Pediatric Sleep Apnea

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Conflict of Interest Disclosures for Speakers

Mariam Ischander, MBChB, FAAP, FCCP has no relevant financial relationships with ineligible companies to disclose.

Learning Objectives

- Upon completion of this course, attendees should be able to:
  - Address the public health burden of pediatric sleep apnea and clinical sequelae.
  - Highlights the importance of timely and appropriate treatment of apnea in children.
  - Empower health care providers to early identify, treat and even prevent pediatric sleep apnea.

Pediatric Obstructive Sleep Apnea (OSA)

- The ATS and the ABP define pediatric OSA as a sleep-related breathing disorder with intermittent upper airway obstruction that disrupts normal sleep patterns.
- A disorder in which there is upper airway dysfunction causing complete or partial airway obstruction during sleep leading to decreased oxygen saturation or arousals from sleep.
- OSA has dramatic effects on childhood behavior, neurodevelopment, metabolism, and overall health.
- Early recognition, evaluation, and treatment are important to prevent long-term consequences.

Etiology of Pediatric Obstructive Sleep Apnea

- Factors that lead to decrease airway diameter or integrity (anatomic, genetic or neuromuscular) can contribute to OSA.

- The upper airway can have an increased risk of abnormal collapse due to both intrinsic and extrinsic factors.

- The intrinsic factors are based on the critical pressure in the airway that is needed to maintain patency.

- The extrinsic factors are fat deposits, hypertrophy of tissues, and craniofacial features that contribute to increased incidence of collapse.

Epidemiology

- The incidence of pediatric OSA peaks between 2-8 years of age due to the increased growth of tonsils and adenoids relative to the size of the upper airway in this age group.

- Risk factors for early-onset OSA include prematurity, Down syndrome, African American race, and daycare attendance.

- The severity can be increased in those with obesity, tobacco exposure, and reduced family income.

- Boys are at an increased risk after puberty, but the prepubertal risk is equal among boys and girls.

Pathophysiology of Pediatric obstructive Sleep Apnea

- The four main features that contribute to OSA are:

-Obesity causes fat deposits to surround the upper airway leading to collapse.

-Lymphoid hyperplasia causes tonsillar and adenoid obstruction of the airway, and the increased relaxation during sleep.

-Neuromuscular dysfunction can be seen in both central and obstructive causes of sleep apnea like Down syndrome, where there is hypotonia, with increased susceptibility of the airway to collapse.

-Craniofacial abnormalities, including Crouzon, Pierre-Robin, or Apert syndromes, cleft lip or palate. Micrognathia, micro or macroglossia, and midface hypoplasia all contribute to decreased posterior oropharynx space and the increased incidence of pediatric OSA

Pediatric sleep apnea and viral respiratory infections

- Viruses may cause hypertrophy of upper airway lymphoid tissue (tonsils and adenoids), which is critical to OSA pathogenesis in children.
- Respiratory viruses are detected in OSA hypertrophic tonsils and are associated with:

- Increased nasopharyngeal levels of miR-155, a potent inducer of follicular T-helper and B-cell proliferation and differentiation.
- Inducing the secretion of nasopharyngeal pro-inflammatory cytokines and growth factors such as vascular endothelial growth factor (VEGF), which may contribute to the enlargement of lymphoid tissues.
- Exacerbating upper airway inflammation in OSA, increased levels of airway proinflammatory cytokines (e.g. TNF-alpha, IL-6, and IL-1alpha) noted.

- All these factors may contribute to increasing nasopharyngeal resistance in the relatively narrow upper airways of young children, predisposing to both, OSA and clinically relevant viral respiratory infections.

Pediatric sleep apnea and viral respiratory infections

- Pathogenic microbiota in the upper airway may be a contributing factor for OSA pathogenesis.

- A recent study by Sarmiento Varón et al. demonstrated that the tonsils in children with OSA have a defective regulatory B cell compartment that is accompanied by tonsillar microbial populations dominated by Firmicutes (predominantly Streptococcus and Staphylococcus), Proteobacteria (mostly Neisseria and Hemophilus), Bacteroidetes (principally Prevotella), Actinobacteria and Fusobacterium.

- Another study demonstrated significant differences in the local lymphocyte response and bacterial community composition in the tonsillar samples of OSA patients.

- Nasopharyngeal microbiome changes dramatically during viral infections in children, so recurrent and/or severe viral respiratory infections may exacerbate the microbial and immune abnormalities of the nasopharyngeal tissue of children with OSA and that this may play a significant role in the pathogenesis of sleep-disordered breathing in the pediatric population.

Pediatric sleep apnea and viral respiratory infections

- The link between viral infections and OSA is bidirectional.
- Sleep-disordered breathing is a critical risk factor for severe viral respiratory infections. Rögnvaldsson et al. identified that OSA was associated with two-fold increase in risk of severe SARS-CoV-2 infections, and the association was not explained by obesity or other comorbidities .
- The pro-inflammatory state of OSA may lead to worsening of airway inflammation and facilitate the inception of cytokine storms as reported in adult and pediatric SARS-CoV-2 cases with multi-organ failure.
- OSA can lead to sleep fragmentation and circadian dysregulation, which can alter antiviral immune responses.

Environmental modifiers

- A systematic review found a significant association between secondhand cigarette smoke and obstructive sleep-disordered breathing.
- Multivariable analysis from a recent study revealed secondhand smoke exposure was related to increased OAHI by 48% in the severe OSAS subgroup after adjusting for race, BMI, and income.
- Poor air quality is a risk factor for habitual snoring in school-aged children.
- Low family socioeconomic status and parental occupations associated with a low educational level increased the risk of OSAS whilst academic and farming parental occupations decreased the risk.
- Children with OSAS were reported to have lower vitamin D levels, especially if they were obese or were of African American ethnicity. Plasma vitamin D levels correlated with AHI and SpO2 nadir, even after controlling for other potential confounders. HOMA-IR and CRP were also significantly associated with vitamin D levels. Vitamin D may play a role in modulating the degree of insulin resistance and systemic inflammation and vitamin D supplementation could be a potentially beneficial

History

- Practitioners should ask about sleep quantity and quality and screen for snoring at every well-child visit. Parents may not tell you unless you ask.

- If there is concern about sleep quality, questions should be asked about frequent night awakenings, unusual sleep positioning, and significant disruption of bed coverings as signs of increased nighttime movements.

- Parents often endorse a history of snoring, mouth breathing, witnessed apneas, frequent nighttime awakenings, and secondary nocturnal enuresis.

- Children with OSA have disrupted sleep, which can lead to behavioral issues, including hyperactivity, irritability, or even aggression.

Physical Examination

- Patients may appear tired or fatigued or hyperactive.
- Allergic shiners and swollen nasal mucosa.
- Micrognathia, macroglossia, high arched palate.
- Adenoidal facies, hypertrophied tonsils, nasal tone of voice and hypertrophied turbinate.
- Childhood obesity, for every kg/m2 increase in BMI above the 50th%ile, there is a 12% increase in the risk for OSA.

Gipson K, Lu M, Kinane TB. Sleep-Disordered Breathing in Children. Pediatr Rev. 2019 Jan;40(1):3-13. doi: 10.1542/pir.2018-0142. Erratum in: Pediatr Rev. 2019 May;40(5):261. doi: 10.1542/pir.405261. PMID: 30600274; PMCID: PMC6557418.

