Disorders of Respiratory Control during Sleep

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Disclosure

I have no conflict of interest to declare

Objective of this talk

- Classification of various syndromes
- Review normative data
- Review various congenital hypoventilation syndrome

Disorders of Respiratory Control in Children

- Brainstem abnormalities
  - Chari
  - Brainstem tumor
  - Achondroplasia
  - Joubert’s
- CNS abnormalities
  - HIE
  - Rett’s syndrome
- Peripheral CR abnormalities
  - Prader willi

Neuromuscular disorders
- Myotonic dystrophy
- Leigh syndrome

Infection related
- RSV
- Post CNS infection

Idiopathic central sleep apnea

Medications
- Narcotics

Definition

- Respiratory Pause
  - Arbitrary duration
  - Lasting 3 – 20 seconds
  - Normal after sigh breath/movement and in REM
- Central apnea (children)
  - Respiratory pause lasting > 20 seconds (Adults 10 seconds)
  - Respiratory pause lasting at least 2 missed breaths that is associated with an EEG arousal or oxygen desaturation of at least 3%.
  - Clinically significant: when results in chronic intermittent hypoxemia/bradycardia → adverse neurocognitive and or cardiovascular outcomes
- Hypoventilation
  - CO2 > 50 torr for > 25% of the TST

Central apnea
Normal pauses during REM

Normative data for central apnea in children
- Breathing = Respiratory rate and tidal volume less variable
- Oxygen desaturation is rare after infancy
- Few respiratory pauses of 8-10 seconds / isolated 25 seconds events are commonly seen in children and infants
- Stage N1 > REM > Stage N2/N3
- Older children rarely have scorable central apneas
- Overall Central sleep apnea occurs at rate < 1/hour

Poett et al 1993
Moss et al 2005
Carkasdon et al 1978

Congenital Central Hypoventilation Syndrome (CCHS)
(Ondine curse)

CCHS
- Rare disease
- Alveolar hypoventilation and failure of autonomic control of breathing during sleep
  - NREM > REM > Awake
  - ± CO2 response
  - ± Oxygen response

Cardinal features:
- Generally adequate ventilation while awake, hypoventilation during sleep
- Hypoventilation both during awake and sleep
- Absent or negligible ventilatory sensitivity to hypercarbia and or hypoxemia
- No evidence of primary neuromuscular, lung, cardiac and brain stem lesions
- Only 1/3 require ventilation both while awake & sleep

Facial dysmorphology
- Decreases in sloping of the forehead
- Increased upper face height and biocular width
- Nasal tip protrusion
- Inferior inflection of the lateral vermilion border of the upper lip

CCHS, Weese-Mayer Gene Reviews 2004
Emily ST. Pediatr Res 2006
Disorders of Respiratory Control during Sleep

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Genetics
- Paired-like homeobox 2B (PHOX 2B) – disease defining gene
- Located on chromosome 4 – encodes a transcription factor which regulates neural crest cell migration and autonomic nervous system development
- Autosomal dominant (95%), novo mutation
- 90% cases are heterozygous for polyalanine expansion mutation in exon 3 of PHOX 2B gene
- Normal sequence is 20 alanine on both chromosome (20/20)

Mutation Symptoms
- 20/24 Adult onset CCHS, Nocturnal ventilatory support
- 20/25 Infancy or later onset, Nocturnal ventilatory support
- 20/26 Neonate onset, Daytime ventilatory support with intercurrent infection, Nocturnal ventilation
- 20/27 to 20/33 Onset at birth, 24 hour ventilatory support, Hirschsprung disease

Genotype-Phenotype correlation
- Mutations with 20/24 and 20/25 have decreased penetrance
- Mutations with > 20/25 are fully penetrant

Clinical presentation
- Can present at any age (most commonly during newborn)
- Newborn period
  - Recurrent desaturation, cyanosis and central apnea during sleep
  - ALTE
  - Unexplained seizures
  - Difficulty with extubation
  - SIDS
- Late-onset: late infancy, toddlers, adolescents and adults
  - Dramatic respiratory failure with sedation and anesthesia
  - Failure to extubate (ventilator dependent)
  - Dramatic respiratory failure with URI
  - Unexplained hypotension
  - Neurocognitive delay
  - Pulmonary hypertension

Respiratory
- Alveolar hypoventilation sleep and or awake
- Hypercarbia
- Central apnea or breath holding spells

Cardiac
- Asystole (5-15 seconds)
- Decreased beat to beat variability
- Decreased HR response to exercise
- Increased frequency of arrhythmias
- Lower BP during awake and higher during sleep

Gastrointestinal
- Constipation
- Esophageal dysmotility
- Hirschsprung disease

Autonomic
- Temperature instability
- Diaphoresis
- Pain insensitivity

Neurocognitive
- Intellectual impairment
- Mood disorders

Ophthalmologic
- Strabismus
- Decreased pupillary reflex

Miscellaneous
- Neural crest tumors
- PHOX 2B

Evaluation
- History and presentation
- Detailed clinical exam
- Nocturnal and daytime PSG
- Brain imaging
- Neuro-metabolic evaluation
- Genetic testing
- PHOX 2B

