Sleep-Related Breathing Disorders

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Introduction

Sleep-related breathing disorders (SRBDs) are common and affect children of all ages. The presentation of these disorders varies from relatively benign snoring to airway obstruction and hypercarbia. SRBDs are divided into four broad classifications that include obstructive sleep apnea (OSA), central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia. Children diagnosed with any of these conditions experience abnormal respiration that is either centrally mediated or caused by upper airway obstruction.

In patients with neurodevelopmental disabilities (NDDs), reported prevalences of SRBDs range from 20% to 79% (Table 6.1) [1–6]. If left untreated, these disorders can result in both systemic and cognitive deficits that may exacerbate baseline deficits. In an effort to avoid this clinical scenario and facilitate an accurate and timely diagnosis, we will present an overview that lays the foundation for this broad, and often complex, topic.

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Establishing a Diagnosis

History

Clinical History

The pediatric office visit offers an excellent opportunity to identify patients with an SRBD. With this in mind, the American Academy of Pediatrics Guideline recommends universal screening for snoring in all children [7]. If snoring is present, the guideline suggests that a detailed sleep history should be performed, focusing on witnessed snoring and apnea events, the sleep environment, and associated sleep problems. Parents of children with an SRBD may report disturbed sleep, gasping, and witnessed apneas. The absence of witnessed apneas does not, however, preclude an SRBD, and as many as one-third of children with CSA have no history of witnessed apneas, desaturations, or abnormal breathing [8].

Parents should be questioned about sleep duration, including typical time to bed and wake times, sleep habits such as bedtime routines, and the setting in which children sleep (e.g., whether they share a room or a bed and whether a television is present) in order to identify modifiable patterns and behaviors. They should also be queried about parasomnias such as night terrors, nightmares, sleepwalking, and enuresis. Secondary enuresis, in particular, has been strongly linked to OSA. In a study by Brooks et al. [9], 47% of children with a respiratory disturbance index (RDI) >1 reported enuresis compared to 17% of children with normal sleep studies ($P = <0.05$).

It is also important to screen for daytime behaviors, including hyperactivity, inattention, and sleepiness. A recent meta-analysis reported that symptoms associated with attention-deficit/hyperactivity disorder (ADHD) are significantly associated with primary snoring and OSA [3]. In light of these findings, the presence of ADHD symptoms should

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Table 6.1 The prevalence of obstructive sleep apnea or sleep-disordered breathing in conditions associated with neurodevelopmental delay

Condition	Prevalence	Criteria
Cleft palate [1]	22%	Sleep-disordered breathing
Angelman syndrome [2]	30%	Obstructive sleep apnea
ADHD [3]	25–35%	Obstructive sleep apnea
Cerebral palsy [4]	58–67%	Sleep-disordered breathing
Down syndrome [5]	30–50%	Obstructive sleep apnea
Prader-Willi syndrome [6]	80%	Obstructive sleep apnea

prompt detailed questioning regarding SRBD symptoms. Overall, daytime sleepiness is less common in children than in adults; however, excessive sleepiness is frequently reported in children with Prader-Willi syndrome (PWS), cerebral palsy (CP), and Down syndrome (DS) [10–12]. Children with OSA and obstructive hypoventilation syndrome are more likely to complain of daytime sleepiness than children with central apnea events. There are, however, a myriad of causes for daytime sleepiness that are unrelated to SRBDs, the most common being poor sleep hygiene. The possibility of hypothyroidism should be considered in complicated medical patients with sleep complaints. Thyroid dysfunction is more common in children with ADHD (5.4%) and PWS (20–30%) than in typical children [13, 14] and is even more common in patients with DS; 40% of all children with this syndrome have abnormal thyroid studies, and 7% present with overt clinical hypothyroidism [15].

Standardized Questionnaires

Efforts to quantify the signs and symptoms of SRBDs have led to the development of a number of sleep questionnaires. However, these questionnaires are limited by their variable sensitivity and focus only on sleep-disordered breathing (SDB). The Pediatric Sleep Questionnaire (PSQ) is widely accepted and thought to have the best ability to predict the presence or absence of OSA. Although this questionnaire has excellent sensitivity (83%) and specificity (87%), it was validated only in healthy children [16]. In a recent study [17] in which the PSQ was used to study children with craniofacial deformities, the majority of patients were syndromic (54.7%), and Pierre Robin sequence was the most common diagnosis. Authors reported a 28% prevalence of likely OSA overall, with rates above 50% in patients with facial cleft and Treacher-Collins and Apert syndromes. Formal validation of this tool, however, has not been carried out for children with NDD and would be problematic given that questions regarding attention would be hard to answer for these children.

The Children's Sleep Habits Questionnaire (CSHQ) has been shown to have a sensitivity and specificity of >70% for SDB in otherwise healthy elementary school children [18]. However, Shott et al. [19], utilizing a questionnaire based on the CSHQ, reported a sensitivity of only 23% and a specificity of 61%.

The OSA-18 has been developed to measure SDB quality of life and was validated in otherwise healthy children [20, 21]. It was subsequently validated in children with syndromic craniosynostosis after being translated into Dutch and was found to be reliable and valid [22].

Elsayed and colleagues [11] used components of several different validated surveys to evaluate 100 children with CP. Symptoms of SDB were identified in 44% of the study population, with school-age children more commonly affected than younger children. It is, however, important to acknowledge the limitations of sleep questionnaires. Few surveys have been used specifically for the evaluation of children with an NDD. In addition, results may be confounded in children with NDD by the behavioral components of the questionnaires. Future study and validation is required prior to widespread implementation.

