Sleep disorders in Rett’s syndrome

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Goals of Presentation

• To identify mechanism involved in the two process model: homeostatic regulation (wake-sleep) and circadian regulation
• To identify common sleep disorders associated with Rett’s syndrome and their association to abnormalities in these regulations.

The Two-process model and effect of sleep deprivation on SWS

• Homeostatic regulation
• Circadian regulation

Homeostatic regulation

Sleep homeostasis and age

Neurobiology of wakefulness - Ascending Reticular Activating System

Sleep homeostasis and age

Neurobiology of wakefulness - Ascending Reticular Activating System
Neurobiology of sleepiness

The sleep/wake flip-flop switch
Pathways promoting wakefulness and sleepiness actively inhibit each other

VLPO = Ventrolateral preoptic nucleus

The hypocretinergic (orexin) system

The flip-flop switch model

Neuroanatomy and neurochemistry of sleep-wake function

Circadian regulation
Function of sleep

Sleep plays an active role in processes such as:
- Synaptic plasticity and memory functions,
- Emotional regulation,
- Metabolic functions and energy balance,
- Macromolecule biosynthesis,
- Removal of toxic substances and metabolic waste, or
- Prophylactic cellular maintenance.

Default state of the organism/cerebral networks or a state of adaptive inactivity.

REM sleep selectively prunes and maintains new synapses in development and learning

Common sleep problems in Rett syndrome

- Sleep problems/disturbances (insomnia, nighttime awakenings)
- Nocturnal screaming and laughing
- Abnormal sleep behavior (bruxism, head banging)
- Seizures/epilepsy
- Sleep disordered breathing
- Electrophysiologic abnormalities

Determinants of sleep disturbances in Rett syndrome in relation to genotype

The prevalence of most sleep problems was highest in those with a p.Arg294* mutation. Severe epilepsy was associated with poorer sleep and increased somnolence.
The trajectories of sleep disturbances in Rett syndrome (21 years from 120 families registered with the Australian Rett Syndrome Database)

Wong et al., Sleep Res., 2015 Apr;24(2):223-33

Electrophysiological findings in RTT

- Focal and generalized slow activity
- Focal, continuous spike activity
- Continued spike and wave in slow-wave sleep (CSWS)
- High amplitude delta activity during Slow-Wave Sleep (SWS)
- Reduced SWS, but increased delta-activity in sleep
- Phasic chin muscle activity during rapid-eye-movement sleep (REMS) – REM sleep without atonia (RSWA)
- Electroencephalographic indices of auditory stimulus discrimination: decreased gamma-band oscillatory responses to familiar and novel voices
- Increased cortical excitability as determined by Transcranial Magnetic Stimulation (TMS)

Polysomnographic (PSG) findings in RTT

Polysomnography (PSG) studies have had conflicting results, with some indicating:

- relatively normal sleep architecture,[1,2],
- while others reported increases [3] or decreases [4,5] in duration of rapid eye movement (REM) sleep

3. Reduced SWS, but increased delta-activity in sleep

Electrophysiological abnormalities associated with poor outcome

Boxplot of EEG spectral analysis and sleep structure analysis.

Comparison of control EEGs' and RTT EEGs' delta power

(4) Comparison of duration of overnight recordings in control EEGs with RTT EEGs revealed no significant differences, but REM sleep and sleep latency were increased in RTT (i.e.; high delta power) compared to controls. (5) Patients with RTT had significantly fewer number of total SWS cycles compared to controls. (6) Patients with RTT had significantly lower SWS percent

Ammannati et al., Pediatr Neurol. 2015 Oct;77:138-45

SWS percent in Age Group

- SWS is diminished in RTT, but difference is reduced by age 6-9.
- This could – however – be explained by increased occurrence of delta-activity by advanced disease.
- REM sleep were not recorded in this study

Ammannati et al., Pediatr Neurol. 2015 Oct;77:138-45

Circadian/sleep efficiency studies in RTT (actigraphy)

- Normal sleep-wake rhythmicity
- Almost all (N=13) showed normal total sleep time (492 mins) but reduced sleep efficiency especially among those with uncontrolled seizures/epilepsy

Ammannati et al., Pediatr Neurol. 2015 Oct;77:138-45

McDonald et al., J. Inherit. Metab. Dis. 2018; 41 (8)
Effect of specific sleep medication (compared to no treatment) on the likelihood of unresolved sleep problem by sleep problem type

- Open design
- Evaluated drugs: melatonin, clonidine, trimeprazine, amitriptyline, respidone, promethazine, others

Sleep disordered breathing

- RTT patients may show higher degree of sleep apnea (including central sleep apnea) and hypventilation
- May also be associated with CDKL5 gene mutation
- Males with MECP2 mutations may show respiratory failure resembling Ondine syndrome.
- Suggest a failure of brainstem respiratory centres to control respiration
- In addition REM sleep may show reduction
- However, in many RTT patients nocturnal saturation are normal.

