Sleep in other Movement Disorders

Carles Gaig

Multidisciplinary Sleep Disorders Unit
Neurology Department
Hospital Clínic Barcelona

Outline

• Dementia with Lewy Bodies
• Progressive Supranuclear Palsy
• Huntington Disease
• Iglon5 Parasomnia

DEMENTIA WITH LEWY BODIES
Sleep disturbances in dementia with Lewy bodies (DLB): REM Sleep behavior disorder (RBD)

Table 1 Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)

1. Central feature (essential for a diagnosis of possible or probable DLB)
   - Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
   - 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 visuospatial ability may be especially prominent.

2. Core features (two core features are sufficient for a diagnosis of probable DLB; one for possible DLB)
   - Fluctuating cognition with pronounced variations in attention and alertness
   - Recurrent visual hallucinations that are typically well formed and detailed
   - Spontaneous features of parkinsonism

3. Suggestive features (if one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)
   - REM sleep behavior disorder
   - Severe neuropsychiatric sensitivity
   - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

RBD in DLB

- RBD in patients with DLB: 50-85%.
- RBD is present in only 2-4% of patients with non-DLB dementia (e.g. Alzheimer disease).
- Neuropathological substrate in RBD: 94-98% synucleinopathy.
- RBD improves diagnostic accuracy:
  - Sensitivity up to 88-90%.
  - Specificity 73%.

Table 2

<table>
<thead>
<tr>
<th>Disorder</th>
<th>N</th>
<th>History of RBD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>166</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>DLB</td>
<td>40</td>
<td>52</td>
<td>80</td>
</tr>
<tr>
<td>Subtotal</td>
<td>206</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>133</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>MCI</td>
<td>86</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Subtotal</td>
<td>154</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

Has RBD in DLB different clinical and polysomnographic features than RBD in Parkinson’s disease or idiopathic RBD?
**RBD in DLB**

- RBD often precedes the onset of dementia / parkinsonism in DLB. (average: by 6 years).
  [Ferman, Neurology 2009]
- Patients with MCI and RBD: usually develop DLB.
  [Molano, Brain 2010; Iranzo, Lancet Neurol 2013]
- 39% of patients with idiopathic RBD develop a DLB.
  [Iranzo, Lancet Neurol 2013]

**Other causes of sleep related abnormal behaviors in DLB**

**Arousal-related events:**

- **Short-lasting episodes** (arousals from NREM and REM sleep):
  - Often apnea-related arousals.
  - Complex, semi-purposeful movements (similar to those of RBD)
- **Long-lasting episodes** (confusional arousals):
  - Lasting several minutes.
  - Often sitting up or getting out of the bed.
  - With confabulation, hallucinations?

**Status dissociatus:**

Extreme form of state dissociation without identifiable sleep stages.
- Patients appear to be either awake or asleep with motor hyperactivity and vocalizations.
- PSG shows no conventional wakefulness, NREM sleep and REM sleep.

[Ratti, Sleep Med 2012; Terzaghi, Mov Disord 2013]

**Other causes of sleep related abnormal behaviors in DLB**

Video
Other causes of sleep related abnormal behaviors in DLB

Other sleep disturbances in DLB

TABLE 1. Previous sleep complaints

<table>
<thead>
<tr>
<th></th>
<th>PD n (%)</th>
<th>DLB n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>15 (51.7)</td>
<td>11 (37.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>6 (20.7)</td>
<td>17 (58.6)</td>
<td>.006</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>1 (3.4)</td>
<td>1 (3.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinical suspicion of sleep-disordered breathing</td>
<td>5 (17.2)</td>
<td>2 (6.9)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n=29 DLB patients

Obstructive sleep apnea (AHI > 15): 26%

PLM index > 15: 61%

[Terzaghi, Mov Disord 2013]
Sleep disturbances in DLB: Summary

- RBD is very frequent in DLB.
- In a patient with dementia, RBD supports the diagnosis of DLB.
- RBD often antedates the onset of cognitive symptoms in DLB.
- Abnormal behaviors during sleep in DLB can be related to other cause (e.g., confusional awakenings).
- Large studies assessing RBD features and other sleep disturbances (using video-PSG) in consecutive patients with DLB are needed.