Physical Exam

General Exam

The physical evaluation should begin with observation of general behavior and sleepiness. Children with obesity hypoventilation syndrome (OHS) in particular may fall asleep easily and appear to be somnolent. Evaluation of body mass index (BMI) is important, as children with obesity are four to six times more likely to have OSA than non-obese children [23]. In children with DS, BMI is associated with an increased risk of OSA, even after adjusting for age and sex [24]. However, the association between obesity and SRBDs may not always be as straightforward. In children with PWS, researchers have demonstrated a lack of association between an elevated apnea-hypopnea index (AHI) and obesity [25].

Head and Neck Examination

A thorough head and neck examination should be considered, as should an evaluation of voice and speech. These evaluations should include as assessment of hyponasality, which may be associated with a lack of nasal airflow due to obstruction at the nose or nasopharynx (e.g., adenoid hypertrophy). The presence of retrognathia and/or micrognathia should be noted, especially for children with other craniofacial issues, as these conditions are more common in children with upper airway obstruction [26]. Midface and maxillary hypoplasias are features of children with DS, Crouzon syndrome, and Angelman syndrome.

The oral cavity and oropharyngeal exams should include an evaluation of dentition, dental occlusion, tongue, palate, and tonsil size and position. Brodsky et al. [27] popularized

a four-point grading system for tonsil size. Using this scale, grade 0 tonsils are surgically absent, grade 1 are located within the tonsillar pillars, grade 2 extend just beyond the tonsillar pillars, grade 3 extend >50% toward the midline, and grade 4 make contact at the midline. This grading system has been shown to have both acceptable inter-observer and intra-observer reproducibility [28]. Relative macroglossia, a condition in which a patient has a normal-sized tongue in a small oral cavity, is common in children with DS. This finding is frequently seen in combination with hypotonia and glossoptosis in children with significant upper airway collapse [29]. The palate should also be evaluated for any evidence of midline defects; these include overt clefts of the hard and soft palate, soft palate submucosal clefting, and the presence of a bifid uvula. Also, dental occlusion should be evaluated using Angle's classification of malocclusion. This classification system defines occlusion as class I (normal), class II (overbite), and class III (underbite). In a small series, class II and III malocclusion significantly correlated with OSA on polysomnography (PSG) [30].

A thorough nasal examination should include evaluation of the nasal mucosa and structures. Signs of mucosal edema or inflammation may indicate a concurrent diagnosis of allergic rhinitis. These findings should be further investigated, as a 2013 systematic review reported a significant association between allergic rhinitis and SDB [31]. Anterior rhinoscopy may also demonstrate other causes of obstruction such as inferior turbinate hypertrophy (Fig. 6.1), septal deviation, or nasal polyps.

Endoscopy

For children in whom nasal pathology is assumed to be a primary issue, nasal endoscopy may be considered; this allows for the detection of posterior septal deviations, visualization of the maxillary sinuses and osteomeatal complexes, and identification of nasal masses, obstruction, or polyps.

More commonly, flexible laryngoscopy is utilized to visualize the entire upper airway, including the nasal cavity, adenoids, oropharynx, pharyngeal walls, base of tongue, lingual tonsils, hypopharynx, supraglottis, and glottis. In young infants, the endoscopic exam should be used to evaluate for nasal obstruction from pyriform aperture stenosis or choanal atresia. Visualization of the adenoid pad is easily performed, well tolerated even in young children, and well correlated with nasal obstruction [32]. For children with NDD, the likelihood of glossoptosis and lingual tonsil hypertrophy is increased. Lingual tonsil hypertrophy is frequently seen in children with DS, children who have undergone previous adenotonsillectomy (T&A), and children with obesity [29, 33].

Laryngomalacia is also well visualized with flexible endoscopy. It is characterized by dynamic supraglottic collapse secondary to shortened aryepiglottic folds and redundant arytenoid mucosa (Fig. 6.2). It is common in children with DS, affecting up to 50% of these children [34]. There should also be a high index of suspicion for laryngomalacia in patients with CP who present with upper airway obstruction [35]. Moreover, it has been reported that the generalized hypotonia seen in children with CP may result in later and more severe presentation of laryngomalacia [36].

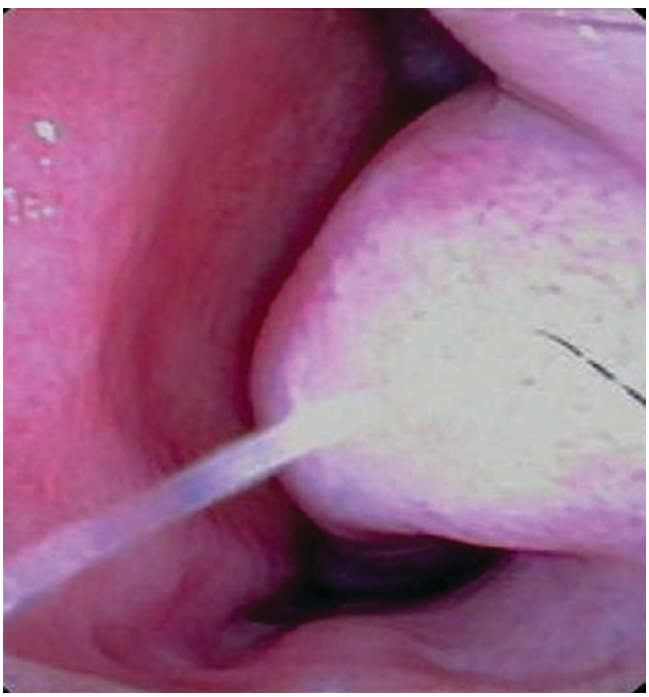

Fig. 6.1 Inferior turbinate hypertrophy

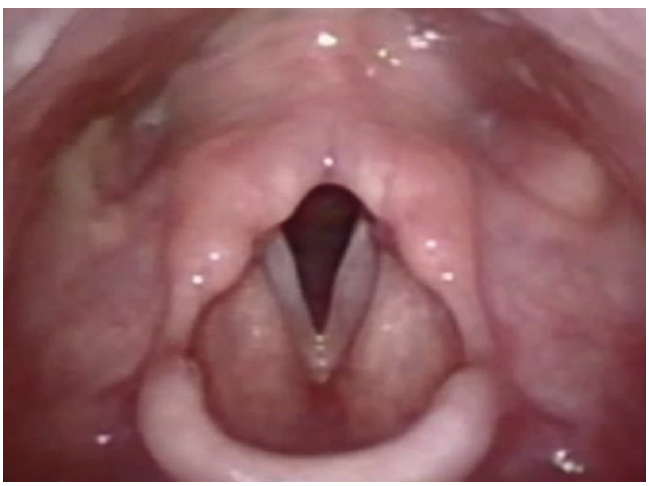

Fig. 6.2 Laryngomalacia with shortened aryepiglottic folds and redundant arytenoid mucosa