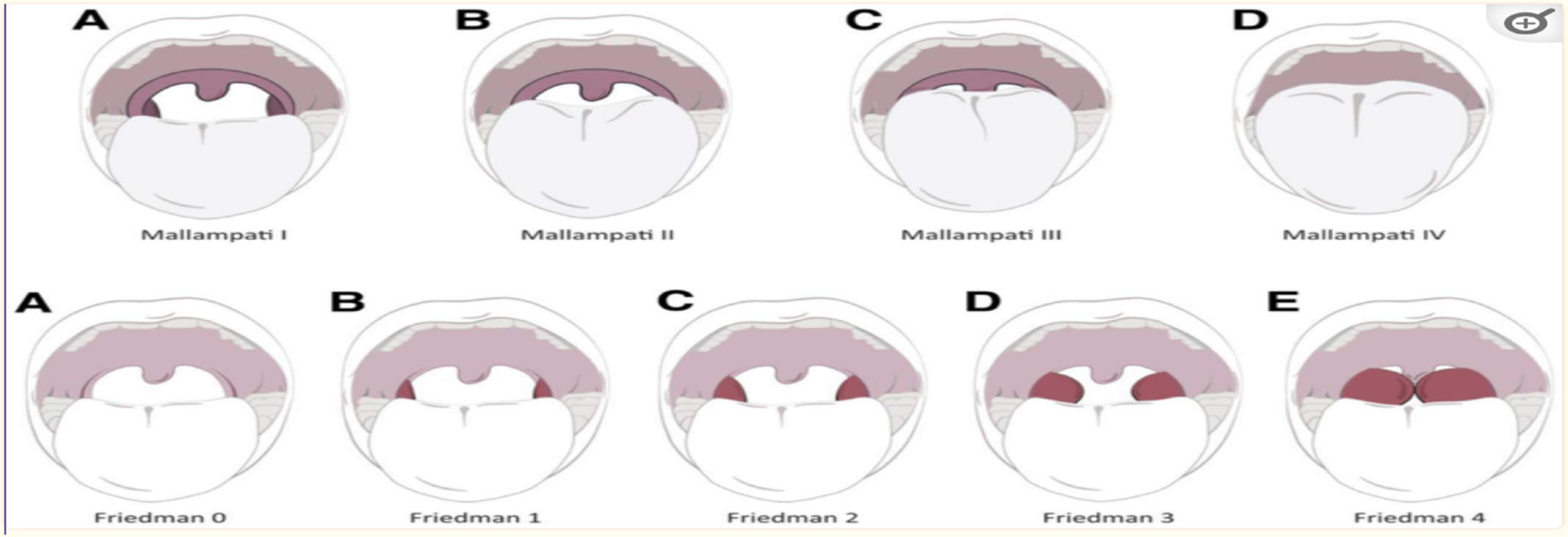


Figure 1:

Mallampati score and Friedman tonsil scale

The Mallampati score, while principally intended to help estimate the relative difficulty of intubation in pre-operative patients, is also useful in assessing the contribution of the upper airway anatomy on obstructive sleep breathing. The Friedman tonsil scale is useful for describing the size of tonsils in children, with a score of 0 representing surgically removed tonsils, and a size of 4 describing large tonsils that meet at the midline. *Image courtesy of Namrita Jain, MD.*

Evaluation

- Nocturnal polysomnography (PSG) is the gold standard for diagnosis of Pediatric OSA.
- Overnight oximetry at home is a tool to provide more information, but it does not replace a PSG in making a diagnosis of OSA.
- Concern about cardiopulmonary process: a chest x-ray and EKG. If appropriate, an echocardiogram for pre-surgical management for children with severe OSA.
- Measuring certain inflammatory biomarkers: kallikrein-1, uromodulin, urocortin-3, and orosomucoid-1, which can be elevated in children with OSA.
- CBC, iron studies, and TSH to look for causes of sleep disruption.
- Imaging studies to assess underlying anatomic abnormalities contributing to OSA, only useful in conjunction with a PSG.

Respiratory Scoring in children

- In adults, apneas and hypopneas are only scored if they are ≥ 10 seconds duration.
- Children have a faster RR than adults, and a lower FRC. They are therefore more likely to desaturate and suffer physiologic consequences from brief apneas. Because of this, obstructive apneas and hypopneas are scored if they are at least 2 breaths duration, even if they are < 10 seconds duration. Hypopneas are defined as a 30% reduction in airflow associated with either arousal or ≥ 3% desaturation. Obstructive events in children occur primarily during REM sleep. Thus, if sufficient REM sleep is not obtained during a polysomnogram, the degree of OSAS is likely to be underestimated.