PROGRESSIVE SUPRANUCLEAR PALSY

Most frequent sleep complaint: Insomnia - fragmented sleep (40%).

- Shorter total sleep time.
- Reduced sleep efficiency.
- Frequent arousals and awakenings.
- Reduced amount of sleep spindles.
- Reduced REM stage.

Sleep disturbances in Progressive Supranuclear Palsy (PSP)

- Most frequent sleep complaint: Insomnia - fragmented sleep (40%).

- Polysomnographic Abnormalities:
  - Shorter total sleep time.
  - Reduced sleep efficiency.
  - Frequent arousals and awakenings.
  - Reduced amount of sleep spindles.
  - Reduced REM stage.

[Montplaisir, Neurology 1997; Arnulf, Sleep 2005; Nomura, Parkinsonism Relat Disord 2012]
**Studies with PSG assessing RBD in PSP**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Number of patients</th>
<th>REM sleep without atonia (RWA)</th>
<th>RBD (RWA + dream enacting behaviors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montplaisir, Neurology 1997</td>
<td>6</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Arnulf, Sleep 2005</td>
<td>15</td>
<td>4 (27%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Sixel-Doring, Sleep Med 2008</td>
<td>20</td>
<td>17 (85%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Nomura, Park. Relat Disord 2012</td>
<td>20</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>61</strong></td>
<td><strong>26 (42.6%)</strong></td>
<td><strong>9 (14.8%)</strong></td>
</tr>
</tbody>
</table>

RBD did not antedate the symptoms of PSP

**REM sleep in PSP**

Impairment of ocular motility can reduce rapid eye movement in REM Sleep.

**Sleep disturbances in PSP: Summary**

- Most frequent sleep problem: insomnia.
- RWA and RBD can occur but less frequently than in synucleinopathies.
- RBD do not antedate PSP
- Additional studies are necessary (and assessing other sleep disturbances, e.g: daytime somnolence).
Sleep in other tauopathies

Guadeloupean Parkinsonism:
- RBD (V-PSG confirmed): 78% patients.
- RBD symptoms antedating parkinsonism: 44% patients.
  [Cochen de Cock, Sleep 2007]

Corticobassal degeneration
- Several case reports of patients with corticobassal syndrome with RWA or RBD.
- None with pathologically proven corticobassal degeneration.
  [Kimura, Sleep 1997; Wetter, Sleep Med 2002; Gatto, Parkinsonism Relat Disord 2007]

HUNTINGTON DISEASE

Sleep disturbances in Huntington Disease

Frequent:
- Present: 90%.
- Significant problem: 60%.

Underreported:
- Overwhelmed by motor and neuropsychiatric symptoms.
- Lack of insight.
  [Taylor, Br J Psychiatry 1997; Goodman, PLOS Curr 2010]

May be relevant:
- May worsen cognitive and psychiatric symptoms.

Poorly studied:
- Few studies available.
  [Goodman, J Neurol 2010; Morton, Exp Neurol 2013]
Insomnia in Huntington Disease

Most frequent sleep problem (66%):
- Sleep onset insomnia.
- Sleep fragmentation - early awakening.

Present early, increases with disease progression
Severity independent of CAG repeat length.

Polysomnographic studies:
- Increased sleep latency.
- Increased wakefulness after sleep onset (WASO).
- Reduced sleep efficiency.
- Reduced N3 and REM sleep
- Increased REM sleep latency

[Arnulf, Arch Neurol 2008; Morton, Exp Neurol 2013]

Insomnia in Huntington Disease

Causes
- Depression and anxiety.
- Motor symptoms: chorea, parkinsonism, dystonia.
- Medications: antidepressants, neuroleptics, tetrabenazine…
- Circadian rhythm disorder
  - Delayed / irregular phase syndrome
  - Actigraphic studies
  - Animals models (R6/2 transgenic mice)
  - Degeneration of the circadian pacemaker
    (The suprachiasmatic nuclei).

