# The Teen Brain and Sleep


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# Disclosure slide

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# Excessive Daytime Sleepiness

- Primary Disorders of Vigilance
  - Idiopathic hypersomnia
  - Kleine-Levin syndrome (periodic hypersomnia)
  - Narcolepsy
  - Secondary narcolepsy (due to brain injury)

# Kleine-Levin Syndrome (recurrent or periodic hypersomnia)

- Seen in adolescents, male:female = 4:1
  - Periods of extreme sleepiness lasting 14-18 hours/day for 1-2 weeks
  - Associated with hyperphagia, anorexia, or hypersexual behavior ~50%
  - May include feelings of depersonalization, amnesia, and cognitive difficulties

  - Between episodes, patients are completely normal
  - May have several episodes/year
  - Episodes become gradually less frequent over time, spontaneously resolve
  - No known etiology nor diagnostic test
  - Lithium or lamotrigine may have benefit

# Narcolepsy

- Characterized by:
  - Overwhelming sleepiness
  - Variable presence of sudden muscle weakness provoked by emotional stimuli, fright, or the anticipation of a reward (cataplexy)
  - Vivid dreams at sleep onset (hypnagogic hallucinations)
  - Transient inability to move when falling asleep/after waking (sleep paralysis)
  - Instability of nocturnal sleep with heightened arousals

# Narcolepsy

- Type 1: with cataplexy
- Type 2: without cataplexy

- Type 1 more common in childhood
  - Onset between 3-17 years old
  - 1/3 of patients have onset within 1$^{st}$ 2 decades of life

# Narcolepsy

- Familial clustering: risk of developing narcolepsy = 1% - 2% for first-degree relatives (20-fold to 40-fold higher increased risk)
  - Haplotype human leukocyte antigen (HLA) DQB1*0602 is present in > 95% of narcolepsy type 1 cases (25% - 30% prevalence in the general population)
- Likely: immune-mediated process that results in near-complete loss of dorsolateral hypothalamic hypocretin secreting neurons
- Hypocretinergic neuron projections: enhance alertness in the ventral forebrain and modulate monoamine release and motor control in the brainstem

# Narcolepsy

- Most disabling clinical manifestation of childhood narcolepsy is profound daytime sleepiness (sleep attacks)
- Despite having slept through the night, the patient may fall asleep involuntarily on multiple occasions during the day (while sitting at a desk, during conversations, and even while eating)
- Sleepiness may be associated with mood swings, inattentiveness, and problems with memory and learning
- Anxiety and feelings of sadness may impair social interactions

# Narcolepsy

- Children < 8 - 10 years old may have subtle cataplexy
  - Transient jaw weakness or head rolling
- Precocious puberty and obesity are commonly seen at onset of narcolepsy type 1
- Sleep disruption by periodic limb movements (PLMs) or REM sleep behavior disorder may be seen

# Narcolepsy

- Diagnosis:
  - Nocturnal PSG (polysomnography) commonly demonstrates sleep-onset REM period, fragmented sleep, and REM sleep without atonia
  - Followed the next day by multiple sleep latency test (MSLT), which commonly demonstrates a decreased sleep latency of < 8 minutes and two or more sleep-onset REM periods
- Must be drug free for 2-3 weeks prior to testing (including stimulants, antidepressants, and sedatives)
- CSF may show absent to very low levels of hypocretin-1 (does not require drug withdrawal)

# Narcolepsy

- Secondary narcolepsy due to anatomic or metabolic brain lesions is rare - can develop in patients with primary brain tumors such as craniopharyngioma, head injury, encephalitis, myotonic dystrophy type 1, and Niemann-Pick disease type C

- Differential diagnosis: abnormal sleep hygiene with consequent insufficient sleep at night, drug-seeking behavior, depression, and circadian rhythm sleep-wake disorders

# Narcolepsy Treatment

- First step in management is counseling
- Narcolepsy is a life-long disorder
- Sleep-wake schedule should be regular, and planned naps of 20-30 minutes should be put in place (home and school)
- Driving and alcohol should be avoided
- The patient should exercise regularly
- Counseling about the choice of a career and course load in college
- Referral to patient and family support organizations
- Initially target the symptom that is most bothersome to the patient