Diagnostic Studies

Laboratory Studies

Laboratory studies are generally not required in the workup of SRBDs, except for children with OHS. These children should undergo an arterial blood gas study to confirm daytime hypercapnia. Blood gas studies may also demonstrate a compensatory respiratory acidosis and hypoxemia [37]. They should also undergo a complete blood count to identify possible polycythemia associated with chronic hypoxemia, as well as thyroid function tests to rule out severe hypothyroidism, which can result in alveolar hypoventilation [38].

Imaging

For children with OSA, lateral neck X-rays have been utilized to evaluate adenoid size. A 2011 systematic review supported the utility of lateral films in children [39]. However, there has been a concerted effort to reduce the radiation exposure of children secondary to imaging studies. In a study by Pearce et al., CT scans were associated with a small but real risk of leukemia and brain cancer [40]. Although the radiation dose from a neck film is notably lower than the dose from a CT scan, these findings highlight the need to limit unnecessary studies. As a result it is currently recommended that lateral neck films be reserved for children who cannot tolerate flexible nasal endoscopy [41]. For infants in whom pyriform aperture stenosis or choanal atresia is suspected, CT imaging without contrast is usually obtained.

Children with idiopathic CSA should undergo imaging of the brain (generally MRI) to rule out a neurologic source for their CSA. A 2011 study [8] of 25 children with primary CSA found that the diagnostic yield of MRIs exceeded 50%.

Sleep cine magnetic resonance imaging (cine MRI) is a useful imaging technique to evaluate children with OSA after T&A. This modality allows for high-resolution examination of the upper airway during drug-induced sleep (Fig. 6.3). Images are collected over a 2-minute period and combined to create a real-time movie that demonstrates airway dynamics. One advantage of the study is that it allows multiple overlapping areas of obstruction to be evaluated simultaneously [42]. This study is typically employed in the 33% of patients who have persistent OSA following T&A [43, 44]. Cine MRI has been employed to successfully identify areas of obstruction in children with DS [45]. The limitations of this modality are that it does not identify obstruction well in the nasal passages or the larynx and that cost and availability are major concerns.

Drug-Induced Sleep Endoscopy

Since the 1990s, drug-induced sleep endoscopy (DISE) has also been used to identify areas of airway obstruction, predominantly in children with OSA on PSG after T&A or in children in whom tonsils and adenoids are small and considered nonobstructive. DISE allows for dynamic examination of the airway during sleep from the nares to the trachea, and it has been shown to be valid and reliable in both adults and children [46–49]. This procedure involves performing flexible fiber-optic examination of the airway while patients receive anesthetic agents to induce sleep (Fig. 6.4).

This procedure is useful for children with a high likelihood of persistent OSA after T&A, such as those with DS, in whom 30–50% reportedly develop persistent or recurrent OSA following T&A [29]. The hypotonia and anatomic abnormalities associated with other NDDs are also likely to contribute to a persistent OSA after surgery.

Polysomnography

In-laboratory PSG is the gold standard for the diagnosis of OSA in children and has been demonstrated to have acceptable test-retest reliability in children [50, 51]. The American Academy of Pediatrics (AAP), the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), and the American Academy of Sleep Medicine (AASM) recommend PSG prior to operative intervention in high-risk patients such as children with obesity, DS, PWS, craniofacial abnormalities, and neuromuscular disease [7, 52, 53]. These guidelines also emphasize the need for repeat postoperative evaluation and PSG in children with a high risk for persistent SRBDs after treatment, as is common in children with NDDs. PSG involves the simultaneous monitoring and recording of multiple physiologic parameters, including electroencephalography, electrooculography, and electromyography (EMG) [54]. Airflow is also monitored via nasal pressure transducer, thermistor, and/or end-tidal capnograph, to determine when respiration has been interrupted [54]. Additional monitoring devices include pulse oximetry, electrocardiography, and surface limb electromyography (EMG) monitoring. Monitors are also placed on the patient's abdomen and chest to detect respiratory effort, allowing for the differentiation between central and obstructive apneas.

The ideal pediatric PSG setting should be child-friendly, with pediatric waiting rooms and age-appropriate beds. It is also essential that accommodations be available for parents [54]. Technicians should be aware that children with NDD may require a significant amount of parental comforting or intervention by child-life specialists in order to optimize the study. Staffing may also be increased for children with NDDs, especially those with behavioral issues.

