How to intercept prodromal Lewy body disorders? The case of REM sleep behavior disorder

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Ten priorities and challenges for Lewy body disease research

- Criteria
- Terminology
- Imaging
- New biomarkers
- Genetics
- Risk factors, earliest signs and prodromal stages
- Multicentre randomized controlled trials of preventive measures
- Pathological staging
- Development of new treatment targets
- Symptomatic treatment

Diagnosis and management of dementia with Lewy bodies
Fourth consensus report of the DLB Consortium

Essential
- Dementia
- Core clinical features
- Fluctuating cognition
- Visual hallucinations
- RBD
- Parkinsonism
- Supportive clinical features
- Sensitivity to antipsychotic; Postural instability; Repeated falls; Severe autonomic dysfunction; Hypersomnia; Hyposmia; Psychiatric symptoms.

Indicative biomarkers
- Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
- Abnormal (low uptake) 123Iodine-MIBG myocardial scintigraphy.
- Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers
- Relative preservation of medial temporal lobe structures on CT/MRI scan.
- Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity + the cingulate island sign on FDG-PET imaging.
- Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

New vision on DLB

Clinical progression

Theoretical evolution of clinical manifestations of Lewy body disease

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**REM Sleep behavior disorder**

- Complex and often violent behaviors occurring during REM sleep.
- Patients 'acting out their dreams' because of the loss of REM atonia.
- 'Idiopathic' = no evident neurological or psychiatric signs

**Typical RBD episode**

- Johann Heinrich Füssli, The nightmare, 1781

**RBD episode**

- Locus coeruleus et sommeil paradoxal.

**RBD - History**

- Typical RBD episode

**Prevalence of ‘idiopathic’ RBD**

- Clinical interview in subjects >70 yo, followed by PSG.
  - Hong Kong (Chiu et al 2000) 0.3%
  - vPSG in 348 subjects > 60 yo, followed by questionnaire.
  - Korea (Kang et al 2013) 1.15%
  - Interview in 539 subjects > 60 yo, followed by PSG.
  - Spain (Pujol et al 2017) 0.74%
  - Questionnaire and home-PSG in 1997 subjects 35-75 yo.
  - Switzerland (Haba-Rubio et al 2018) 1.06%
Neurodegeneration risk

Risk Factors for Neurodegeneration in Idiopathic Rapid Eye Movement Sleep Behavior Disorder: A Multicenter Study

The final diagnosis was
- PD 41.9%
- DLB 50.5%
- MSA 7.5%

Keywords:

Accepted 3 September 2008

The basal ganglia as a whole are broadly responsible for sensorimotor coordination, including response to extrinsic stimuli and the modulation of motor function. The nigrostriatal system, in particular, plays a pivotal role in motor control and is implicated in various neurodegenerative diseases such as Parkinson’s disease (PD). This review aims to summarize the available evidence on nigrostriatal and cognitive functions, focusing on the role of the basal ganglia in PD and other related disorders. The nigrostriatal system comprises dopaminergic neurons in the substantia nigra (SN) that project to the striatum, particularly the caudate nucleus and putamen. The functional connectivity and metabolic changes in these brain regions are critical for understanding the disease progression and treatment outcomes. As such, imaging studies using techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have been extensively utilized to assess the nigrostriatal dopaminergic function in PD and other neurodegenerative disorders. This review will explore the relationship between nigrostriatal and cognitive functions, highlighting the importance of this system in the clinical management of PD.

The relationship between nigrostriatal and cognitive functions is an area of active research. In PD, cognitive impairment often precedes motor symptoms and affects multiple domains such as executive function, memory, and attention. Imaging studies have shown that nigrostriatal dopaminergic degeneration is correlated with cognitive decline, which is consistent with the involvement of dopamine in cognitive processes such as attention, learning, and emotional regulation. Additionally, the relationship between nigrostriatal function and attention-demanding tasks has been studied using SPECT imaging, where decreased uptake in the caudate and putamen (with sparing of the ventrolateral nucleus of the caudate) has been observed in PD patients compared to controls. The correlation between nigrostriatal dopaminergic function and cognitive performance in PD has been further explored using the Stroop color-word test, a task that requires sustained attention and executive function. The Stroop interference score, which reflects the difference between interference and congruency conditions, has been shown to be correlated with nigrostriatal dopaminergic function in PD patients, with decreased uptake indicating increased cognitive demands.