Assessment after diagnosis and f/u
- Screen for associated abnormalities
- Assessment of respiratory physiology
  - Spontaneous awake and sleep breathing
  - Tidal volume, HR, ETCO2
- Respiratory effort and airflow
- Hypocarbic & hypercapnic ventilatory responses
- ECHO (PHT)
- Ophthalmological examination
- 72 hour Holter monitoring
- Transient arrythmia and prolonged QT syndrome

CCHS, Weese-Mayer Gene Reviews 2004
Genetic testing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Test method</th>
<th>Mutation detected</th>
<th>Frequency of detection</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHOX 2B</td>
<td>Targeted mutation analysis</td>
<td>Polyalanine repeat expansion of PHOX 2B</td>
<td>92%</td>
<td>yes</td>
</tr>
<tr>
<td>PHOX 2B</td>
<td>Sequence analysis</td>
<td>Non-polyalanine repeat sequence variants</td>
<td>8%</td>
<td>yes</td>
</tr>
</tbody>
</table>

Genetic testing

- Ambry Genetics
- Children's Memorial Hospital Chicago

Polysomnography findings

Cardiac rhythm disturbance in CCHS

<table>
<thead>
<tr>
<th>Cardiac rhythm disturbance in CCHS</th>
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</thead>
<tbody>
<tr>
<td>Life long disease – No cure, respiratory stimulants DO NOT work!</td>
</tr>
<tr>
<td>Suppl. oxygen alone is NOT adequate and may be dangerous</td>
</tr>
<tr>
<td>Ventilatory support</td>
</tr>
<tr>
<td>- Tracheostomy / ventilation and back up rate and battery</td>
</tr>
<tr>
<td>- Generator, ambu bag</td>
</tr>
<tr>
<td>- Evaluate exercise tolerance</td>
</tr>
<tr>
<td>- Extra care with URIs, sedatives, swimming/diving, alcohol</td>
</tr>
<tr>
<td>- Diaphragmatic pacing</td>
</tr>
<tr>
<td>- Those who require 24 hour ventilation</td>
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<tr>
<td>- Relief from cumbersome daytime ventilation and helps ambulation</td>
</tr>
<tr>
<td>- Still require nocturnal ventilatory support</td>
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</table>

Rapid-onset Obesity with Hypothalamic dysfunction, Hypoventilation & Autonomic Dysregulation (ROHHAD)

- Clinically apparent between 1.5 – 7 years
- Essential features
  - 0 – 2 year: Normal growth and development
  - 2-8 years: Rapid and dramatic weight gain (4-6 months)
  - Most by age 6, facio-truncal, adipomastia
  - Others symptoms
    - ~ 3 years: Hypothalamic dysfunction
    - ~ 3.6 years: Autonomic dysfunction
    - ~ 6 years: Hypoventilation
    - ~ 13 years: Neural crest tumors
- PHOX 2B: Negative
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Clinical features
- Hypothalamic dysfunction
  - Diabetes insipidus
  - Abnormal thirst
  - Hyperprolactinemia
  - Hypothyroidism
  - Secretary GH abnormalities
  - Adrenal insufficiency
- Neural crest tumors
  - Ganglioneuroblastoma
- Autonomic abnormalities
  - Abnormal pupillary reflex
  - strabismus
  - GI dysmotility
  - Temperature instability
  - Decreased pain sensation
- Neurocognitive deficits
  - Developmental delays (30%)
  - Behavioral issues (50%)

Presentation
- Rapid onset obesity
- Respiratory failure following URIs
- Cardio-respiratory arrest can follow general anesthesia
- Hypoventilation (low SaO2 and elevated CO2)
  - Sleep and later awake
- Other symptoms
  - Unexplained seizures
  - Headaches
  - Cor-pulmonale
  - Sudden death

Management
- Similar to CCHS
- Screening for neural crest tumors
- Holter monitoring
- Endocrinology testing

- Weight loss – very important
- Nocturnal ventilatory (NIV) ~ 50 – 60%
- Tracheostomy and ventilation (24 hours vent support)
Cranio-cervical junction abnormalities

- Chiari Malformation

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Type 1</td>
<td>Herniation of cerebellar tonsils at least 5 mm into upper cervical spine +/- brainstem involvement, cervical syringomyelia, hydrocephalus</td>
</tr>
<tr>
<td>Type 2</td>
<td>Herniation of both cerebellum and brainstem into spinal canal. Usually accompanied by a myelomeningocele / Hydrocephalus</td>
</tr>
<tr>
<td>Type 3</td>
<td>Most severe form of CM, associated with occipital encephalocele.</td>
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<tr>
<td>Type 4</td>
<td>Associated with cerebellar hypoplasia. Parts of the cerebellum are missing, and portions of the skull and spinal cord may be visible.</td>
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Presentation

