnea in neurodegenerative disorders

- Should be individualized
- CPAP , BiPAP
- CPAP, Bilevel with back up rate
- CPAP, Bilevel with adaptive pressure support servoventilation (APSSV)
- Tracheostomy with assisted ventilation
- Nocturnal oxygen therapy- some case reports in periodic breathing (especially with heart failure, stroke)

CPAP Precautions

- Increased central apnea
- Increased intra thoracic pressure → reduced cardiac output → hypotension
- May increased $PaCO_2$
- APSSV may be helpful in periodic breathing provide varying amount of ventilatory support (minimal during hyperpnea phase, maximal during apnea phase)

Multisystem Atrophy

Former name “Shy Dragger syndrome”
MSA-P
MSA-C

Nocturnal stridor and MSA

- Strained, high-pitched inspiratory sound
- Should suspect MSA (particular with other neurological sign)
- 13-42% with MSA
- Most frequent during sleep
- Laryngoscope findings: restriction of vocal cords abduction or completely immobility
- Normal awake laryngoscopic findings do not rule out nocturnal stridor
- PSG is important for diagnosis
- Treatment: CPAP, tracheostomy (late stage)

Stridor

- Important sign of MSA
- Pathology- controversial
- Hypothesis:
  - Dystonia hypothesis – hyperactivity of laryngeal adductor muscle
  - Lesion of nucleus ambiguous – hypoactivity of posterior cricoarytenoid muscle

Anatomy of laryngeal muscles

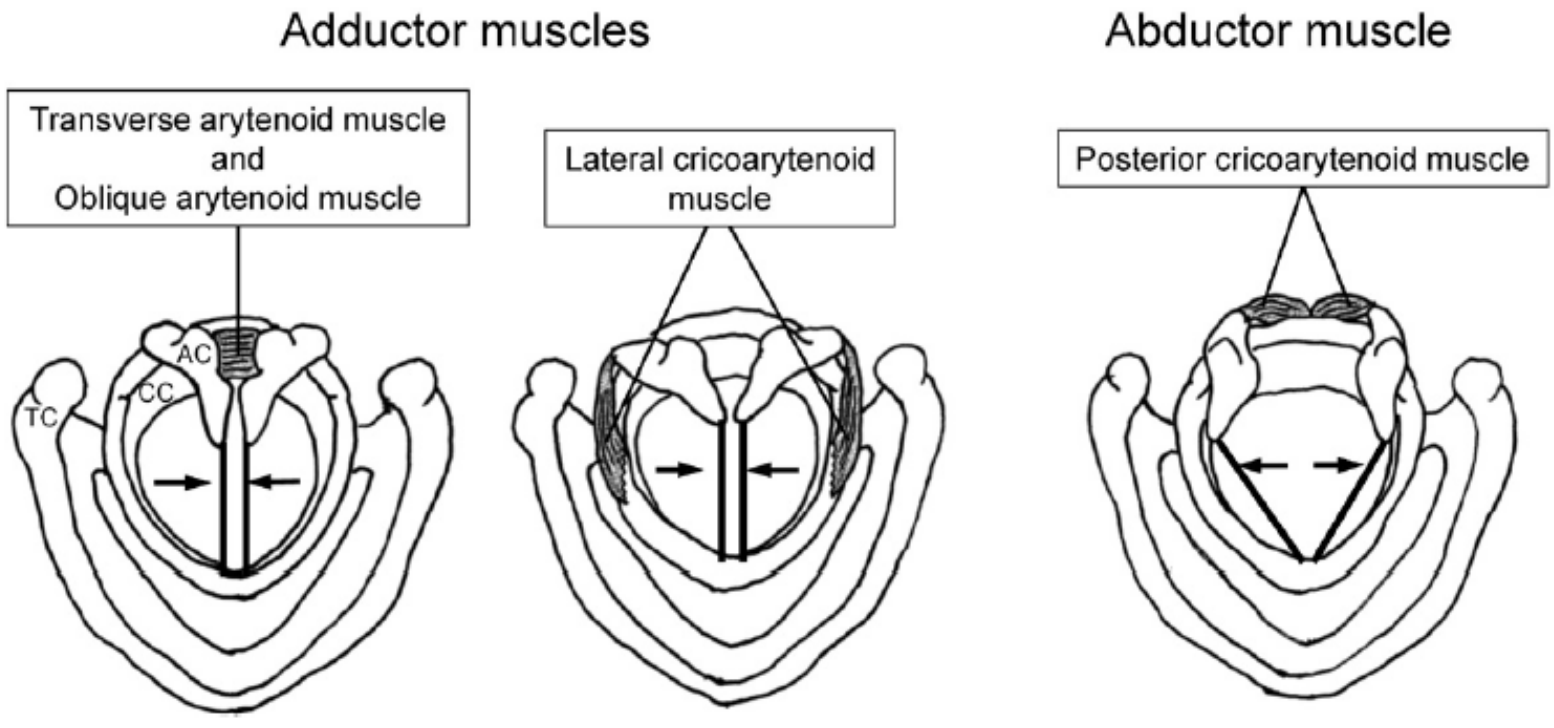

Fig. 1. Fundamental functional anatomy of the intrinsic laryngeal muscles, which may play a role in the mechanisms causing laryngeal stridor. The transverse arytenoid muscle, oblique arytenoid muscle, and lateral cricoarytenoid muscle are responsible for adduction of the vocal cords. The posterior cricoarytenoid muscle is the only intrinsic laryngeal muscle that causes abduction of the vocal cords. Arrows indicate the direction in which the vocal cords move. AC, arytenoid cartilage; CC, cricoid cartilage; TC, thyroid cartilage.

Insomnia in PD

- RLS
- PLMS
- Nocturia
- Cramp
- Painful dystonia
- Tremor
- OSA
- Circadian rhythm sleep DO

Conclusion (RBD)

- RBD observed in 30-60% in PD
- iRBD preceded neuro symptom up to 30 yrs
- RBD potential early biomarker for neurodegenerative disease, especially synucleinopathies
- iRBD potential therapeutic target for preventive Rx
- RBD marks a subtype of PD

Conclusion(SDB)

- Treatment of sleep disordered breathing in neurodegenerative disease must be individualized
- PSG is important for diagnosis and CPAP, BiPAP trial
- May improved cognitive function, mood

Conclusion (SDB)

- Inspiratory stridor:
  - important sign of MSA
  - Progressive, life threatening
  - Treatment with CPAP or tracheostomy in severe case

Conclusion (EDS, Insomnia)

- Excessive day time sleepiness
  - Drug
  - Sleep apnea
  - Fragmented sleep – search for etiologies
- Insomnia
  - Primary Sleep disorder
  - Due to Parkinson disease

Thank you for your attention