In children, an apnea is defined as two or more consecutive breathing cycles without airflow [55]. Hypopneas are defined as a reduction in airflow of ≥30% associated with either an arousal or an oxygen desaturation ≥3% [55]

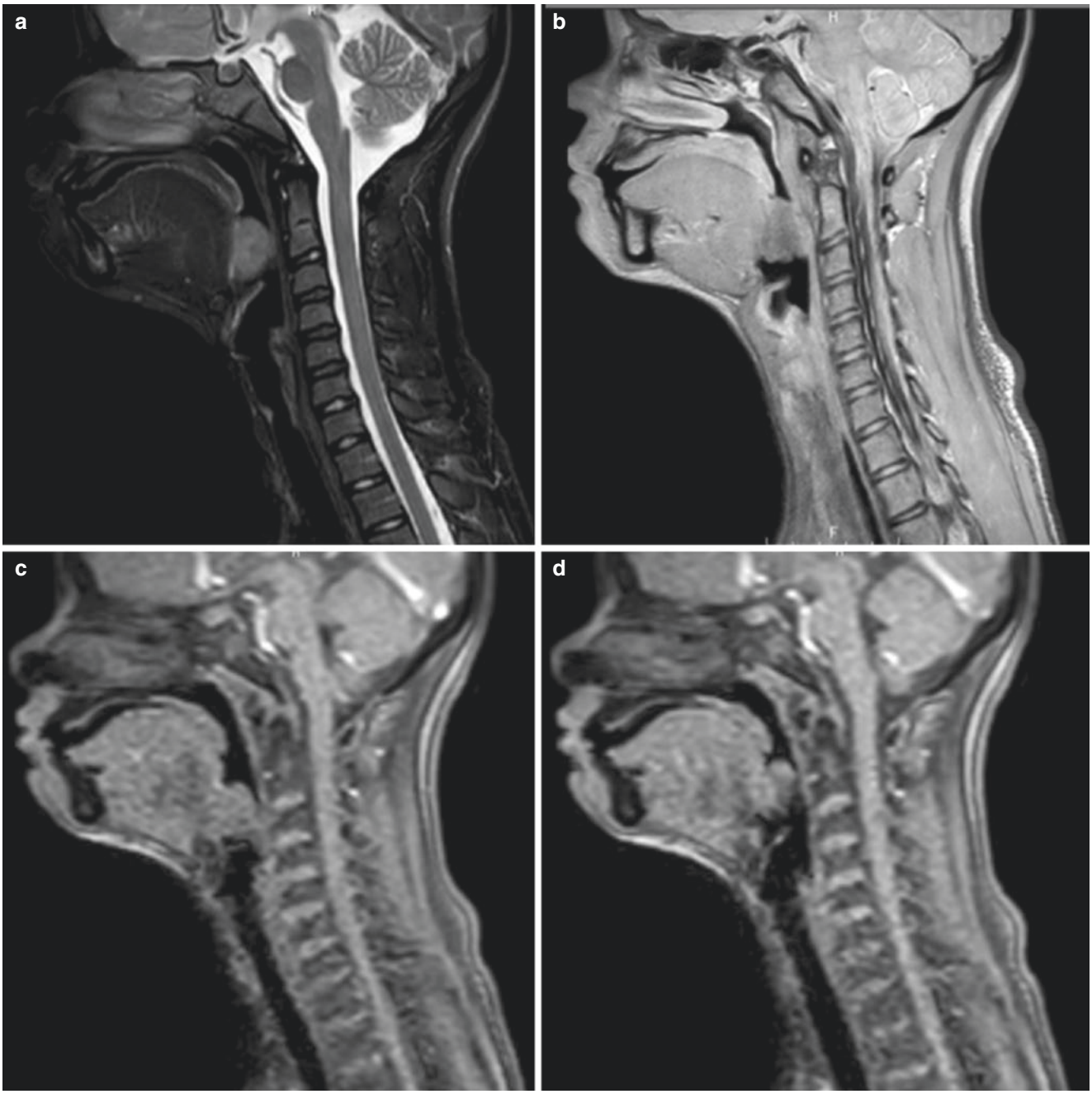

Fig. 6.3 Sagittal cine MRI of the upper airway. This MRI demonstrates lingual tonsillar hypertrophy in both T2 (**a**) and T1 images (**b**). It also demonstrates dynamic obstruction from lingual tonsils during inspiration (**c**) and expiration (**d**)

(Table 6.2). Apneas and hypopneas are further characterized as central or obstructive, based on the absence or presence of respiratory effort. Apneas and hypopneas are tabulated as events per hour and reported as indices, including the apnea-hypopnea index (AHI), obstructive apnea-hypopnea index (oAHI), and central apnea index (CAI) (Table 6.3) [55]. Based upon normative data, an obstructive AHI >1 is considered abnormal [7, 56]. The severity of OSA is subsequently categorized as mild when the obstructive AHI >1 and <5, moderate OSA when the obstructive AHI ≥5 and <10, and severe OSA when the obstructive AHI ≥10. CSA is diagnosed when the central apnea-hypopnea index is ≥5 events/