# Narcolepsy Treatment – excessive sleepiness

- Methylphenidate
- Dextroamphetamine, amphetamine, dextroamphetamine mixture
  - Loss of appetite, suppression of growth, exacerbation of anxiety, nervousness
- Modafinil, armodafinil
  - Headache, SJS, decreases oral contraceptive potency
- Sodium oxybate (restrictions - GHB)
  - Tremor, constipation, bed-wetting, exacerbation of sleep apnea, weight loss, exacerbation of depression

# Narcolepsy - Cataplexy

- Sodium oxybate (dual purpose)
- Venlafaxine, protriptyline, clomipramine (SSNRI, TCAs)
  - Drowsiness, weight gain, tremor
- Fluoxetine, sertraline (SSRIs)
  - Nervousness, insomnia, increased risk suicidal thoughts

# Narcolepsy - PLMs

- Gabapentin, elemental iron, clonazepam
  - Drowsiness (with gabapentin and clonazepam), constipation and abdominal discomfort (with iron)

# Sleep-Related Breathing Disorders

- Obstructive sleep apnea (OSA)
- Central sleep apnea
- Sleep-related hypoventilation disorders

# Central sleep apnea syndromes (CSAS)

- Central sleep apnea with Cheyne-Stokes breathing
- Central sleep apnea due a medical disorder without Cheyne-Stokes breathing
- Central sleep apnea due to high altitude periodic breathing
- Central sleep apnea due to a medication or substance
- Primary central sleep apnea
- Primary central sleep apnea of infancy
- Primary central sleep apnea of prematurity
- Treatment-emergent central sleep apnea

# CSAS prevalence higher among

- Older adults
- Males
- Those with certain comorbid medical conditions such as heart failure, stroke, acromegaly, renal failure , atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases
- Patients with chronic opioid use including methadone

# CSAS DDx

- Obstructive sleep apnea
- Periodic limb movements of sleep
- Rotating shift workers
- Narcolepsy
- Respiratory disease
- Medication use
- Drug or alcohol abuse

# Secondary CSA

- Variety of brain tumors
- Chiari malformation
- Spinal cord tumors or malformations (spina bifida)
- Brain injury (stroke, trauma, infection)
- Genetic disorders (Trisomy 21, Prader-Willi)
- Epilepsy
- Medications
- Achondroplasia and craniosynostosis syndromes

# Obstructive Sleep Apnea

- Prevalence: ~2%; increased in those with premature birth, African American ethnicity
- Etiology:
  - Adenotonsillar hypertrophy
  - Craniofacial anomalies (micrognathia or maxillary hypoplasia)
  - Neuromuscular disorders (myotonic dystrophy or congenital myopathies)
  - Obesity
  - Conditions such as Down syndrome, Prader-Willi syndrome, achondroplasia, Crouzon syndrome, kyphoscoliosis, and cerebral palsy

# Obstructive Sleep Apnea

- Clinical manifestations:
  - Snoring not consistently observed in infants and those with neuromuscular disorders (may have stridor and laryngomalacia)
  - Habitual snoring, mouth breathing, restless sleep, increased sweating, bed wetting, parasomnias and teeth grinding, morning fatigue, waking with headaches, somnolence, hyperactivity and inattentiveness, mood swings, failure to thrive (in infants) or excessive weight gain (older)
  - Primary snoring - mildest form of sleep-related upper airway obstruction, ~8% of children, characterized by snoring $\geq$3 nights/week without associated apnea, increased arousals from sleep, or gas exchange abnormalities

# Obstructive Sleep Apnea

- Metabolic syndrome may develop as a consequence:
  - Insulin resistance, hyperglycemia, hypertension, dyslipidemia, abdominal obesity, and proinflammatory and prothrombotic states
- Neurobehavioral manifestations:
  - Inattentiveness, mood swings, impaired academic performance, hyperactivity, and sleepiness
- May have unusual postures or sleep positions

# OSA - diagnosis

- Nocturnal pulse oximetry in the home environment may be used for making the diagnosis when clinical symptoms and signs of OSA are obvious
- Normal # oxygen desaturation events is ~1/hour of sleep
- >3 drops in oxygen saturation < 90% level may suggest OSA
  - False negative rate ~70%
- PSG: indicated for patients with neurodevelopmental disabilities such as Down syndrome, epilepsy, or cerebral palsy who have restless or unrefreshing sleep