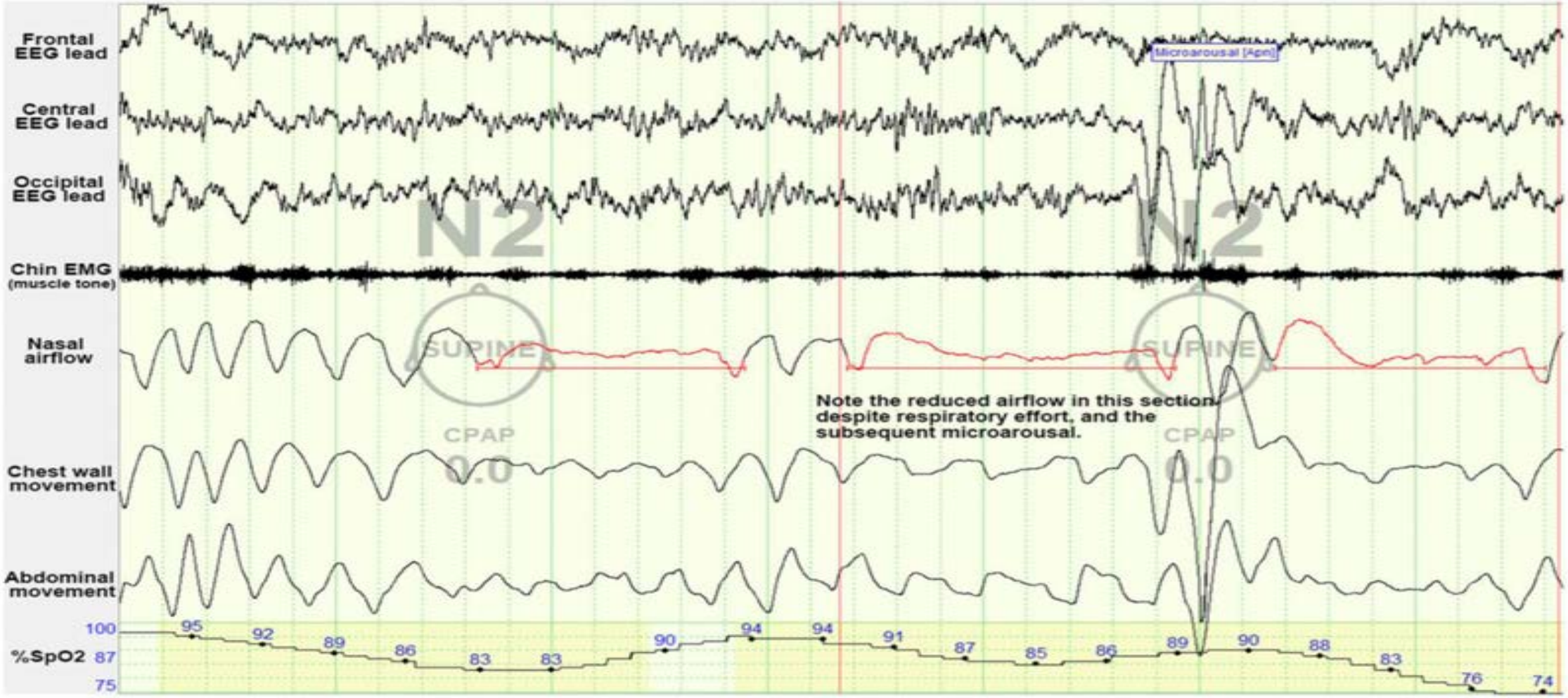
Respiratory scoring in Children

- Sleep Related Hypoventilation in children: >25% of total sleep time spent with CO2 above 50 mmHg (in adults if there is increase in CO2 to >55 for ≥ 10 minutes or there is ≥ 10 mmHg increase in CO2 during sleep (in comparison to awake supine value) to a value exceeding 50 mmHg for ≥ 10 minutes.

- Sleep related hypoxemia: ≥ 5 minutes of total sleep time spent with oxygen saturation at or below 90% in children (88% in adults), The desaturation is not fully explained by sleep-related hypoventilation, obstructive sleep apnea, or other sleep-related breathing disorder

Obstructive Sleep Apnea

Gipson K, Lu M, Kinane TB. Sleep-Disordered Breathing in Children. Pediatr Rev. 2019 Jan;40(1):3-13. doi: 10.1542/pir.2018-0142. Erratum in: Pediatr Rev. 2019 May;40(5):261. doi: 10.1542/pir.405261. PMID: 30600274; PMCID: PMC6557418.



Evaluation

- PSG will measure the apnea/hypopnea index (AHI), which is the average of the apnea and hypopnea episodes per hour of sleep.
- Children up to 13 years old: An AHI of 1 or greater is abnormal, although there is some controversy over the clinical significance of an AHI 1 to 1.9 events/hour.
- AHI of 1 to 4.9 events/hour is mild OSA, 5 to 9.9 events/hour is moderate, and more than 9 events/hour is severe.
- From 13 to 17 years of age: either pediatric or adult criteria can be used based on the clinical picture and patient development. Because children have higher airway integrity and less risk of collapse like adults, their PSG is usually dominated by hypopnea events rather than frank apnea.
- hypercarbia may also be present in the pediatric population that is absent or less common in the adult OSA population.

Emerging Diagnostic Techniques

- Drug-induced sleep endoscopy (DISE) for evaluating the anatomical site of airway obstruction. It may be helpful in the absence of adenotonsillar hypertrophy or where there was a discrepancy between the clinical findings and severity of sleep apnea. There is a lack of consensus in the optimal anesthesia protocols for DISE and the scoring system to define abnormality.
- 3D cone beam computed tomography (CBCT) is preferred to diagnose airway obstruction over standard CT due to its low radiation dose. Using CBCT, Hsu *et al*. demonstrated that airway volume and cross-sectional area of the nasopharynx is smaller in children with moderate-severe OSA. It is not ready for clinical practice.

Treatment

- Both surgical and non-surgical interventions.
- A trial of leukotriene inhibitors (montelukast) may be appropriate for pediatric patients with mild to moderate OSA as it may decrease adenotonsillar size significantly after three months of treatment, leading to a decrease in AHI in appropriate patients.
- Intranasal steroid for six weeks improves AHI for mild to moderate OSA.
- The combination of intranasal steroids and leukotriene inhibitors, leads to clinically significant decrease in AHI in most patients.
- Systemic glucocorticoids are not effective in the treatment of pediatric OSA.

Treatment

- **Adenotonsillectomy (A&T).** Which is recommended for most patients with an AHI > 9 events/hour and those with mild or moderate disease with significant symptoms.
- **Partial tonsillectomy** is also an option that decreases both postoperative complications and recovery time, but it has been shown that tonsillar regrowth rates are between 7.2% to 16.6%.
- **Lingual tonsillectomy** and uvulopalatopharyngoplasty, have limited data and shown to be non-superior.

Complications

- Surgical intervention is not benign and should be carefully considered.
- A&T surgical risks/complications are:

- localized pain, decreased oral intake, dehydration, bleeding, secondary infection, respiratory compromise, velopharyngeal insufficiency, and subglottic stenosis. Also, during surgery bronchospasm or laryngospasm.

- The increased degree of severity of OSA is predictive of a higher rate of post-surgical complications, and those with more severe OSA may require longer monitoring in the PACU or inpatient ward after surgery.

Treatment

- **Watchful Waiting**" for up to six months can be appropriate for mild to moderate OSA to correct underlying problems, like obesity or allergic rhinitis.
- **Continuous positive airway pressure (CPAP).** PAP should be considered during the perioperative phase before A&T for severe OSA, if the child is not a good surgical candidate or has persistent moderate to severe OSA despite surgery.
- Compliance can be difficult for children, and the use of the same mask over time has the potential to change the facial structure.

Treatment

- **Oral appliances (OAs)** have been shown to decrease AHI in adults, there have not been enough studies on pediatric populations to know their efficacies or which patients might benefit from these. Changing OAs to accommodate a child's growth would also require frequent refitting.
- **Rapid maxillary expansion** is a potential option for prepubertal patients and may be especially useful for those with high arched palates and non-obese patients with residual OSA after A&T.
- **Myofunctional therapy** is a new area of study in the treatment of both pediatric and adult OSA. This consists of retraining the muscles of the oral cavity and oropharyngeal structures, as well as proper tongue positioning. There is limited data about efficacy in children, with only small studies on pediatric patients with OSA.
- **Weight loss:** can improve OSA if obesity is a concern
- **Limit exposure to second-hand smoke** and tobacco use in the house.

CPAP Adherence

- <50% of the children were consistently using CPAP for >4 h.
- High adherence: likely those using CPAP after AT, and those with lower BMI, high levels of obstructive events and higher pressures.
- Least adherent: likely those without developmental delay or with highest BMI.
- A large cross-sectional analysis of those on PAP therapy within a single insurance company in the USA also showed poor compliance. Only 46.3% of 20533 subjects used PAP for ≥4 h on 70% of nights in a 30-day period in the first 90 days of treatment.
- Patient engagement programs were associated positively with adherence.
- CPAP therapy is clearly not as user friendly as we would like!

Technological advances in PAP therapy

- They now record data on respiratory indices during use.
- A recent study sought to examine the accuracy of these data by comparing them to the data obtained during overnight PSG. They found that the device indices tended to underestimate the degree of residual obstruction and therefore could not be relied upon to guide adjustments in treatment.
- Deliver a constant tidal or minute volume by adjusting the delivered pressure within set parameters in response to measurements of the patient's breathing.
- In a study of 19 children with hypoventilation, average volume-assured pressure support (AVAPS) was shown to be superior to conventional BiPAP in control of P_{tcCO2} parameters .
- In a study of adolescents, an autotitrating CPAP mode was shown to derive very similar pressures to those recommended following in-laboratory PSG testing .