- Infancy: CM with hydrocephalus or meningo(myelo)cele
  - Stridor, apnea, ALTE, wheezing, OSA, CSA
- Later childhood or adults: Isolated CM (most common)
  - Aspiration, apnea, OSA, CSA, hypoventilation, bradypnea
- Adult: incidental finding
  - Headaches, neck pain, scoliosis, ataxia, OSA, CSA
  - Severe the degree of brainstem compression – severe apneas

Problems associated with CM

- Vocal cord paralysis - stridor
- Dysphagia / aspiration
- Respiratory muscle weakness
- Scoliosis
- Sleep disordered breathing
  - Central sleep apnea (25%)
  - Obstructive sleep apnea (35%)
  - Hypoventilation
  - Bradypnea
  - Prolonged expiratory apnea and cyanosis (PEAC)
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Management of respiratory abnormalities

- Isolated hypoxemia: supplemental oxygen
- Mild central apnea: supplemental oxygen
- Bradypnea/hypercapnia: BiPAP with ST mode
- Sleep fragmentation: Positive pressure ventilation
- Associated OSA: CPAP, T&A not successful

Surgical perspective

- Cranio-cervical decompression
  - Onset of brain stem dysfunction
  - Severe degree of central sleep apnea/hypoventilation
- Relief of hydrocephalus
  - Shunt
- Tracheostomy and ventilation
  - Irreversible brain stem damage

Prader-Willi Syndrome (PWS)

- Neuro-developmental disorder
- Failure to express paternal genes in the 15q11-q13 domain
- Associated abnormalities:
  - Hypothalamic dysfunction
  - Autonomic nervous system dysfunction
  - Peripheral chemoreceptor dysfunction
  - Very high arousal threshold
- Incidence: 1 in 15 - 30,000 births

Prader-Willi Syndrome

- Neonatal hypotonia and failure to thrive in the first year
- Hyperphagia with morbid obesity after the second year
- Cognitive impairment
- Behavioral issues
- Hypogonadism
- Peculiar facies

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Sleep Disorders in PWS

- Sleep disturbances
  - Subjective sleep problems are more common with UPD
- Hypersomnia
  - In >90% cases, mean sleep latencies < 5 min
  - Independent of OSA or obesity
  - REM sleep fragmentation, MOSEMs during MSLT
  - Secondary narcolepsy with cataplexy
- OSA
  - Majority of PWS develop OSA with time
- Central sleep apnea
  - More common with deletions
- Hypoventilation & Nocturnal desaturations
  - Abnormal arousal responses to hypoxia and hypercapnia

Nixon GM et al, Pediatr Pulmonol 2002

Treatment of SDB

- Obesity:
  - Life style modification:
- Sleep disturbances
  - Sleep hygiene
- OSA
  - Adeno-tonsillectomy
  - CPAP
- CSA/Hypventilation:
  - BIPAP ST mode with a rate
  - Tracheostomy / ventilation
- Hypersomnia/Narcolepsy:
  - Stimulants

Effect of Growth Hormone on Sleep Apnea in PWS

- GH therapy: Improves behavior, activity, hypersomnolence, ventilation, respiratory muscle strength, ventilatory responses
- Sudden deaths reported
  - Within 4 months on GH and in sleep
  - OSA suspected as contributor
- Hypothesis for sudden death while on GH
  - Adeno-tonsillar hypertrophy (may be IGF-1 mediated) → OSA
  - Intercurrent URI → OSA
  - Vulnerable to Upper airway resistance / abnormal arousal
  - Autonomic instability (ppt. arrhythmias)

Goldstone AP et al, Recommendations for the Diagnosis and Management of Prader-Willi Syndrome 2008

Sudden Death in PWS?

- Within 4 months on GH and in sleep
- OSA suspected as contributor

Screening of PWS while on GH

- If GH therapy is considered: Baseline PSG
- If OSA present – treat OSA before initiation of GH
  - Adeno-tonsillectomy
  - CPAP
  - Weight loss - strict dietary regimen
- Start low dose and ramp up - while on GH
  - Sleep history, UA exam, PSG after 2 months
  - Then every 6 month
  - Clinical follow up every 3 months
  - Symptoms of OSA
  - Weight
  - Tonsils
  - IGF-1
- Concern for OSA: Discontinue GH and treat OSA

Goldstone AP et al, Recommendations for the Diagnosis and Management of Prader-Willi Syndrome 2008

PWS and GH

- Current evidence suggest that there is no clear link between association of sudden death and GH therapy
- Sudden death is reported in PWS with and without GH therapy
- No clear evidence of increase in OSA on GH, however need close monitoring while on GH
- Normal PSG does not predict survival

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Joubert Syndrome
- Autosomal recessive
- Hypotonia, developmental delays
- Hypoplasia of cerebellar vermis
- Incidence - 1:100,000 in U.S

Abnormal breathing patterns in Joubert
- Periodic hyperpnea (tachypnea)
- Central apneas
- Periodic breathing
- Frequent desaturation
- OSA
- Irregular breathing

PSG findings in Joubert

Thank you