# OSA - diagnosis

- PSG also indicated when nonsurgical treatment, such as a positive airway pressure (PAP) device, is used
- PSG can distinguish OSA from obstructive hypoventilation (the latter shows end-tidal $CO_2$ level >50 mm for $\geq$25% of the recording time) and central sleep apnea
- The severity of the sleep disordered breathing can also be quantified using the apnea-hypopnea index (# of apneas or hypopneas/ hour of sleep, apnea-hypopnea index, AHI).
- Endoscopy by ENT of the upper airway to assess the sites of upper airway occlusion in sleep

# OSA - treatment

- Mild OSA (AHI < 3) is treated with topical nasal corticosteroids at bedtime
- Significant improvement can be demonstrated in PSG measures and adenoid size over 6 weeks
- Dust mite precautions and treatment of environmental allergies should also be addressed

# OSA - treatment

- For moderate (AHI 3-9) or severe OSA (AHI $\geq$ 10), the first step in management is usually adenotonsillectomy (T&A), to which most patients respond favorably
- Children < 3, with craniofacial anomalies, or severe OSA constitute high-risk groups and careful monitoring in the postoperative period for respiratory compromise because of upper airway edema is essential
- A clinical and, if necessary, PSG reevaluation should occur 2 to 3 months after adenotonsillectomy to assess response
- Supraglottoplasty in infants with stridor and poor weight gain

# OSA - treatment

- A PAP breathing device should be considered for residual OSA
- PAP devices are approved for use by the FDA in children weighing > 14 kg
- Sleep-related obstructive hypoventilation of neuromuscular disorders may require bilevel PAP
- Weight-reduction measures are indicated in overweight patients
- Orthodontic consultation and oral appliances are indicated in those with retrognathia and tongue prolapse.
- Rapid maxillary distraction used in children with OSA who have a high arched palate and consequent narrowing of the nasal passages (opens up the suture between the two edges of the hard palate, promotes local bone development, and flattens shape of the palate, thus indirectly increasing diameter of nasal passages)

# Congenital central hypoventilation syndrome

- Rare genetic disorder: defect in the PHOX2B (paired-like homeobox 2B) gene: heterozygous 5 - 13 amino acid expansion of 20 polyalanine tract in exon three, known as polyalanine repeat mutations
- PHOX2B encodes a transcription factor for central and peripheral nervous system development
- Presents with cyanosis and apnea occurring primarily during sleep
- Increased risk for Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma)
- Treated with tracheostomy and positive pressure ventilation

# Other Hypoventilation Syndromes

- **Late-onset central hypoventilation syndrome (LO-CHS)**
- Also due to *PHOX2B* mutations, but present later as follows:
  - Apparent life-threatening events, cyanosis, or unexplained seizures during sleep
  - Respiratory depression or difficulty weaning from a ventilator after anesthesia or after an intercurrent infection
  - Lack of ventilatory response (apparent distress) during exposure to hypercarbia or hypoxemia (prolonged underwater swimming, breath-holding, pneumonia)
  - Unresolved CSA after treatment for OSA
  - Unexplained cognitive delay with a history of cyanosis
  - Unexplained cor pulmonale

# Other Hypoventilation Syndromes

- **Rapid-onset obesity with hypothalamic dysfunction (ROHHAD)**
  - Presents in early childhood with a rapid and dramatic gain in weight, but not height, followed by endocrinologic disorders and central hypoventilation
  - Excessive weight gain is usually the first feature and is often very rapid and associated with hyperphagia.
  - Followed by a variety of associated abnormalities in HPA (including Cushing-like features, GH deficiency, precocious puberty, hyperprolactinemia, central hypothyroidism, and/or hypernatremia +/- DI), with autonomic dysregulation including temperature instability. Affected children may have severe behavioral issues, developmental delay, and/or seizures.
  - Lack *PHOX2B* mutations, but also develop neuroectodermal tumors