Alternative To PAP Therapy

- Two recent small studies examined the potential for use of high flow nasal cannula (HFNC) therapy in infants and young children with OSA.
- KWOK *et al*. found it was possible to improve oxygenation and significantly reduce obstruction with HFNC in infants, when using PSG to guide titration.
- IGNATIUK *et al*. studied 22 young children. They successfully titrated HFNC settings in all subjects, with 19 proceeding to home use. However, of those with 12-month follow-up, nearly half discontinued due to intolerance of the therapy, suggesting that HFNC has similar challenges with adherence.

Corrective Surgery

- Children with SDB due to craniofacial abnormalities may benefit from corrective surgery. For those with abnormalities affecting the lower face, external mandibular distraction is a technique that has been the focus of recent research.
- This intervention's effects on PSG were described in 31 neonates with Pierre Robin sequence pre-operatively (mean age 13 days) and post-operatively (mean age 80 days). While there was a significant reduction in obstructive events and improvements in sleep efficiency and oxygenation, 15 of the 31 continued to have severe obstruction with ≥10 events/hour.

Down Syndrome (DS)

- In DS children, inhaled corticosteroids, montelukast and CPAP are not that effective.
- Alternative surgical techniques have included tongue-base reduction, lingual tonsillectomy, revision adenoidectomy, epiglottopexy, supraglottoplasty, inferior turbinate reduction, uvulopalatopharyngoplasty, midline posterior glossectomy and genioglossus advancement. But there was insufficient evidence for any of these therapies, weight management was considered important.
- Hypoglossal nerve stimulation showed some promise as a safe and effective therapy for OSA in 20 non-obese DS children with severe OSA and failed CPAP after AT.
- Hypoglossal nerve stimulation resulted in a median 85% reduction in AH. Assessment of neurocognitive scores and behavior before and 6.5 months after surgery in nine DS individuals (mean age 15 years) showed clinically significant improvements in all.

Prader-Willi syndrome (PWS)

- Patients with PWS have a high rate of SDB and this can be aggravated by initiation of growth hormone therapy. One study of 112 PWS children assessed before and after starting growth hormone therapy at a median age of 1.9 years (range 0.1–13.5 years) found that 13% developed worsening OSA needing medical intervention after initiation. Thus, these children need assessment after starting growth hormone

- Although a recent longitudinal study of 62 PWS children found that starting growth hormone early (<12 months of age) did not result in more OSA. In this study, severity of OSA lessened in both younger and older children with time, perhaps reflecting another age-related effect on OSA scores.

- PWS children may be helped by AT, with a meta-analysis of seven studies finding a mean post-operative improvement in AHI of 7.7 events per hour. It is important to recognize that the most common complication of AT (in 14%) was velopharyngeal insufficiency.

Beckwith-Wiedemann Syndrome

- A small study of tongue reduction surgery for macroglossia in 36 patients with Beckwith–Wiedemann syndrome (age 7 days to 51.3 months) evaluated the effect on OSA in a subset of 12 patients with both pre- and post-operative PSG. Post-operative PSG showed a significant reduction in AHI *versus* pre-operative PSG, from 30.9±21.8 to 10.0±18.3 events/hour. However, it should be noted that residual AHI remained high, and patients would be likely to require further OSA treatment.

Sickle Cell Disease

- OSA is an important complication in sickle cell disease and has been found to be associated with neurological complications and acute chest syndrome in a review of 203 705 hospital discharges.

- Treatment with noninvasive ventilation may influence the risk of these complications.

Patient/Family Education

- Parents should be educated at well-child checks to be vigilant about signs and symptoms of pediatric OSA, including loud nightly snoring, frequent nighttime awakenings, secondary nocturnal enuresis, and behavioral changes in their children.

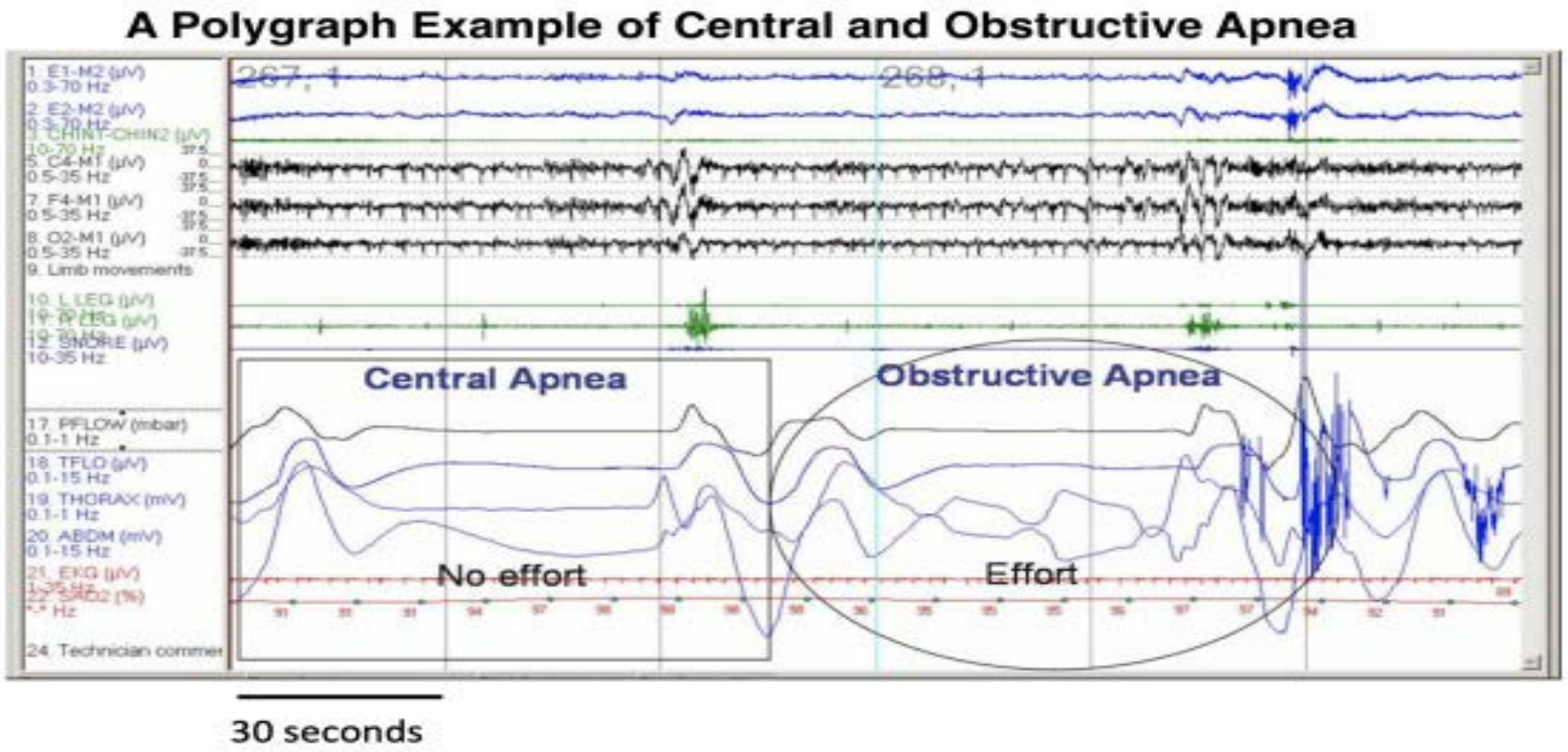
- Parents of overweight and obese children should be educated about the consequences of obesity and the increased risk of pediatric OSA.

