PARASOMNIAS
&
RLS
Objectives

- Develop an understanding of causes of abnormal experiences or behaviors during sleep

- Gain general understanding of RLS
Outline

- Parasomnias
  - NREM
  - REM
- RLS
- Definitions
- Clinical features
- Etiology and consequences
- Research tools
OVERVIEW OF PARASOMNIAS
Parasomnias

- Disorders of arousal

- Undesirable events or experiences during entry into sleep, within sleep, or during arousal from sleep

- Stage transitions (mainly to and from sleep)
Parasomnias

- 3 states of human “consciousness”: wake, NREM, REM
- Under normal physiologic conditions, distinct boundaries
- Temporary unstable states of dissociation lead to a “mixture” of features from both states
  - Wake + NREM
  - Wake + REM
Parasomnias

- **NREM parasomnias**
  - Disorders of arousal
    - Sleep walking
    - Sleep terrors
    - Confusional arousals
  - Sleep-related eating disorder

- **REM parasomnias**
  - REM Sleep Behavior Disorder
  - Recurrent isolated sleep paralysis
  - Nightmare disorder
Parasomnias

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NREM PARASOMNIAS
NREM Parasomnias

- Disorders of arousal consisting of complex behaviors initiated during partial arousals from slow wave (N3) sleep

- Events are usually during the first third of the major sleep episode

- Conceptually, certain parts of the brain are asleep and certain parts are awake; latter likely due to loss of inhibition
NREM Parasomnias

- Most episodes are brief but in children can last 30-40 minutes

- Characteristics
  - Eyes open, glassy look
  - “High level” cognitive functions (judgement, social interaction, planning) absent
  - Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode
  - Limited or no associated dream imagery
  - Partial or complete amnesia
Confusional Arousals

- Occur in bed (unlikely sleep walking)
- Often start with the patient sitting up and looking around
- Usually simple behavior
- Talking common
- Sometimes complex behaviors, including sexual behavior
Sleep Walking

- Usually though not always begin as a confusional arousal
- Patient leaves the bed and may walk or run around
- Often agitated/aggressive behavior
- Usually simple behavior
- Sometimes complex and protracted, including sexual behavior (“sexsomnia”)
- Ambulation may terminate spontaneously often in inappropriate places.
- Sleepwalker may return to bed but not necessarily
Sleep Terrors

- Accompanied by cry or piercing scream
- Behavioral manifestations of fear
- Autonomic activation: tachycardia, tachypnea, flushing, diaphoresis, mydriasis
- May be accompanied by incoherent vocalizations
- Getting out of bed uncommon but can occur
- Violent behavior may occur especially when attempts are made to block or retrain the individual
NREM Parasomnias

- Involve disinhibition of “basic drive states”: feeding, sex, aggression

- “Central pattern generators elicit primal fixed action patterns that would otherwise have been inhibited by the prefrontal cortex during wake” (ICSD-3)
NREM Parasomnias

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Fig. 3 | Sleep–wake dissociation in disorders of arousal. The coexistence of non-rapid eye movement sleep-like patterns in the frontoparietal associative cortices and hippocampus (blue shading) and wake-like patterns in the motor cortex and limbic structures (red shading) might underlie behavioural and cognitive dissociation during parasomnia episodes.
Indispensable Methods

- Intracranial EEG can be used to capture focal EEG recordings that have high “resolution”
  - Intracranial grids
  - Depth electrodes (“stereo EEG”)

https://www.epilepsy.com
Example: Patient in slow wave sleep. Then has an episode marked by sitting up in bed, utters unintelligibly, doesn’t respond to questions posed by his mom or tech. At onset of episode EEG changes from typical NREM activity to wake-like pattern in supplementary sensorimotor area, cingulate, and amygdala. However, EEG in hippocampus and frontal cortex remain identical to activity in slow-wave sleep.

NREM Parasomnias

- Onset usually <35 years of age and usually in childhood or adolescence
- Confusional arousal occur in 15% of adults in USA
- Sleep walking most common: up to 40% of children with at least 1 lifetime episode, 5% of adults with episode in adulthood
- Sleep terror prevalence: 2-3% of adults
NREM Parasomnias

Fig. 4 | A pathophysiological model of disorders of arousal. A combination of predisposing and priming factors leads to increased slow-wave sleep instability that promotes the occurrence of disorder of arousal episodes, potentially triggered by precipitating factors.