[Morton, J Neurosci 2005]

Other sleep problems in Huntington Disease

Excessive daytime sleepiness:
- 16-32%
- No SOREMPs in the MSLT.
- Normal Hypocretin-1 levels in CSF.
- Cause:
  - Disturbed nocturnal sleep.
  - Medications (neuroleptics, antidepressants).
  - Not increased frequency of obstructive sleep apnea syndrome.

Abnormal movements and behaviors during sleep
- REM sleep behavior disorder (12%; Absent in asymptomatic carriers).
- Increased PLMS (24%; RLS not increased).

[Arnulf, Arch Neurol 2008; Gaus, Sleep 2008; Morton, Exp Neurol 2013; Van Wamelen, Sleep 2013]
Sleep disturbances in Huntington Disease: Summary

- Frequent (insomnia).
- Overlooked.
- Multifactorial origin:
  - Secondary to psychiatric disturbances.
  - Related to motor symptoms.
  - Adverse effect of medications.
  - Degeneration of neural systems regulating the wake-sleep.
- Present early (in premanifest carriers?), increases with disease progression.

Sleep disturbances in other polyglutamine diseases - Spinocerebellar ataxias

- Restless legs syndrome: SCA 3; less frequently in SCA 1, 2 and 6.
- Periodic leg movements in sleep: SCA 1, 2, 3 and 6.
- Subclinical REM sleep without atonia: SCA 2.
- REM sleep behavior disorder: SCA 3.
- Stridor (due to vocal cord palsy): SCA 3.

[Schöls, Neurology 1998; Iranzo, Mov Disord 2003; Boesch, Mov Disord 2006; Boesch, Sleep Med 2006; Rodriguez-Labrada, Mov Disord 2011]

IGLON5 parasomnia
Patients identification

Clinical Features (n = 8 patients)

Five women.
Median age at disease onset: 59 yrs [range 52–76].
All 8 had abnormal sleep movements and behaviors with obstructive sleep apnea.

Clinical course

<table>
<thead>
<tr>
<th>Chronic: n = 6</th>
<th>Subacute: n = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration: Median 5 yrs</td>
<td>Disease duration: 2 and 6 months</td>
</tr>
<tr>
<td>Presenting and major symptom:</td>
<td>Presenting and major symptom:</td>
</tr>
<tr>
<td>• Sleep disorder: 4</td>
<td>• Gait instability / falls: 2</td>
</tr>
<tr>
<td>• Gait instability / falls: 2</td>
<td></td>
</tr>
<tr>
<td>Associated symptoms:</td>
<td>Associated symptoms:</td>
</tr>
<tr>
<td>• Bulbar symptoms: 6</td>
<td>• Sleep disorder: 2</td>
</tr>
<tr>
<td>• Dysautonomia: 6</td>
<td>• Bulbar symptoms: 2</td>
</tr>
<tr>
<td>• Chorea: 4</td>
<td>• Central hypoventilation: 2</td>
</tr>
<tr>
<td>• Central hypoventilation: 2</td>
<td>• Dementia: 1</td>
</tr>
<tr>
<td>• Dementia: 1</td>
<td></td>
</tr>
</tbody>
</table>

Neuroimaging and laboratory tests: Normal or negative.

HLA typing (in 4 patients): DQB1*0501 and DRB1*1001 alleles.

Treatment:
All patients had immunotherapy (e.g: IV steroids, cyclophosphamide, IVIg, rituximab).
1 patient responded with gait improvement but died suddenly several days after.