- Providers must recognize the importance of education regarding sleep issues to facilitate discussions with caregivers and specialists when there is evidence of pediatric OSA

Pearls

- Adenotonsillectomy is the first-line therapy for children and adolescents with obstructive sleep apnea in the context of adenotonsillar hypertrophy.
- In-laboratory sleep studies remain the gold standard for the diagnosis of sleep-disordered breathing in patients younger than 18 years.
- Coordination between the primary care provider, sleep study center, sleep physician, anesthesiologist, surgical team, and caregivers will provide the best outcome.

Central and Obstructive Apnea, Polygraph. The image depicts an example of central and obstructive apnea. Rana AM, Sankari A. Central Sleep Apnea.
[Updated 2023 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK578199/
Contributed by A Sankari, MD



Central sleep apnea

- In children, a CSA is defined as a reduction in airflow of at least 90% without respiratory efforts, lasting at least 20 s, or more than two baseline respiratory cycles associated with an at least 3% reduction in oxygen saturation (SpO_2) and/or an arousal and/or an episode of bradycardia in infants.
- A central apnea index (CAI) ≤ 1 event per hour is widely considered as normal, whereas CAI ≥ 5 events per hour is currently proposed as a pathological threshold.
- CSA affects less than 5% of healthy children. CSA occurs mainly in children with underlying medical conditions, such as Chiari malformation, with only a few studies reporting CSA in children outside this context.

Central Sleep Apnea

- In newborns and infants, CSA is often related to immaturity or dysmaturity of the brain's respiratory control, and apnea of prematurity is a common indication for sleep consultation in the NICU.
- The relationship of immature control of breathing to BRUEs (brief, resolved, unexplained events, formerly "ALTE") and sudden infant death syndrome remains unclear.
- Apart from the relatively common idiopathic and transient causes of CSA in very young children, rare causes of CSA that must be excluded include congenital central hypoventilation syndrome (CCHS) and brainstem abnormalities such as Chiari malformation.

Central sleep apnea in otherwise healthy term Infant

Hayashi A, Suresh S, Kevat A, Robinson J, Kapur N. Central sleep apnea in otherwise healthy term infants. J Clin Sleep Med. 2022 Dec 1;18(12):2813-2817. doi: 10.5664/jcsm.10228. PMID: 35962944; PMCID: PMC9713904.

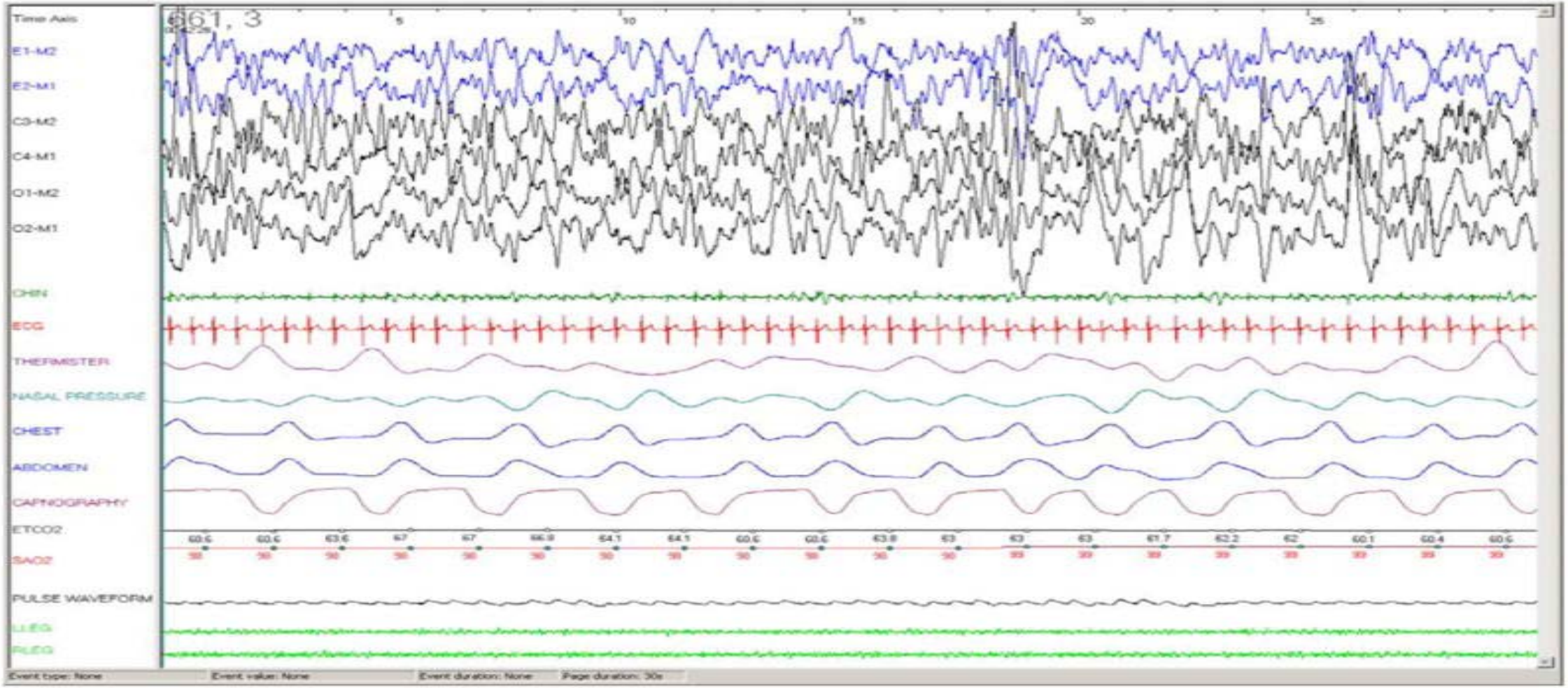
- A recent study showed that central sleep-disordered breathing in healthy term infants, remains poorly understood and its outcomes not well reported.
- 52 term infants with PSG-proven CSA severe enough to warrant supplemental oxygenation, excellent overall outcomes was reported with successful cessation of oxygen therapy in almost all cases within 1 year of use. Investigations including neuroimaging, cardiac imaging, and metabolic screen, were normal and did not contribute to change in management.
- Oxygen therapy greatly reduced the frequency of central events and improved oxygen saturation parameters on PSG, without a significant difference emerging in $TcCO_2$ level-related parameters.

