Sleep and Neurodegenerative Disorders

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Disclosures

• None
Outline

- Sleep in normal aging
- Sleep in Alzheimer’s disease
- Sleep problems in PD and related disorders
- REM sleep behavior disorder
Dementia is a growing problem

- More than 25 million people worldwide with Dementia
- Increasing incidence of AD and other Neurodegenerative diseases

Neurodegenerative disorders

- **Disease**                                     **Lesion component**
  - Alzheimer’s disease                           \(\alpha\)-synuclein
  - Fronto-temporal dementia                      tau and TDP-43
  - Vascular dementia                             microangiopathy
  - Parkinson's disease                           \(\alpha\)-synuclein
  - Dementia of Lewy body type                    \(\alpha\)-synuclein
  - CBD                                           \(\alpha\)-synuclein
  - Multiple system atrophy                       \(\alpha\)-synuclein
  - Huntington’s disease                          CTG repeats
Sleep disturbances in Neurodegenerative disease

- Neurodegenerative diseases are characterized by disruption in both circadian rhythm and sleep architecture
- Other sleep disorders:
  - OSA
  - RLS/PLMS
  - REM sleep behavior disorder
  - Hypersomnias

The Anatomical Hallmark of Alzheimer’s Pathology: Amyloid Plaques and Neurofibrillary Tangles in Brain

Amyloid Plaques:
contain large amounts of a 42 amino acid peptide termed "β-amyloid", or Aβ42

Neurofibrillary tangles:
rich in cytoskeletal proteins, especially the microtubule-associated protein, "tau".
In the tangles: heavily phosphorylated proteins, which may cause aggregation and precipitation of the cytoskeleton.
Sleep disturbances are a common feature of AD

Polysomnogram in AD patients:
- Reduced sleep efficiency
- Increased Wake time after sleep onset
- Reduced time spent in N2; N3 and REM sleep
- Increased stage 1
- Increased latency to sleep and REM

Sleep disturbances in Mouse models:
Increased time awake and aberrant circadian rhythms

Kunerman et al, 2011

Aberrant rhythms seen in both humans and animal models

Wisor et al, 2005
A vicious cycle

Sleep improves clearance of metabolites and Aβ

Sleep clears CSF metabolites and reduced clearance seen when animals are forced to stay awake

Reduced Amyloid beta clearance with awake

Xie et al Science, 2013
Sleep disturbances may predict dementia and Aβ pathology

- In community dwelling older adults, shorter sleep was associated with greater beta amyloid burden
- Findings suggest poor sleep may accelerate AD

Spria et al, JAMA, 2013

Aβ levels controlled by sleep wake cycle

Amyloid beta has a normal circadian rhythm, increases with awake and reduced with sleep. SD worsens Abeta levels

Kang et al, Science, 2009
OSA exacerbates Aβ pathology

OSA patients have more amyloid beta and tau burden  Bu et al, Sci Rep, 2015

CPAP improves cognitive function and sleep quality among patients with AD

Sleep in Huntington’s disease

Sleep problems pre-date Huntington’s disease. Increased arousals, increased WASO and shifts between different stages

Lazar et al, Ann of Neurology, 2015
Sleep problems in PD and related disorders

- Daytime Hypersomnina
- Circadian rhythm dysfunction, especially phase advancement
- Sleep fragmentation
- RLS and PLMS
- REM sleep behavior disorder
- Nocturnal Hallucinations
- Obstructive sleep apnea

Levodopa improves sleep only marginally

<table>
<thead>
<tr>
<th>Polysomnogram parameter</th>
<th>Pre*, N = 12</th>
<th>Post**, N = 12</th>
<th>Significance</th>
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<tbody>
<tr>
<td></td>
<td>Mean (%)</td>
<td>SD (%)</td>
<td>Mean (%)</td>
</tr>
<tr>
<td>SE*</td>
<td>75.4</td>
<td>15.3</td>
<td>86.4</td>
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<tr>
<td>WASO†</td>
<td>16.9</td>
<td>14.2</td>
<td>7.9</td>
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<tr>
<td>Stage I</td>
<td>25.7</td>
<td>12.5</td>
<td>31.8</td>
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<td>Stage II</td>
<td>45.0</td>
<td>15.6</td>
<td>48.1</td>
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<tr>
<td>Stage III</td>
<td>0.5</td>
<td>1.2</td>
<td>0.6</td>
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<tr>
<td>REM‡</td>
<td>11.8</td>
<td>8.6</td>
<td>11.5</td>
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<tr>
<td>L S IV (min)</td>
<td>31.13</td>
<td>15.86</td>
<td>20.63</td>
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<tr>
<td>L REM IV (min)</td>
<td>114.27</td>
<td>68.22</td>
<td>168.21</td>
</tr>
</tbody>
</table>

* = Sleep efficiency, † = Wake after sleep onset, ‡ = Rapid eye movement sleep, § = Sleep latency, ‡ = Latency of 1st REM sleep, * = Pre-levodopa, ** = Post-levodopa
REM behavior disorder

- RBD is a Disorder of abnormal motor activity during dream sleep
- Abnormal motor activity:
  - Simple: Talk, shout, laugh, irregular jerk/s
  - Complex: swearing, gesturing, punching, kicking, leaping from bed, running