Outcome:
Death: 6 patients
5 at home suddenly 2 during wakefulness
1 in the ICU 2 during sleep
1 Unknown
Features of the Sleep Disorder

1) Total sleep time and sleep efficiency were mildly-moderately reduced.

2) Onset and re-entering sleep as an undifferentiated NREM or poorly structured N2 sleep with abnormal movements and behaviors.

3) REM sleep behavior disorder.

4) Normal N3 stage present.

5) Stridor with obstructive sleep apnea.

Vocalizations and simple and finalistic movements during NREM sleep

video

Vocalizations and simple and finalistic movements during NREM sleep

video
**Undifferentiated NREM sleep (UN-NREM)**

- Prolonged periods of irregular theta EEG activity.
- Without vertex waves, K complexes, sleep spindles, delta slowing and rapid eye movements.
- Associated with EMG activity with vocalizations and movements.

**Poorly structured N2 sleep (P-S N2)**

- Sparse but well defined K complexes or spindles at 12–14 Hz.
- Associated with EMG activity with vocalizations and movements.

**Poorly structured N2 sleep (P-S N2)**

- Sparse but well defined K complexes or spindles at 12–14 Hz.
- Associated with EMG activity with vocalizations and movements.
REM Sleep Behavior Disorder

Normal N3 Sleep (usually at the end of the night)
Agrypnia excitata

- Inability to sleep associated with a generalized motor and autonomic hyperactivation.
- Is a syndrome occurring in three different conditions:
  - Fatal Familial Insomnia.
  - Delirium Tremens.
  - Morvan Syndrome.

Prominent sleep disorder:
- Insomnia - Reduced sleep efficiency.
- No K complexes or spindles.
- No delta waves (stage N3 absent).
- Stages N1 and REM present with abnormal vocalizations and movements.
- Sleep-wake cycle disrupted: diurnal sub-wakefulness or stupor.

[Lucaresi, Sleep Med Rev 2001; Provini, Sleep Med 2011; Guaraldi, Sleep Med 2011]

Sleep breathing disorder

- Stridor:
  - Present in 6 patients.
  - During sleep, particularly in stage N3.
  - Absent during wakefulness.

- Vocal cord palsy demonstrated by laryngoscopy.

- Associated with Obstructive Sleep Apnea:
  - AHI: 20 to 97.
  - CPAP or tracheostomy eliminated stridor and obstructive sleep apnea.

Antigen Identification

Rat brain immunolabelled with patients' CSF

Immunohistochemistry on rat neurons

Immunoprecipitation and Mass Spectrometry = IgLON5

Testing of IgLON5 antibodies in serum or CSF of 298 controls
Positive in serum but not CSF in only one patient with Progressive Supranuclear Palsy
Neuropathological Features

In 2 patients:
- Slow progression (59 yrs male, duration 6 yrs)
- Subacute progression (76 yrs female, duration 6 months)

Neuronal loss and tau deposits seen only in neurons

- Hypothalamus
- Tegmentum of the brainstem
  - Laterodorsal tegmental area
  - Periaqueductal grey matter
  - Pedunculopontine nucleus
  - Magnocellular nuclei
  - Nucleus ambiguus

No other abnormal protein deposits (e.g. beta-amyloid or alpha-synuclein)
No inflammatory infiltrates

IgLON5 parasomia: conclusions

1. IgLON5 antibodies identify a novel neurological syndrome associated with prominent sleep dysfunction.

2. The sleep disorder is characterized by a distinctive non-REM sleep dysfunction with simple and finalistic behaviors, REM sleep behavior disorder, and stridor with obstructive sleep apnea.

3. Associated symptoms include gait dysequilibrium, chorea, and brainstem dysfunction.

4. Pathological examinations suggest a novel neuronal tauopathy with predominant brainstem and hypothalamic involvement.

5. The full clinical range of this syndrome, the definite neuropathological substrate, and whether the underlying pathophysiology is degenerative or autoimmune remains to be clarified.