Central apnea

- A recent single-center cohort study of 95 children (aged ≥1 month, mean±SD age 3.7±4.5 years) with CAI ≥5 events/hour at a tertiary sleep clinic found only one case in a child without any comorbidities. In their cohort, CAI ≥5 events/hour was associated with Chiari I malformation, complex syndromes including Down syndrome, Prader Willi Syndrome and Beckwith–Wiedemann syndrome, neuromuscular conditions, Pierre Robin sequence, encephalopathy and epilepsy syndromes.
- A co-existent significant obstructive element (OAHI ≥5 events per hour) was noted in 39% of patients.
- A variety of treatments were used depending on underlying cause and comorbidities, including supplemental oxygen, ventilatory support, neurosurgery, caffeine and acetazolamide. The vast majority of patients showed improvement in CAI at follow-up, including the 23% managed expectantly. Obstructive parameters did not show a similar improvement.

30 second epoch from a polysomnography recording in a 7-month-old girl with **meningomyelocele with Arnold Chiari malformation and central hypoventilation**. Note excellent CO2 waveform and good expiratory plateau.

Beck SE, Marcus CL. PEDIATRIC POLYSOMNOGRAPHY. Sleep Med Clin. 2009 Sep;4(3):393-406. doi: 10.1016/j.jsmc.2009.04.007. PMID: 20161110; PMCID: PMC2739664.



Congenital Central Hypoventilation Syndrome

- Congenital central hypoventilation syndrome (CCHS) is a rare condition characterized by alveolar hypoventilation secondary to impaired central respiratory control and reduced response to hypoxemia and hypercapnia.

- Typically, do not experience dyspnea or increase their respiratory rate to compensate.

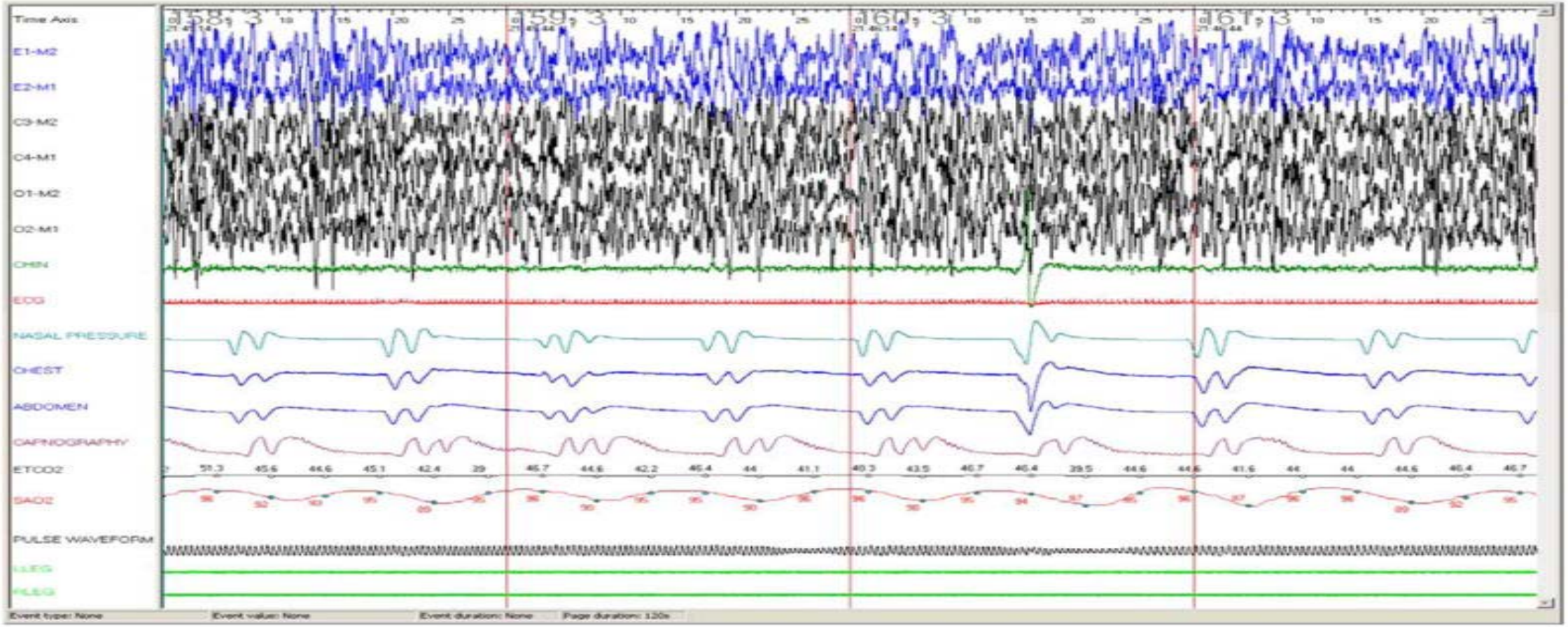
- Most often is caused by PHOX2B gene.

History

- A history of pauses in breathing while asleep is a frequent presenting concern for parents with young infants.
- Irregular breathing patterns are the rule rather than the exception in the first several months of life. Specifically, periodic breathing (PB) which is a particular breathing pattern that is defined by the presence of at least three episodes of central pauses lasting for at least 3 s interspersed by less than 20 s of normal breathing.
- PB may be physiological in preterm infants, due to the immaturity of the breathing centers, but it may also be a pathological finding.

60 second epoch PSG recording in a 4-month-old infant with periodic breathing showing pathological periodic breathing, with characteristic repeated short central apneas and desaturations. Note also high amplitude delta waves, typically seen in infants.

Beck SE, Marcus CL. PEDIATRIC POLYSOMNOGRAPHY. Sleep Med Clin. 2009 Sep;4(3):393-406. doi: 10.1016/j.jsmc.2009.04.007. PMID: 20161110; PMCID: PMC2739664.



Central Sleep Apnea

- Cheyne–Stokes breathing (CSB), which is characterized by a prolonged crescendo–decrescendo pattern of respiration, followed by a central event, either apnea or hypopnea.
- CSB occurs mainly in adult patients with congestive heart failure (CHF), and is much less frequent among children, even in children with CHF.
- CSB can be exceptionally observed in children with associated diseases and heart defects.
- Sleep bradypnea may also be observed in children, but its description and pathophysiological significance is limited by the lack of well-defined normal values of respiratory rate of children during sleep.

Cheyne-Stokes Breathing

Singh J, Zaballa K, Kok H, Fitzgerald N, Uy C, Nuth D, Castro C, Irving C, Waters K, Fitzgerald DA. Cheyne-stokes respiration in children with heart failure. Paediatr Respir Rev. 2022 Sep;43:78-84. doi: 10.1016/j.prrv.2022.03.001. Epub 2022 Mar 8. PMID: 35459626.