NREM Parasomnias

- Often occur during periods of increased N3 sleep, such as in recovery from sleep deprivation
  - Concurrent systemic illness
  - Physical or emotional stress
  - Medications: lithium, phenothiazines, sedative/hypnotics
- No clear association between childhood NREM parasomnias and adult psycho- or neuro-pathology
- No structural brain pathology
REM PARASOMNIA: REM SLEEP BEHAVIOR DISORDER (RBD)
RBD

- Dream-enactment behavior
  - Yelling out, complex behaviors such as punching or otherwise fighting others

- Dream content violent/action packed

- Activity commensurate with dream content (recalled on awakening): highly suggestive
RBD

- Asleep
- Eyes usually closed
- Occur in 2nd half of the night
- Amnesia may not necessarily be present
RBD

- Minimal diagnostic criteria:
  - Repeated episodes of sleep-related vocalizations and/or complex motor behaviors (based on clinical history or PSG)
  - PSG shows REM without atonia (RWA)
  - No other explanation
RBD

- Results from dysfunction of brainstem nuclei mediating RWA
- May be associated with narcolepsy or structural brainstem lesions
- When “idiopathic”, often portends high risk of future neurodegenerative disorder

Hogl, Stefani, Videnovic, Nature Reviews 2018
RBD

- Idiopathic RBD: implications
  - Extensive literature suggest that RBD reflects high risk of underlying α-synucleinopathy
  - α-Synuclein is a predominantly neuronal protein that is a key component of Lewy bodies (seen in PD and DLB) and glial inclusions seen in MSA
  - RBD is often a prodromal feature of α-synucleinopathies
At least 50% of individuals with idiopathic RBD go on to develop an α-synucleinopathy

- 33.1% at 5 y
- 75.7% at 10 y
- 90.9% at 14 y

RBD

- Intensive work to identify biomarkers for neurodegeneration in RBD
- Clinical features: olfactory, autonomic, neuropsychiatric, motor signs and symptoms
- Imaging
  - MRI (iron, neuromelanin imaging)
  - Dopamine transporter SPECT scan
  - PET imaging
  - Cardiac MIBG
  - Transcranial doppler ultrasonography

Postuma et al. Brain, 2019
RBD

- Electrophysiology
  - Severity of REM atonia loss
  - Heart rate variability
  - Quantitative EEG in sleep and wake

Postuma et al. Brain, 2019
RBD

- Therapeutics targeted at underlying pathology in development

- “At-risk” or “Prodromal” disease detection and intervention on horizon
RLS

- Unpleasant or uncomfortable urge to move the legs during periods of rest, particularly in the evenings, transiently relieved by movement

\[ \text{U} = \text{urge to move the legs, usually associated with unpleasant leg sensations} \]
\[ \text{R} = \text{rest induces symptoms} \]
\[ \text{G} = \text{getting active (physically and mentally) brings relief} \]
\[ \text{E} = \text{evening and night make symptoms worse} \]
RLS

- Diagnostic criteria International Restless Legs Syndrome Study Group:
  - An urge to move the legs (or other body parts), usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (or other body parts).
  - The urge to move/unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.
  - The urge to move/unpleasant sensations partially or totally relieved by movement (walking, stretching) at least as long as the activity continues.
  - The urge to move or unpleasant sensations are worse in evening or night than during the day (or this was present at some point).
RLS

- Uncomfortable sensations:
  - Antsy
  - Crawling
  - Creeping
  - Tingly
  - Pain
  - Burning
  - Soreness
RLS

- Symptoms typically begin in the evening when the patient gets into bed to sleep or earlier during “winding down”

- They have to get up and walk around, rub their legs, other maneuvers. This provides temporarily relief

- Consequently patients have sleep-onset insomnia, and this in turn affects daytime function

- Depression and anxiety often comorbid
During sleep, periodic limb movements often occur
- Periodic movements of lower extremities
- Typical: flexion of leg at hip and knee, extension at ankle

These may lead to awakening, in turn fragmenting sleep

Many patients have daytime sleepiness or fatigue
RLS

- Diagnosis is predominantly clinical

- Suggested immobilization test (SIT)
  - Patient asked to remain still without leg movement for 1 hour
  - Subjective report of sensory symptoms
  - Frequency of periodic limb movements during this hour can be quantitated
  - Multiple SITs maybe used on research basis
RLS

- Primary RLS is that not associated with other disorders

- Secondary RLS is seen in pregnancy, anemia, neuropathy, spinal cord injury, uremia, medications

- Often familial—genetic heterogeneity likely
  - Linkage studies and GWAS identified several potential loci
  - MEIS1, MAP2K5, BTBD9 LBXCOR1
  - Related to embryonic neuronal development
RLS

Iron deficiency may cause or exacerbate RLS

Treatment involves dopamine agonists/levodopa, calcium channel blockers (a2-delta subunit of voltage-gated calcium channels; gabapentin etc), opioids

Pneumatic compression
THANK YOU

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