# Restless legs Syndrome (RLS)

- Prevalence of RLS in childhood ~2%
- ~25% - 40% of adult subjects with RLS report onset of symptoms in childhood or adolescence
- Among adults, the disorder is more common in women
- Childhood RLS is equally common in boys and girls and occurs worldwide

# RLS - Symptoms

- Urge to move the limbs that may be accompanied by an uncomfortable or unpleasant sensation in the legs (bugs)
- Urge is worse during periods of rest or inactivity
- Urge to move the limbs and the associated uncomfortable/unpleasant sensation are relieved partially or totally by movement
- Urge to move the limbs and the accompanying uncomfortable sensation are worse in the evenings
    - Mimics: myalgias, leg edema, arthritis, growing pains, paresthesias, and leg cramps

# RLS - diagnosis

- Important to use child appropriate terms in discussing the symptoms
- Children may describe a ‘‘need to move’’ or ‘‘need to kick the legs’’
- Encouraging children to depict their leg discomfort in drawings may be helpful
- Home video observations may reveal a pattern of repetitive leg kicking and rubbing one leg against the other
- Nocturnal PSG may be required in nonverbal children for the documentation of PLMs (present in ~80% of children and adults with RLS)

# RLS and PLMs

- PLMs defined as a series of ≥4 EMG identified limb movements that last 0.5 - 5 seconds and occur at intervals of 5 - 90 seconds, typically in nonREM sleep
- The physiologic PLM index (movements per hour of sleep) is < 5
- The partial arousals triggered by PLMs may activate nonREM parasomnias (confusional arousals or sleepwalking)
- Frequent arousals from the accompanying sensory discomfort or motor disturbance may lead to daytime fatigue and inattentiveness
- There is clinical overlap between ADHD and RLS

# RLS and growing pains

- “Growing pains” refers to symptoms of discomfort in the lower extremities in children that may include musculoskeletal, arthritic, and RLS symptoms
- A subset of children with growing pains may indeed have RLS
- Historical clinical clue to distinguish possible causes of growing pains is that rest and immobility will worsen RLS but relieve musculoskeletal causes
- Clinical overlap between the 2 conditions, and they run together in families

# RLS Features in Children

- Genetic susceptibility, autosomal dominant (AD) transmission, central nervous system iron deficiency, and dysregulation of dopaminergic neurotransmission all seem important
- Strong family history (~75% of first-degree relatives)
- An element of anticipation may exist c/w AD inheritance

- Contrasted to adult-onset RLS, that seems polygenetic

# RLS - Pathophysiology

- Systemic iron deficiency - common predisposing factor for RLS and PLMs in children
- Serum ferritin levels <50 ng/mL have a significantly higher PLM index as compared to those with levels >50 ng/mL
- PLM index decreases following oral iron replacement therapy
- Iron is a cofactor for tyrosine hydroxylase, a rate-limiting step in the conversion of tyrosine to dopamine. Also, dopamine receptor agonists such as ropinirole or pramipexole alleviate symptoms of RLS in adults
- Secondary RLS from conditions such as peripheral neuropathy, diabetes mellitus, chronic renal disease, and spinal cord lesions is less common in children

# RLS - Treatment

- Serum ferritin should be part of the initial assessment of children with RLS
- Ferritin levels <30 - 35 ng/mL may be associated with RLS
- Since serum ferritin is an acute phase reactant, during a systemic infection the level may be falsely elevated
- Medications can exacerbate RLS such as risperidone, SSRIs, diphenhydramine, and antiemetics
- When possible, meds that may worsen RLS should be discontinued

# RLS - Treatment

- First step is correction of systemic iron deficiency
- Oral iron tablets or solutions of ferrous sulfate or gluconate at 3 - 6 mg/kg/d
- Side effects of oral iron include constipation, dark stools, and abdominal discomfort
- Correction of iron deficiency may take weeks or months
- If intolerance to oral iron, IV iron sucrose in a bolus of 3- 6 mg/kg (max dose 120 - 150 mg)
- Symptomatic relief from the discomfort of RLS can be provided by a low dose of an agent such as gabapentin (50 - 100 mg at bedtime)
- No data on the use of dopaminergic agents like ropinirole or pramipexole in older teens