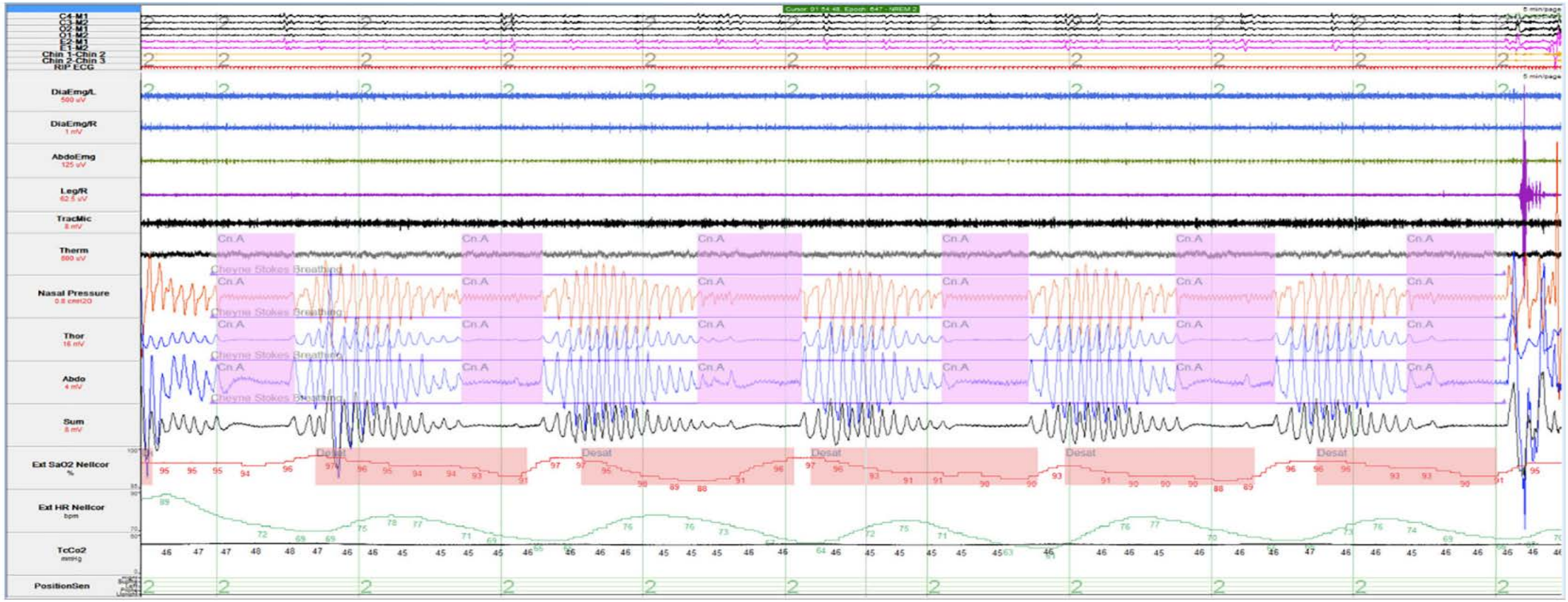


Fig. 1a. Diagnostic component of the polysomnographic data represented in the 5-minute epoch during stage 2 of sleep.

Physical Examination

- In infants with suspected CSA: Assessment of the infant's tone.

- In older children with suspected CSA:

-Exam to exclude intracranial or brainstem abnormalities, which may be physically impinging on the centers of respiratory control in the medulla and pons.

-A basic fundal examination for papilledema.

Diagnosis

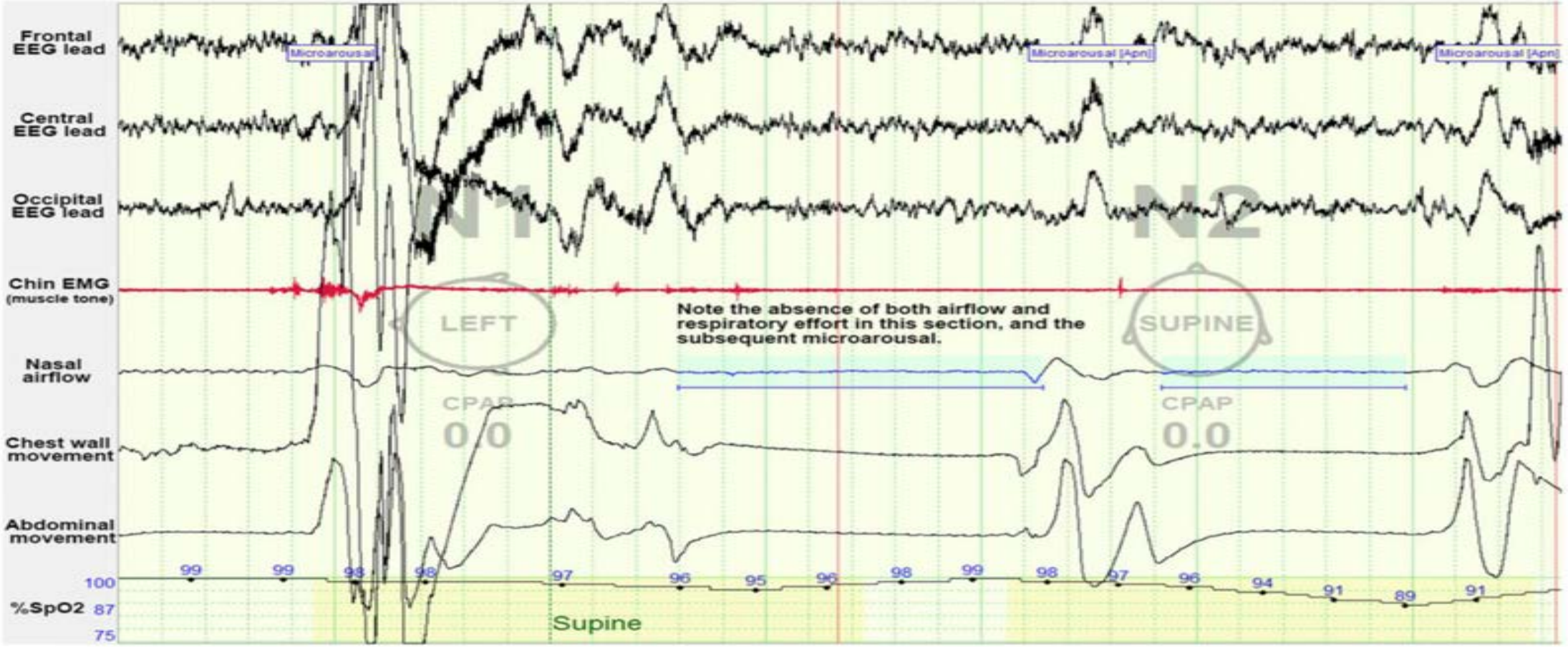
- A PSG
- Rett syndrome is associated with CSA.
- Patients with congenital central hypoventilation syndrome typically present in infancy and may demonstrate absence of respiratory distress despite hypoxemia and hypercapnia during cyanotic episodes (milder forms present later in life).

PSG findings

- In children, CSA is formally defined as the reduction of airflow by 90% or more for at least 20 seconds; for 2 breath cycles if associated with an arousal, a 3% or greater decrease in arterial oxygen saturation, or a decrease in heart rate to less than 50 beats/min for at least 5 seconds; or a heart rate less than 60 beats/min for 15 seconds in infants.
- The hallmark of CSA is that there is no respiratory effort during these events.
- Although not standard practice, a CO_2 stimulation challenge may be useful in differentiating atypical periodic breathing or otherwise idiopathic central apneas in young infants from the intractable chemosensory dysfunction seen in CCHS.

Central Sleep Apnea

Gipson K, Lu M, Kinane TB. Sleep-Disordered Breathing in Children. Pediatr Rev. 2019 Jan;40(1):3-13. doi: 10.1542/pir.2018-0142. Erratum in: Pediatr Rev. 2019 May;40(5):261. doi: 10.1542/pir.405261. PMID: 30600274; PMCID: PMC6557418.



