“Why use a RBD cohort in clinical trials for PD”

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REM behaviour disorder

• Occurs in manifest PD (50%) and in premotor PD (about 15% of cases).

• Idiopathic RBD is associated with subclinical features of manifest PD:
  - abnormal DAT SPECT,
  - hiperechogenicity of substantia nigra
  - abnormal MIBG uptake
  - depression, constipation

• In longitudinal studies IRBD patients frequently develop a synucleinopathy (e.g. PD, DLB, MSA)
Rapid eye movement sleep behaviour disorder

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

44 patients with IRBD

After a mean follow up of 10 years, 82% were diagnosed with either PD or DLB or MSA
Estimated rates of conversion from the diagnosis of IRBD (n=174)

- 33% at 5 years
- 76% at 10 years
- 91% at 14 years

Iranzo et al. PLOS One 2014
69-year-old man was diagnosed as having RBD at age 58 years

During a ten year follow-up period, development of hyposmia, constipation, depression and mild cognitive changes.

Parkinsonism was never detected

Serial DAT SPECT imaging showed progressive subclinical substantia nigra damage.

Diagnosis: Premotor PD

Died at age 77 of lung cancer.
**Neuronal loss**

**Lewy bodies**

**CNS**
- Olfactory bulb
- Dorsal motor vagal
- Subcoeruleus
- Substantia nigra
- Amygdala
- N. basalis of Meynert

**PNS**
- Stellate ganglia
- Paravertebral chain
- Cardiac plexus
- **Myenteric plexus**
Estimated rates of conversion from the diagnosis of IRBD (n=174)

33% at 5 years
76% at 10 years
91% at 14 years

Iranko et al. PLOS One 2014
• 62 patients with iRBD
• 21 converted at follow up
• Compared to those remaining disease free, patients destined to develop disease had worse baseline olfaction and vision test

Olfaction and color vision identify early-stage synuclein-mediated neurodegenerative diseases

Postuma 2011
Olfactory dysfunction predicts early transition to a Lewy body disorder in idiopathic RBD

- 34 PSG confirmed RBD cases studied
- Olfactory testing with Sniffing Stick test
- Prospectively followed for 4.9 years: 9 (26%) developed a Lewy body disorder
- Compared to patients who remained disease free, patients who went on to develop disease had lower olfactory scores at baseline

Mahlknecht et al. Neurology 2015
Decreased DAT SPECT and TCS as risk markers for PD: a prospective study

43 Idiopathic REMs BD

DAT-SPECT + SN Sonography

27 Individuals with DAT-SPECT and/or Hyperechogenicity

15 Individuals with normal examens

After 2.5 years Follow-up

8 Individuals affected by Parkinsonism

NONE affected by Parkinsonism

Iranzo et al. Lancet Neurol 2010
Parkinson risk in idiopathic RBD

• Test the ability of prodromal markers to identify patients at higher risk

• 30% developed disease at 3 years; 66% at 7.5 years

• Advanced age, olfactory loss, abnormal color vision, subtle motor dysfunction and no use of antidepressants identified higher risk of disease conversion

Postuma 2015
Markers of disease progression in IRBD

• **No change with time**
  - Olfactory tests
  - Color vision tests
  - Hyperechogenicity of the nigra

• **Worsens with time**
  - DAT scanning
Longitudinal assessment of olfactory function in idiopathic REM sleep behavior disorder

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**UPSIT score does not change over a 4 years follow-up**
Serial dopamine transporter imaging of nigrostriatal function in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study

Alex Iranzo, Francesc Valdeoriola, Francisco Lomeña, José Luis Molinuevo, Mónica Serradell, Manel Salamero, Albert Cot, Domèneq Ros, Javier Pavía, Joan Santamaria, Eduardo Tolosa

*Figure 2:* \(^{123}\text{I}-\text{FP-CIT}\) uptake ratios in the left putamen (A), right putamen (B), left caudate nucleus (C), and right caudate nucleus (D) at baseline and at follow-ups

20 iRBD, 20 HC, 3 year follow-up

Iranzo et al. Lancet Neurol 2011
Why use a RBD cohort in clinical trials for PD?

- IRBD is a specific prodromal PD marker
- IRBD is an indicator of an evolving synucleinopathy.
- In iRBD, olfactory and color vision tests, DAT-SPECT and TCS: **markers of short term phenoconversion**.
- Serial DAT-SPECT (but not serial olfactory and color vision tests): **marker of disease progression**.
• Thank you very much for your attention!!