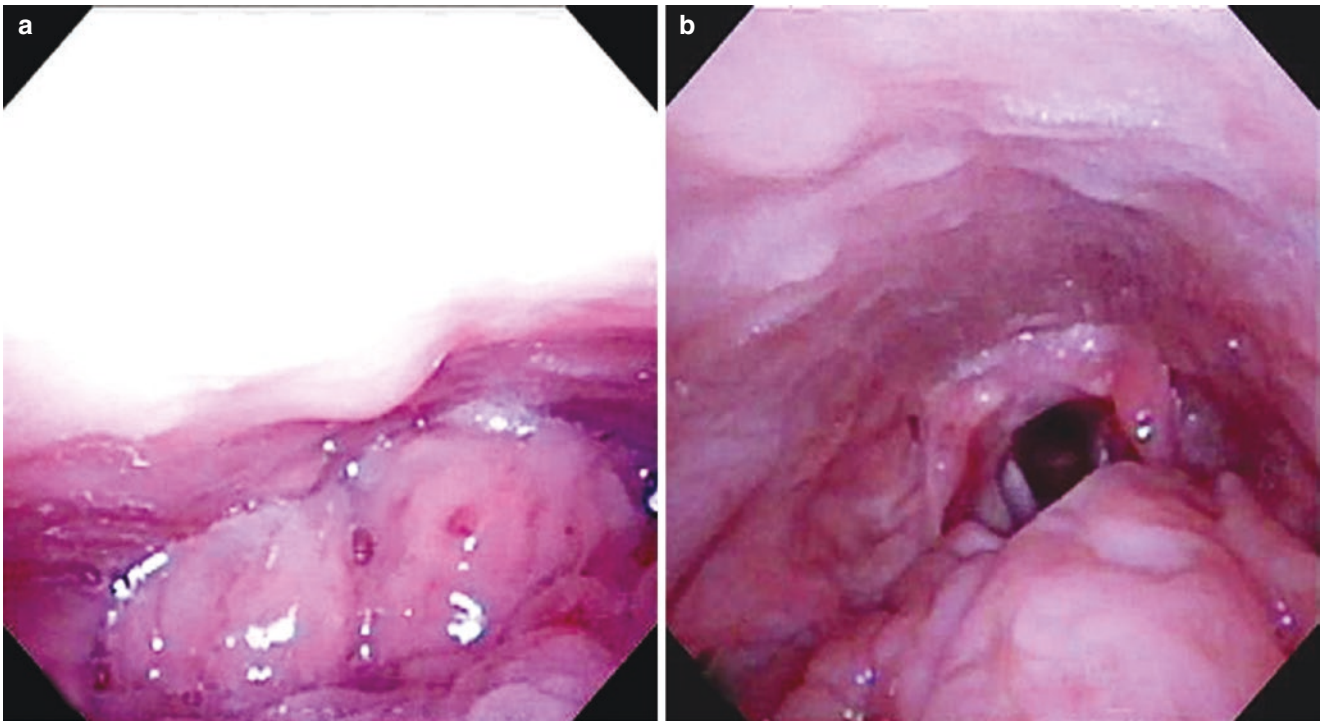

Fig. 6.4 This is a hypopharyngeal image taken during drug-induced sleep endoscopy. Image (**a**) demonstrates complete airway obstruction by the lingual tonsils, while (**b**) demonstrates persistent airway obstruction at the level of the lingual tonsils despite jaw-thrust maneuver

Table 6.2 Definitions of common terms used to describe respiratory events seen in sleep-related breathing disorders (SRBDs) [55]

Term	Definition
Obstructive apnea	Absence of airflow for 2 breaths associated with the presence of respiratory effort
Hypopnea	A reduction in airflow of ≥30% along with either an arousal or an oxygen desaturation ≥3% from the baseline
Central apnea	Absence of airflow without respiratory effort for 2 breaths in addition to:
	For children >1 year old: duration >20 s *or* an arousal *or* ≥3% oxygen desaturation
	For children <1 year old: decrease in heart rate to <50 beats per minute for at least 5 s *or* decrease in heart rate to <60 beats per minute for 15 s
Hypoventilation	25% of the total sleep time is spent with pCO2 >50 mm Hg
Respiratory effort	An arousal that is associated with increased respiratory effort, snoring, and related arousals increased pCO2 for the duration of two breaths

Hg mercury, *pCO2* partial pressure of carbon dioxide

Table 6.3 Definitions of common terms used to describe polysomnography parameters [55]

Term	Definition
Apnea-hypopnea index (AHI)	The number of apneas and hypopneas per hour of sleep averaged over the total sleep time
Obstructive apnea-hypopnea index (oAHI)	The number of obstructive apneas and hypopneas per hour of sleep averaged over the total sleep time
Central apnea index (CAI)	The number of central apneas per hour of sleep over total sleep time
Respiratory distress index (RDI)	The number of apneas, hypopneas, and RERAs per hour of sleep averaged over total sleep time
Oxygen desaturation index (ODI)	The number of arterial oxygen desaturations/hour (typically >3–4%)

hour. Some labs score respiratory effort-related arousals (RERAs). A RERA is defined as an arousal that is associated with increased respiratory effort, snoring, and increased peripheral arterial carbon dioxide ($PaCO_2$) for the duration of two or more breaths (Table 6.2). RERAs per hour are frequently added to the AHI and reported as the respiratory distress index (RDI) (Table 6.3).

Oxygen desaturations, defined as a decrease of 3% or 4%, are also tabulated and may be reported as the oxygen desaturation index (ODI) (Table 6.3). Standard PSG studies also report the percentage of sleep when CO_2 levels are >50 mm Hg. Hypoventilation is diagnosed in children when CO_2 levels are >50 mm Hg for >25% of the total sleep time [55].

Obstructive Sleep Apnea

Case Vignette #1

History: The parents of an 8-year-old girl with DS reported that their child had mild snoring but no history of apnea. They noted some increase in disruptive behavior at school and the recent onset of nocturnal enuresis.

Diagnostic workup: Physical examination revealed obesity, macroglossia, and tonsillar hypertrophy. PSG was performed, revealing an AHI of 18, with an obstructive AHI of 16.5 events/hour.

Treatment: The patient underwent T&A, with resolution of symptoms. Postoperative PSG revealed persistent OSA, with an AHI of eight events/hour and an obstructive AHI of 7.5 events/hour.

Key Points

History

- All children should be screened for snoring in conformity with AAP recommendations.
- Secondary enuresis is more common in patients with OSA than in healthy children.

Diagnostic Workup

- Obesity increases this child's risk of OSA and hypoventilation.
- Neither clinical history nor questionnaires are sufficient to differentiate snoring from sleep apnea. PSG is the gold standard for diagnosis.

Treatment

- T&A is first-line therapy for OSA.
- This patient is at increased risk of persistent OSA and should also undergo postoperative PSG.