In conclusion, the nigrostriatal dopaminergic system plays a significant role in both motor and cognitive functions, and its assessment through imaging techniques is crucial for understanding the disease progression and developing effective therapeutic strategies. Further research is needed to elucidate the mechanisms underlying the relationship between nigrostriatal dopaminergic function and cognitive impairment in PD, which could ultimately lead to improved clinical care and management strategies.
What predicts cognitive decline in de novo Parkinson’s disease?

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Transmission of β-amyloid in clinical and subclinical rapid-eye-movement sleep behaviour disorder (RBD) with Parkinson’s disease

Respiratorias, Bunyola, Spain

Centro de Investigacion y Desarrollo en Neurodegenerativas (CIBERNED), Barcelona, Spain

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Table 4: Diagnostic accuracy of clinical factors combination

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<tr>
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<th>Beta co-efficient</th>
<th>95% CI</th>
<th>p-value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.8</td>
<td>0.2</td>
<td>0.02</td>
<td>80%</td>
<td>67%</td>
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<tr>
<td>2.</td>
<td>0.3</td>
<td>0.1</td>
<td>0.03</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>3.</td>
<td>0.2</td>
<td>0.1</td>
<td>0.05</td>
<td>40%</td>
<td>95%</td>
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Abbreviations: CI = confidence interval; ODL = dementia with Lewy bodies; NPV = negative predictive value; PPV = positive predictive value; RBD = rapid-eye-movement sleep behaviour disorder.

Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

Neurology 2011;77:875-882

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Assessment of α-synuclein in submandibular glands of patients with idiopathic rapid-eye-movement sleep behaviour disorder: a case-control study

J Neurol Neurosurg Psychiatry 2013;93:136–140

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Alpha-synuclein

Entire nervous system α-synuclein immunoreactivity in idiopathic REM sleep behavior disorder

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Introduction

Magnetic resonance imaging (MRI) and single photon emission tomography (SPECT) have been established as reliable tools to support the diagnosis of idiopathic rapid eye movement (REM) behavior disorder (RBD) in clinical practice.

Susceptibility-weighted imaging of the substantia nigra (SN) both at 7 and 3 Tesla (T) has been described in the SN in susceptibility-weighted imaging has been described in the SN in MRI and SPECT images of patients with RBD with either normal (A) or abnormal (B) MRI and SPECT images.

Conclusion:

7T-MRI and SPECT images of patients with RBD with either normal (A) or abnormal (B) MRI and SPECT images show that 7T-MRI can differentiate patients with PD from healthy subjects with high accuracy in both 7T and 3T MRI. The abnormal aspect of the SN in susceptibility-weighted imaging has been described in patients with PD and is reportedly able to differentiate patients with Parkinson's disease (PD) from healthy subjects (HS) with high accuracy in both 7T and 3T MRI. Furthermore, patients with Multiple System Atrophy (MSA), those with idiopathic RBD, however longitudinal study is warranted.

<table>
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<tr>
<th>MRI Diagnosis</th>
<th>SPECT Diagnosis</th>
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<tr>
<td>Normal</td>
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<tr>
<td>Abnormal</td>
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60% of patients with RBD have evidence of nigro-striatal dysfunction. We aimed at evaluating SN 7T-MRI in patients with RBD and blindly evaluated by an expert neuroradiologist, according to recently published criteria.

Individual clinical, demographic, MRI and SPECT data of RBD patients.

The metabolite pattern of idiopathic REM sleep behavior disorder reflects early-stage Parkinson's disease.

The metabolic pattern of idiopathic REM sleep behavior disorder reflects early-stage Parkinson's disease.

On the other hand it is possible that RBD with abnormal SN are responsive to therapies and useful in the differential diagnosis of PD. It is reasonable to speculate that the abnormal aspect of the SN reflects the nigro-striatal dysfunction and it is useful in the differential diagnosis of PD.

Cortical functioning: PDRP

The metabolic pattern of idiopathic REM sleep behavior disorder reflects early-stage Parkinson's disease.

Detecting the Cognitive Prognostic of Dementia with Lewy Bodies: A Prospective Study of REM Sleep Behavior Disorder

Structural MRI and DAT SPECT

Seven Tesla MRI of the substantia nigra in patients with rapid eye movement sleep behavior disorder.

- 60% of RBD patients
- 89% of RBD patients with abnormal DAT SPECT
Is it possible to reduce the risk?

Arnaldi et al. / Sleep Med Rev. 2016

When iRBD will convert?

Arnaldi et al. / Sleep Medicine Reviews 36 (2017) 62–85

RBD as prodromal Lewy Body Disorder?

Predictive markers for early conversion of RBD to neurodegenerative synucleinopathy diseases

Grazielli!!!