# Parasomnias

- Most common in preschool-age children and gradually decrease in incidence over the first decade
- Prevalence rate ~40% for sleep terrors, ~25% for sleep enuresis, and ~15% for sleepwalking
- ~90% preschoolage children manifest $\geq$1 parasomnia

# Non-REM Sleep Parasomnias

- Termed disorders of arousal and include:
  - Confusional arousals
  - Sleep terrors
  - Sleepwalking
- Occur at the transition from deep nonREM (sleep stage N3) sleep to lighter stages of non-REM sleep (N2 or N1) or wakefulness
- More likely during the first third of night (N3 sleep prevalent)

# Confusional Arousals

- Most common between 2 - 5 years old
- Child abruptly awakens within 2 to 3 hours of sleep onset, sits up in bed, and moans or cries out while appearing confused and only partially responsive to verbal commands
- Autonomic dysfunction (sweating, flushed face, or piloerection) is minimal
- Duration of event = 5 - 20 minutes, during which child remains inconsolable
- Following morning, the child has no recollection of the event

# Sleep Terrors

- Also occur within 2 to 3 hours of sleep onset out of N3 sleep
- Abrupt crying, screaming, sweating, piloerection, and agitation occur (autonomic dysfunction)
- Child becomes extremely agitated for several minutes, once again with amnesia for the event in the morning

# Sleepwalking

- Again occurs from non-REM sleep early in the night
- Child may simply sit up in bed or climb out of bed and wander about the room or house and carry out nonpurposeful activities with no recollection of the events the following morning

# Non-REM Sleep Parasomnias

- All 3 non-REM sleep parasomnias run in families
- OSA, RLS, GERD, and anxiety may act as precipitating factors (by activating partial arousals from sleep)
- Non-REM sleep parasomnias most frequently arise during N3 sleep
- Can be mistaken for nocturnal frontal lobe seizures
  - Typically much briefer in duration (seconds) and occur randomly through the night during N1 or N2 sleep.
  - Also run in families AD fashion
  - Can also be mistaken for conversion disorder
  - Requires sleep EEG and/or PSG to diagnose

# Non-REM Sleep Parasomnias

- Treat any underlying triggering factors
- Troublesome, recurrent non-REM sleep parasomnias may require prophylaxis with clonazepam for 4 - 6 months
- Environmental safety measures such as dead bolts and motion sensors may be necessary to prevent injury

# REM sleep disorders – Nightmare Disorder

- Recurrent episodes of awakening from sleep with recall of intensely disturbing dreams, usually with fear or anxiety, and/or anger, sadness, disgust, and other dysphoric emotions
- Full alertness occurs immediately upon awakening with intact
- May be associated with a delayed return to sleep
- Dream descriptions in preschool-age children may be simple versus in older children may elaborate
- Due to active inhibition during REM sleep, bodily movement is rare

# Nightmare Disorder

- Recurrent nightmares in children may be due to physical, emotional, or sexual abuse as well as separation anxiety or generalized anxiety
- Psychological evaluation to assess for anxiety, stress, and other potential underlying factors
- Cognitive-behavioral therapy for intense, disturbing nightmares (dream image rehearsal therapy)

# REM Sleep Behavior Disorder (RBD)

- Aggressive or violent motor dream enactment accompanied by REM sleep without atonia (PSG)
- Infrequent during childhood but may be seen in narcolepsy or various neurodevelopmental disorders, brainstem lesions, or use of SSRIs
- Motor dream enactment in sleep (yell out, kick, or flail the extremities)
- May cause injury to cosleeping adult or sibling
- Unlike in adults, not associated with degenerative disorders such as synucleinopathies (PD, MSA, DLB)

# RBD

- PSG -  preserved muscle tone in REM sleep at baseline, with episodes of motor dream enactment
- Melatonin (1 - 3 mg at bedtime), clonazepam (0.25 - 0.5 mg at bedtime), or discontinuation of predisposing medications are treatment options

# Conclusions

- Sleep disorders can occur at all times of night
- Sleep disorders can impact daytime function
- Failure to address sleep disorders can have short- and long-term negative effects
- Patients with epilepsy, headache, neurodevelopmental disabilities, and learning disabilities = especially likely to benefit from addressing their co-morbid sleep conditions

# Questions?