Additional diagnostic procedures (DISE, cine MRI) may be necessary to determine further treatment options for this child. OSA is reported to occur in 2–4% of children and is defined as a complete or partial upper airway obstruction during sleep with respiratory effort. The diagnostic criteria for pediatric OSA from the AASM require (1) the presence of snoring or (2) labored, paradoxical, or obstructed breathing during sleep or (3) sleepiness, hyperactivity, behavioral problems, or learning problems during the day [57] In addition to having one of these symptoms, the patient must have a PSG that demonstrates either one or more obstructive apneas, mixed apneas, or hypopneas or a pattern of obstructive hypoventilation for at least 25% of sleep time. This pattern of obstructive hypoventilation must be associated with hypercapnia (partial pressure of CO_2 in arterial blood >50 mm Hg and with either snoring, flattened inspiratory nasal pressure, or paradoxical thoracoabdominal motion). Risk factors for this disorder include a history of prematurity, male sex, obesity, and NDDs [53, 55, 56, 58–60]. Studies of children with NDDs have found that OSA is diagnosed in greater than 50% of those with DS, PWS, and craniofacial syndromes such as Goldenhar, Apert, and Crouzon syndromes and Pierre Robin sequence [6, 17, 61]. However, authors of these studies also note that these prevalence numbers are likely underestimated because of inconsistent evaluation and screening of affected children. Pijpers and colleagues [62] reported that when children with syndromal craniofacial synostosis were screened for OSA, the number of children recognized to have OSA doubled from 26% to 53%. Persistent OSA is also common in children with craniofacial anomalies, obesity, and CP [63, 64].

For children with untreated OSA, there is concern for both cardiovascular and neurocognitive sequelae. The consequences of hypertension in particular may be long lasting, with pediatric hypertension increasing the likelihood of elevated blood pressure and metabolic syndrome in adulthood [65]. Children with OSA are also at an increased risk of psychosocial problems, including poor socialization, poor school performance, and aggressive behavior [66]. In children with DS, OSA has been linked to a reduction in verbal IQ score and disruptive school behavior [67, 68]. Moreover, OSA disease severity in these children has been linked to diminished visuoperceptual skills such as spatial orientation [69]. With increased OSA severity, psychosocial problems associated with OSA may also worsen. Research has shown that in children with PWS, increased OSA severity is associated with increased daytime inactivity and autism-related behavior [10].

Management

T&A is first-line therapy for children with OSA and is effective in 66% of patients [43]. Given that children with NDDs are deemed high-risk surgical candidates, the AAP and the AAO-HNS recommend hospital admission after T&A as well as follow-up to evaluate for possible persistent disease. Incomplete resolution of OSA is more common in children with NDD, especially for those with DS, PWS, and craniofacial abnormalities [67, 70, 71].

For children with persistent or recurrent OSA after T&A, a number of medical and surgical options exist. Continuous positive airway pressure (CPAP), medications, weight loss, and surgery are all treatment options, and the selection of the appropriate option depends on the site of obstruction and the degree of OSA. Nasal CPAP has been approved for use in children since 2006. This therapy can be effective; however, finding an appropriately sized mask is difficult in children with craniofacial issues or in those who are small, as few masks are made specifically for children. Additionally, research indicates that CPAP adherence is often suboptimal, with one multicenter study [72] reporting that usage in a setting with standardized support was only 3.8 h per evening. Moreover, even when CPAP is tolerated, there is concern that prolonged CPAP usage may contribute to long-term craniofacial changes [73].

The use of medications for the treatment of OSA may be effective in children with mild or low moderate disease severity. A 6-week course of nasal steroids has been shown to reduce the AHI by an average of 4.9 events/hour in children with OSA and adenotonsillar hypertrophy [74]. Similarly, oral montelukast has been shown to reduce the AHI by 1.8 events/hour after 12 weeks of use [75]. A large retrospective study [76] of 752 children, with mild OSA, reported an 80% response rate to a combined intranasal corticosteroids and oral montelukast. For the 445 children who underwent PSG before and after surgery, the reduction in the obstructive AHI was 3.1 events/hour. Resolution of OSA was seen in 62% of children.

Weight loss should also be considered and is strongly advocated for overweight and obese children. Medical weight loss programs are first-line therapy in this regard. Increasingly, however, bariatric surgery is being performed in adolescents with severe OSA. Although outcomes in children are limited, bariatric surgery has been shown to result in significant improvement in OSA severity in adults [77].

Further surgery may be considered for children with persistent OSA following T&A, especially if they are not good candidates for CPAP due to nocturnal seizures, drooling, or other safety concerns. It typically addresses obstruction at the base of the tongue, the palate, or both and often requires that cine MRI or DISE be carried out to determine the site of obstruction. For children with DS or obesity, lingual tonsillar enlargement has been identified as a common site of obstruction after T&A [33, 45]. For infants with laryngomalacia or older children with sleep-state-dependent laryngomalacia, supraglottoplasty should be considered. A systematic review of supraglottoplasty outcomes (after T&A) reported OSA resolution rates of 58–72% [78]. Durvasula et al. [79] evaluated supraglottoplasty outcomes in children with NDDs and syndromic children and found that 67% had resolution of OSA after surgery; however, in children with CP, surgical failure was more common.

Central Sleep Apnea Syndromes

Case Vignette #2

History: The parents of a 3-month-old male reported a history of PWS and stridor, but no history of apnea or acute life-threatening events.

Diagnostic workup: Physical examination revealed global hypotonia and audible inspiratory stridor with mild retractions. The rest of the physical examination was unremarkable. Tonsils were small (1+).

PSG was performed and showed an obstructive AHI of nine events/hour with a CAI of eight events/hour.

Treatment: The patient was started on 1/8 L of oxygen. Repeat PSG showed a residual CAI of 2.5 events/hour.

Key Points

History

- Children with PWS are at increased risk of CSA.

Diagnostic Workup

- The patient required PSG to determine the type (central versus obstructive) and severity of apnea prior to intervention.

Treatment

- Oxygen therapy has been demonstrated to be effective in children with PWS and CSA.
- A single study reported that patients with OSA and CSA may have improvement in both conditions with treatments traditionally used for OSA, such as adenotonsillectomy or supraglottoplasty.