Laboratory Tests and Imaging

- In infants in the first few months after birth with classical periodic breathing or brief episodes of irregular breathing pattern without abnormal neurologic examination findings, no further evaluation may be needed.

- Premature infants with signs of especially persistent or frequent episodes of apnea of prematurity may benefit from assessment of serum partial pressure of carbon dioxide with a blood gas test.

- In patients with severe and refractory CSA in the neonatal period, CCHS should be excluded by genetic testing for *PHOX2B* mutation.

- In older children with CSA of unknown cause, MRI of the head and neck is an important imaging modality for excluding Chiari malformation and other brainstem issues.

Management

- **Apnea of prematurity**: Caffeine therapy
- **Idiopathic CSA**: Carbonic anhydrase inhibitor acetazolamide, which increases respiratory drive by shifting the partial pressure of CO_2 threshold.
- Even in the absence of overt nocturnal hypoxemia, supplemental oxygen works in some patients by stabilizing or reducing the responsiveness of the peripheral chemoreceptors; however, significant sleep fragmentation often persists in patients treated with oxygen alone.
- **Refractory CSA or CCHS**: Nocturnal PAP, generally Bi-level with a backup respiratory rate or an assist-control ventilator mode.
- **Chiari I malformation:** Neurosurgical evaluation for consideration of surgical decompression.

Neurodevelopmental Consequences of Sleep Disordered Breathing

- SDB in children is associated with behavioral, cognitive, academic and emotional difficulties. It is unclear whether these effects are purely due to sleep disruption, or other factors like hypoxia.
- MRI identified Lower cortical thickness and lower tissue volume is seen in certain areas of both grey and white matter in children with OSA.
- Diffusion tensor imaging (DTI) MRI shows lower white matter integrity in children with severe *versus* mild OSA.
- Functional MRI shows differences in activity in certain brain regions in children with OSA compared to healthy controls.
- The changes noted on MRI correlate with worse scores on neurocognitive testing, suggesting that OSA might be the underlying cause of these neurobehavioral changes.

Are Neurodevelopmental Consequences of Childhood OSA Reversible with treatment?

- It is unclear! Two recent studies suggest that neurobehavioral effects may be less modifiable than hoped.
- WATERS *et al*. randomized children with mild OSA to early adenotonsillectomy (AT) (within 2 months) or delayed AT (after a cognitive assessment at 12 months). Both groups showed improvements in cognitive scores at 12 months; there was no treatment-attributable improvement in the AT group *versus* the delayed AT group.
- LUSHINGTON *et al*. studied children with OSA treated with AT. Despite improvements in sleep, quality of life and polysomnography (PSG) indices at 6 months and 4 years after treatment, there were no significant improvements in behavior *versus* controls.

Neurobehavioral Morbidity In Children With Mild SDB

- Yu et al. conducted a study and compared baseline characteristics of 861 children recruited into two randomized controlled trials, the Pediatric Adenotonsillectomy Trial for Snoring (apnea-hypopnea index < 3) and the Childhood Adenotonsillectomy Trial (apnea-hypopnea index 2–30). Among symptomatic children who were adenotonsillectomy candidates, there were more abnormalities in executive function, inattention, and hyperactivity in the cohort with lower apnea-hypopnea levels (milder group).
- Snoring children without frequent apneas may still be at risk for deficits in executive function and attention, which suggests that snoring is a behavioral risk factor for neurobehavioral morbidity.

Cardiac Consequences of Sleep Disordered Breathing

- The heart may also be affected by childhood OSA, with both ventricular dysfunction and remodeling seen. These changes are typically subclinical but could provide some of the mechanism for cardiovascular morbidity seen in later life.

- Recent evidence suggests that diastolic dysfunction may normalize after AT, but structural changes persist despite treatment.

- Further research is required to understand whether diagnosing and treating OSA early in life reduces the risk of permanent cardiac remodeling.

Cardiac Consequences of Sleep Disordered Breathing

Childhood OSA is associated with adverse changes to blood pressure (BP) profile, and these changes may persist into adulthood.

BROOKS *et al*. found that children with moderate-severe OSA had higher rates of systolic hypertension than healthy controls. Systolic BP (SBP) and diastolic BP correlate with apnea–hypopnea index (AHI).

A recent 10-year follow-up study showed that childhood OSA has long-term effects on BP parameters that last into adulthood, independent of whether the OSA itself persists.

Cardiac Consequences of Sleep Disordered Breathing

- In comparison to healthy controls, those with moderate-severe OSA 10 years earlier (obstructive AHI (OAHI) of ≥5 events/hour on PSG) had higher night-time SBP, reduced nocturnal SBP dipping, higher mean arterial pressure (MAP), and reduced night-time MAP dipping at follow-up (age 16–25 years).

- BP is normally lower during sleep than wake states, known as “night-time dipping”. Loss of this normal night-time BP reduction is a precursor to the development of overt hypertension and is a risk factor for adverse cardiovascular outcomes.

- There is now good evidence of reduced night-time dipping in childhood OSA .

Underlying Mechanisms For Cardiovascular Changes

- OSA is associated with a pro-inflammatory state, with raised cytokines.
- Erythropoietin has been suggested as a potential biomarker candidate for pediatric OSA.
- In a study of 115 children (mean age 6.8 years), 86 children with OSA had significantly higher serum erythropoietin levels compared to non-OSA children (29 children), their levels correlating with AHI.
- Elevated sympathetic drive caused by frequent arousals and intermittent hypoxia. Some studies show higher catecholamine levels in OSA *versus* healthy controls, but others show no effect.

Modifiability of cardiovascular effects

- It is unclear whether adverse cardiovascular changes can be improved by treating OSA.
- A small study of 12 adolescent subjects with obesity and OSA treated with CPAP for 12 months showed improvements in heart rate and heart rate variability that would be associated with reduction in cardiovascular risk, despite body mass index (BMI) z-score remaining stable.
- A recent meta-analysis concluded that, overall, clinic and ambulatory BP showed no statistically significant changes after treatment with AT. However, subgroup analysis of patients with pre-existing hypertension showed significant improvements in overall BP parameters.
- These improvements were more marked at night, with restoration of night-time dipping.
- Residual OSA after AT is also common (approximately 50% in the studies analyzed). Analysis of outcomes for only those whose OSA was successfully treated might demonstrate a stronger beneficial effect.

Obstructive Sleep Apnea and Mental Health Disorder in Pediatric Population

- In a large retrospective population-based study by Kendzerska et al. of children who underwent PSG for sleep disorder assessment, OSA diagnosis/treatment was associated with an improvement in some mental health indicators, such as fewer new mental healthcare encounters compared with no OSA and lower odds of mental health care encounters compared with before OSA treatment.

Clinical Pearls

- Childhood SDB can have a long-term impact on cardiovascular health, brain structure and function.
- Due to the adverse consequences of sleep apnea, it is important not only to proceed with early diagnosis but also to implement adequate treatment that is guided by the pathophysiological determinants of the disease in each child.
- Pulse oximetry may be a screening tool but does not replace PSG in diagnosing OSA.
- Adherence limits use of positive airway pressure in children with OSA
- Clinicians should consider assessing neurobehavioral function in children with mild sleep-disordered breathing who snore to detect potential deficits in executive function and attention.

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