Seizures correlates with high delta power and lower SWS

Clinical severity of patients with RTT were recorded and documented. Seizures are a characteristic of RTT. Patients with RTT were separated into two groups: patients who showed no seizures and patients who experienced seizures

- (A) Patients with RTT who experienced seizures correlated negatively with lower SWS percent.
- (B) In addition patients with RTT who experienced seizures correlated negatively with lower cycles during sleep.

Disturbance of phasic chin muscle activity during rapid-eye-movement sleep

- Disturbance in phasic chin muscle activity during rapid-eye-movement sleep (REMS): REM sleep without atonia
- Observed in RETT syndrome, infantile spasms, severe myoclonic epilepsy in infancy (SMEI), severe nocturnal enuresis, and autism (1).
- Commonly observed in adult patients with Parkinson’s disease (PD), hypocretin deficient narcolepsy and REM sleep Behavior Disorder(2)
- Due to involvement of subceroleus (sublatoro-dorsal nucleus) in the pontine region(2)

Sleep and epilepsy

Sleep efficiency and seizures

Actigraphy-derived sleep efficiency was significantly lower among those whose parents reported that they had seizures that were not controlled by medications at the time of the study (N = 5, M = 72.32%, SD = 6.30), compared to those with no history of seizures and those whose seizures were well controlled (N = 7, M = 79.05%, SD = 6.37)

References:

Clapping-suppressed focal spikes in EEG may be unique for the patients with rett syndrome: a case report.

Continuous centrotemporal spikes in the EEG, and clapping supressed focal spikes in EEG

- Female, 4 years old, presented with a significant regression in her spoken language skills, hand stereotypes (hand clapping and handwringing), a wider based gait with difficulties in balance, repeated abnormal behaviors (bruxism and head banging)
- EEG showed slow activity in background and revealed a specific feature that continuous centrotemporal spikes can be supressed by the repeated hand clapping

Lv et al. BMC Neurol. 2016 Jun 13;16:9

Epilepsy and RTT

- Affects 50-90%
- Early onset
- Often dyskinetic movements.
- Associated with significant comorbidity
- Often refractory to medical treatment
- Often requiring polypharmacology and non pharmacological treatment (e.g. ketogenic diet, vagus stimulation)
- Some AED (topiramate) may interphere with respiration


Evoked potentials

Generally: all modalities show abnormalities associated with cognitive and disease progression impairment, suggesting general involvement of multiple brain areas including brain stem:
- Visual Evoked Potential (VEP): impaired responses including abnormal response to increased spatial frequency
- Event-related potentials (ERP): longer ERP latencies and smaller ERP amplitudes suggesting slowed information processing and reduced brain activation
- Somatosensory-evoked potentials (SEP): "giant" responses, suggesting cortical hyper-excitability
- Transcranial Magnetic Stimulation: abnormal excitatory and inhibitory motor responses
- These data underly significant influence brainstem, midbrain and cortical network as expressed by abnormal excitation/inhibition.

Krajnc N. J Child Neurol. 2014 Oct;29(10):NP118-21

Induced gamma oscillations differentiate familiar and novel voices in children with MECP2 Duplication and Rett syndromes

MECP2 Duplication

RTT

Gamma-band oscillatory activity, since abnormalities in gamma activity are thought to reflect deficits in excitatory-inhibitory balance, and are associated with coordination of neural activity, and support of higher-order cognitive processes such as attention and memory, including auditory object representation


Summary

- Sleep and wake are under complex homeostatic and circadian regulation
- This is regulated by several nuclei in brainstem, mid- and forebrain
- Patients with Rett syndrome present multiple abnormalities especially in sleep regulation causing severe sleep problems (insomnia, sleep fragmentation, abnormal behavior, breathing abnormalities, seizures) and multiple associated electrophysiological abnormalities.
- This suggest that the wake-sleep regulatory systems are involved in disease and its advancement.