CSA is defined as a reduction or cessation of breathing without associated respiratory effort. This may manifest as an apnea with ≥90% reduction in airflow or as a hypopnea where there is a 30 to <90% reduction in airflow. Except in infants or young children, central events should be associated with one or more of the following symptoms: sleepiness, difficulty falling or staying asleep, awakening short of breath, snoring, or witnessed apneas. Overall, CSA occurs in approximately 5% of children undergoing PSG [8]. The *International Classification of Sleep Disorders* has delin-

eated nine subgroups of CSA syndromes. Those that are most commonly seen in children include primary CSA, CSA of prematurity, primary CSA of infancy, and CSA caused by a medical disorder (Table 6.4). Each of these CSA syndromes is described below.

Primary Central Sleep Apnea

Primary CSA is idiopathic CSA that meets the general criteria for CSA and is not associated with Cheyne-Stokes breathing. In cases in which there are central and obstructive apneas, >50% of these apneas must be central events in order to be classified as CSA.

Management

In patients with primary CSA, effective supportive therapies include supplemental oxygen and CPAP [80–82]. Baldassari and colleagues reviewed the effect of T&A on 101 children with both OSA and CSA. Following T&A, children experienced a significant reduction in both obstructive and central apnea events; 90% of children with mild CSA (defined as a CAI >1 and <5) had complete resolution of the disease [83].

Primary Central Sleep Apnea of Prematurity

Primary CSA of prematurity is defined as central apnea demonstrated on PSG in an infant <37 weeks' conceptional age at the time that symptoms are first noted and are not explained by associated sleep, medical, or neurologic conditions. The diagnostic criteria require that an apneic or cyanotic episode be observed or that a sleep-related central apnea, desaturation, or bradycardic episode be detected using hospital monitoring. In addition, monitoring (including, but not limited to PSG) must demonstrate recurrent central apneas >20 seconds or periodic breathing for ≥5% of total sleep time. Immaturity of the respiratory control system is considered to be the primary reason for primary CSA of prematurity, and the prevalence of this condition is related to gestational age and birth weight [84]. It is diagnosed in nearly all infants born at <29 weeks or with a birth weight of <1000 g, 54% of infants born at 30–31 weeks, 15% of infants born at 32–33 weeks, and 7% of infants born at 34–35 weeks [84]. This condition typically resolves by 36–40 weeks' conceptional age [85]. Literature describing the relationship of this disorder to subsequent development is scant. A review of 19 infants with post-hemorrhagic hydrocephalus found that 26% had central apneas [86]. A study of 60 premature infants with observed CSA reported that 27 (45%) were confirmed to have CSA on PSG; the majority of these children had perinatal asphyxia or intraventricular hemorrhage [87].

Table 6.4 Sleep-related breathing disorders divided by category as delineated in the *International Classification of Sleep Disorders* of the American Academy of Sleep Medicine (3rd Edition) [57]

Sleep-related breathing disorders	Categories
Obstructive sleep apnea disorders	Obstructive sleep apnea, adult
	Obstructive sleep apnea, pediatric
Central sleep apnea syndrome	Central sleep apnea with Cheyne-Stokes breathing
	Central apnea due to a medical disorder without Cheyne-Stokes breathing
	Central apnea due to high-altitude periodic breathing
	Central 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
Sleep-related hypoventilation disorder	Obesity hypoventilation syndrome (OHS)
	Congenital central alveolar hypoventilation syndrome
	Late-onset central hypoventilation with hypothalamic dysfunction
	Idiopathic central alveolar hypoventilation
	Sleep-related hypoventilation due to a medication or substance
	Sleep-related hypoventilation due to a medical disorder
Sleep-related hypoxemia disorder	Sleep-related hypoxemia
Isolated symptoms and normal variants	Snoring
	Catathrenia (sleep-related groaning)

Primary Central Sleep Apnea of Infancy

The diagnostic criteria for primary CSA of infancy mirror the criteria for primary CSA of prematurity (defined above) except that the onset of symptoms occurs ≥37 weeks' conceptual age. As with primary CSA of prematurity, immaturity of the respiratory control system is considered to be the primary reason for this condition. Symptomatic CSA occurs in 0.5% of infants, whereas 2% of healthy asymptomatic full-term infants will have at least one observed central event [88]. Most children are diagnosed clinically, and the diagnosis is confirmed by overnight PSG and the exclusion of other sleep, medical, or neurologic disorders that may result in CSA. Older infants can present with an acute life-threatening event (ALTE), which prompts evaluation. Prolonged apnea events will cease for some children by 43 weeks' conceptional age [88], but for others, these events may take several years to resolve. The presence of laryngomalacia in infants should also raise concern for possible CSA. In a study by Tanphaichitr and colleagues, infants with laryngomalacia were found to have a CSA prevalence of 46.3%. In this study, children with underlying neurologic disease, hypotonia, or a syndrome were 2.5 times more likely to have CSA than otherwise healthy children; however, this finding did not reach the level of statistical significance (Odds ratio = 2.5, $P = 0.13$) [89].

Central Sleep Apnea Due to a Medical Disorder

CSA is frequently identified in children with neurologic diseases or deficits. For example, 68% of children with a Chiari II malformation are diagnosed with CSA [90]. CSA has also been reported in children with PWS and epilepsy disorders. For children with PWS, CSA is more common in infancy (43%) than in children older than 2 years of age (5%) [91]. CSA has also been reported in patients with Rett syndrome and may occur with apneas while awake [92]. D'orsi et al. [93] note that nocturnal CSA events may be mistaken for seizure activity in children with Rett syndrome.

Management

Full-term and premature infants with CSA are generally managed with supportive therapy. Depending on the severity of disease, interventions include observation, oxygen supplementation, and pharmacologic therapy. Observation may be employed when children have mild CSA and are in a monitored setting. Oxygen therapy may be utilized to support infants until CSA resolves. The utility of oxygen therapy for CSA in children with NDDs has only been demonstrated in PWS. In a study of 10 infants with PWS, Urquhart and colleagues reported a reduction in median CAI from 15.9 to 4.4 events/hour using supplemental oxygen [94]. Both caffeine and theophylline have been used as central nervous system stimulators in children with CSA. Currently, caffeine is preferred because of its longer lasting effect and safety profile [95].