Epidemiology

- Prevalence rates of 0.3 to 0.5%\textsuperscript{1}
- More often effects adults over age of 50, but can be seen as early as age 10-12
- More common in men than women (85% in men)\textsuperscript{2}
- With antidepressant use, seen more often in younger patients and women (45% in one sample)
  - 1. Ohayon et al, 1997
  - 2. Schenck and Mahowald, 1996
**Idiopathic RBD**

- RBD present alone without concomitant medical/neurological disorders - IRBD
- IRBD accounts for up to 60% of cases
- Association with Synucleinopathies and Tauopathies
- IRBD is often a harbinger of future neurodegenerative disease
- However, RBD may follow onset of neurodegenerative disease

**Secondary or symptomatic RBD**

- Sporadic manifestation of other neurological disease
  - ALS; Limbic encephalitis; Brain stem strokes; MS; Epilepsy; Autism; Tourette’s syndrome
  - Drug induced: Tricyclics; SSRIs; Bisoprolol-either during treatment or withdrawal
  - ETOH withdrawal
RBD in Neurodegenerative disorders

Synucleinopathies:
- Parkinson's disease
- Multiple System Atrophy
- Dementia of Lewy Body Type

Tauopathies:
- Progressive Supranuclear Palsy
- Alzheimer’s disease
- Corticobasal Degeneration
- Pick's disease

RBD in Parkinson's disease

- RBD is seen in up to 35% of Parkinson’s disease patients\(^1\)
- When patients with IRBD are followed:
  - 65% eventually developed Parkinsonism in one study\(^2\)
  - 48% of cases with Parkinsonism had preexisting RBD in another study\(^3\)
- REM sleep without atonia and motor behavior seen in up to 60% of patients

RBD in MSA

- RBD is much more closely associated with MSA than Parkinson’s disease
- Nearly all patients with MSA have RBD\textsuperscript{1,2}
- Pontine atrophy in MSA with involvement of structures generating REM atonia may be a reason

\begin{itemize}
  \item 1. Olson et al, Brain 2000
  \item 2. Vetrugno et al, Sleep Med 2004
\end{itemize}

RBD and DLB

- Clear association between the 2 not studied
- RBD is considered a supportive feature in diagnosis of DLB
- RBD and cognitive decline precede Parkinsonism and Hallucinations
- Path studies show that predominance of RBD patients that later develop Dementia have Neuronal loss in Substantia Nigra and Locus Coeruleus along with Lewy bodies\textsuperscript{1,2}

\begin{itemize}
  \item 1. Boeve et al, Mov Disorders, 2001
  \item 2. Turner, J Geria Psych Neurology, 2002
\end{itemize}
RBD in Tauopathies

- RBD is much less common in Tauopathies
- 10-20% of cases of PSP may have REM without atonia\(^1\)
- 5% of AD patients may have symptoms of RBD\(^2\)
- Much more rare in CBD and Picks

\(^1\) Arnulf et al, Sleep 2005
\(^2\) Gagnon et al, Sleep 2005

Periodic Leg Movements (PLM)

- Periodic flexion of ankle, knee and thighs with fanning of toes
- Pathological PLMS occur >5 times per hour/sleep
- Polysomnography is required to quantify PLMS
- 80-85% of RLS patients have a PLMS index >5
- PLMS also occur in a variety of sleep and neurological disorders
Clinical Features

• Simplex or complex motor behavior during sleep
• Often present with injuries to self or bed partner due to violent behavior during sleep
• Dreams often involve attack by animals or humans
• Behavior mirrors dream content
• Most recall the dream content
• Normal levels of aggressiveness during daytime

Clinical features

Very often co-exist with other sleep disorders such as:
  – Obstructive Sleep apnea
  – Narcolepsy
  – Restless legs/Periodic limb movements of sleep
Co-existing Sleep disorders worsen underlying RBD
Note: RBD-like behavior in OSA during apnea related arousals

1. Iranzo et al, Sleep 2005
**Atonia in REM sleep**

- REM Sleep “on” neurons in LDT and PPN (Cholinergic neurons)
- REM atonia is induced by complex mechanism involving LDT, LC and subceruleus regions which stimulate medial medulla-NMC&NGC.
- NMC&NGC inhibit spinal motor neurons via reticulospinal tract causing atonia

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**Mechanisms of REM atonia**

*Boeve et al, Mental and behavioral dysfunction in Mov Disorders; 2003*
Loss of REM atonia in RBD

Pathology of RBD

Pathology of IRBD represents a continuum with involvement starting in brain stem and ascending cranially. Clinically patients express RBD, followed by Parkinsonism and finally Dementia.
Diagnostic Criteria

A. Violent or injurious behavior during sleep
B. Limb or body movement during dream
C. At least one of the following:
   1. Potentially harmful sleep behaviors
   2. Dreams appear to be “acted out”
   3. Sleep discontinuity
D. PSG demonstrates following in REM sleep
   1. Augmented Chin EMG
   2. Simple or complex motor behaviors
   3. Absence of epileptic activity
E. Symptoms not associated with other psych disorders
F. Other sleep disorders may be present but not the cause of behavior

PSG in RBD
RBD in Lab

Summary

- Sleep dwindles with aging
- Sleep disturbances are a common feature of neurodegenerative diseases
- Sleep disturbances can pre-date onset of dementia
- RBD is common and can predict onset of neurodegenerative disease
- Treating sleep disorders can prevent progression of dementia