Sleep-Related Hypoventilation Disorders

Sleep-related hypoventilation is characterized by decreased gas exchange and elevated levels of CO_2 (i.e., hypercapnia) during sleep or both during wakefulness and sleep in children with obesity hypoventilation syndrome. Hypoventilation during sleep is defined as >25% of total sleep time with the CO_2 level ˃50 mm Hg, whereas awake hypoventilation is defined as $PaCO_2$ >45 mm Hg. Clinicians should be aware of the increased risk of hypoventilation in children with severe OSA, obesity, or DS [96, 97].

There are six hypoventilation disorders delineated in the *International Classification of Sleep Disorders*: obesity hypoventilation syndrome (OHS), congenital central alveolar hypoventilation syndrome (CCAHS), sleep-related hypoventilation due to a medical disorder, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, and sleep-related hypoventilation due to medication or substance. Our discussion will be limited to OHS, CCAHS, and sleep-related hypoventilation due to a medical disorder.

Obesity Hypoventilation Syndrome

Children with OHS have hypoventilation when awake and asleep [98]. To meet the diagnostic criteria for this disorder, children must have an awake $PaCO_2$ >45 mm Hg as well as severe obesity, with a BMI >95th percentile and no additional reason for hypoventilation [99]. OHS is estimated to occur in 10–20% of obese adults, and 80–90% of patients with OHS have coexisting OSA [57]; however, OHS has been infrequently reported in children and has not been reported specifically in children with NDDs [100].

Congenital Central Alveolar Hypoventilation Syndrome

CCAHS, formerly known as Ondine's curse, is a rare genetic disorder characterized by failure of automatic central respiratory control during sleep that is associated with a *PHOX2B* gene mutation [101]. This condition has an estimated incidence between 1:10,000 and 1:200,000 live births, and only a few hundred cases have been reported worldwide [102, 103]. Children born with CCAHS are usually healthy-appearing infants with cyanosis or feeding difficulty. Occasionally, these children are undiagnosed until they have cardiovascular collapse. Associated autonomic abnormalities may also be noted, including

Hirschsprung disease and neural tumors such as neuroblastoma. Daytime hypoventilation may also be seen. Virtually all of these children require mechanical ventilation during sleep, and some will also require daytime mechanical ventilation [104]. Documentation of nocturnal hypoventilation and *PHOX2B* testing are required to establish a definitive diagnosis. This condition has been described in one patient with DS [105].

Sleep-Related Hypoventilation Due to a Medical Condition

In this disorder, sleep-related hypoventilation is present along with lung disease, cardiac disease, chest wall abnormalities, or a neuromuscular disorder. OHS and CCAHS must also have been ruled out. This condition manifests in children with Chiari malformation when hypoventilation is thought to result from brainstem herniation [106]. In children with PWS, neurologic deficits may result in pathologic hypoventilation.

Management

Children with OHS should all be screened for OSA. Although subsequent treatment is often multifaceted, it generally includes CPAP. Weight loss, either medical or surgical, is also important for these patients [107]. CCAHS is a lifelong medical condition. Nearly all children require positive-pressure ventilation via tracheostomy in infancy. As they age, nocturnal mechanical ventilation, bi-level positive airway pressure, and diaphragmatic pacing may be management options [108].

Sleep-Related Hypoxemia

Sleep-related hypoxemia is diagnosed when nocturnal arterial oxygen saturation levels are ≤90% for ≥5 min in children or ≤88% for ≥5 min in adults, without sleep-related hypoventilation. Although CSA or OSA can be present, sleep-related hypoxemia is diagnosed only if it is believed that neither of these disorders is the primary cause of the hypoxemia. This condition is thought to be secondary to neurologic or parenchymal lung disease. Sleep-related hypoxemia has been documented in children with PWS but may represent an underreported entity in other forms of NDD [109–111].

Management

Sleep-related hypoxemia is treated with nocturnal supplemental oxygen therapy. Evaluation of daytime oxygenation should be carried out in order to determine if daytime oxygen supplementation is also required. Treatment of the underlying pulmonary or neurologic disease may also improve this condition over time.

Snoring

Habitual snoring is reported by parents in 7.5% of children [59]. In patients referred for PSG, snoring (previously referred to as primary snoring) will be diagnosed in up to 40% of children [112]. In these patients audible snoring is appreciated during the study with an AHI <1. Patients with NDD appear to have similar prevalence rates, with primary snoring reported in 40% of children with ADHD and 29% of children with DS [112, 113]. Snoring is often considered a benign entity; however, multiple studies have demonstrated cognitive deficits in children with snoring compared to non-snoring controls [114, 115]. It should be noted that while children with habitual snoring scored lower than controls in these studies, the majority of scores remained within the normal range [116]. Children with habitual snoring have also been reported to have behavioral impairment, similar to that seen in children with OSA, when compared to controls [116, 117].

Management

There is no reliable way to distinguish primary snoring from OSA by history in children [118]. PSG is currently the only definitive way to rule out OSA and confirm a diagnosis of snoring. Presently, prospective research is required to evaluate possible treatment options to address the morbidity associated with primary snoring.

Conclusion

SRBDs are commonly seen in children with NDDs, and expeditious treatment requires a thorough diagnostic approach. The workup should include a detailed clinical history, a focused physical examination, and overnight PSG. Treatment options include surgical therapies, positive airway pressure, and oxygen supplementation. Because children with NDDs are at an increased risk of persistent and recurrent SRBDs following treatment, they require close ongoing follow-up to monitor disease resolution. Timely and appropriate management of SRBDs in children with NDDs is essential for minimizing associated morbidities.

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