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First Description and Consensus Definitions for Obstructive Sleep Apnea in Pediatrics

In 1976, Guilleminault and colleagues authored the first definitive report of pediatric obstructive sleep apnea (OSA), describing a series of eight children ranging in age from 5 to 14 years who had loud snoring, breathing pauses in sleep, daytime symptoms including sleepiness, altered school performance, daytime behavior, morning headache, abnormal weight, and progressive development of hypertension as well as enuresis, in association with polysomnographic evidence of respiratory abnormalities similar to those seen in adult OSA [1]. In these children, respiration was reported to be normal during wake, but in sleep, marked abnormalities were observed, including apneas, or cessation of breathing, dozens to hundreds of times on a single night, in association with greatly disturbed sleep, a reduction of slow wave sleep, and sinus arrhythmia [2]. These early publications helped initiate use of the term OSA "syndrome," or OSAS.

About 20 years later, the American Thoracic Society described pediatric obstructive sleep apnea syndrome as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupt normal ventilation during sleep and normal sleep patterns" [3]. The most recent definition of pediatric OSA from the American Academy of Sleep Medicine (AASM) includes the following parameters: the presence of snoring; labored, paradoxical, or obstructed breathing during sleep; and/or sleepiness, hyperactivity, behavioral problems, or learning problems; plus polysomnographic evidence of one or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep (i.e.,

an AHI $\geq$1), or a pattern of obstructive hypoventilation [4]. Obstructive hypoventilation is further given to be constituted by at least 25% of total sleep time with hypercapnia ($PaCO_2$ >50 mmHg (*N.B.* a surrogate noninvasive measure for arterial CO2 may be used per AASM Manual for Scoring of Sleep and Associated Events) in association with either snoring; flattening of the inspiratory nasal pressure waveform, a phenomenon known as "flow limitation" (Fig. 34.1), and/or paradoxical thoracoabdominal motion [4]. These criteria apply to those under the age of 18 years.

Within this definition, several types of abnormal respiratory events are relevant, with the essential underlying factor of each being increased upper airway resistance. These include the following:

- *Apneas*, defined as a drop in oronasal thermal airflow peak signal excursion by $\geq$90% of pre-event baseline. Obstructive apnea is scored for pediatrics if the event is at least two breaths in duration and associated with respiratory effort throughout the entire period; if respiratory effort is absent for part of this duration, a mixed apnea is scored [5].
- *Hypopneas*, defined as a peak signal excursion drop of at least 30% from pre-event baseline using the nasal pressure or alternate sensor, for at least 2 breaths; associated with either a $\geq$3% oxygen desaturation or an EEG arousal. Unlike apneas, hypopneas need not be subdivided into obstructive or central etiology, as it is not possible to definitely determine contributions from reduced central drive or increased airway resistance without a direct quantitative measure of effort (such as esophageal manometry). Nonetheless, obstructive hypopneas in particular are suggested by presence of snoring, inspiratory flow limitation, which is characterized by flattening of the nasal pressure inspiratory waveform, or induction of paradoxical thoracoabdominal movement associated with the event [5]. Regarding hypopneas in particular, studies evaluating OSAS in children must be taken in the context of the era in which they were conducted, as the definition for hypop-

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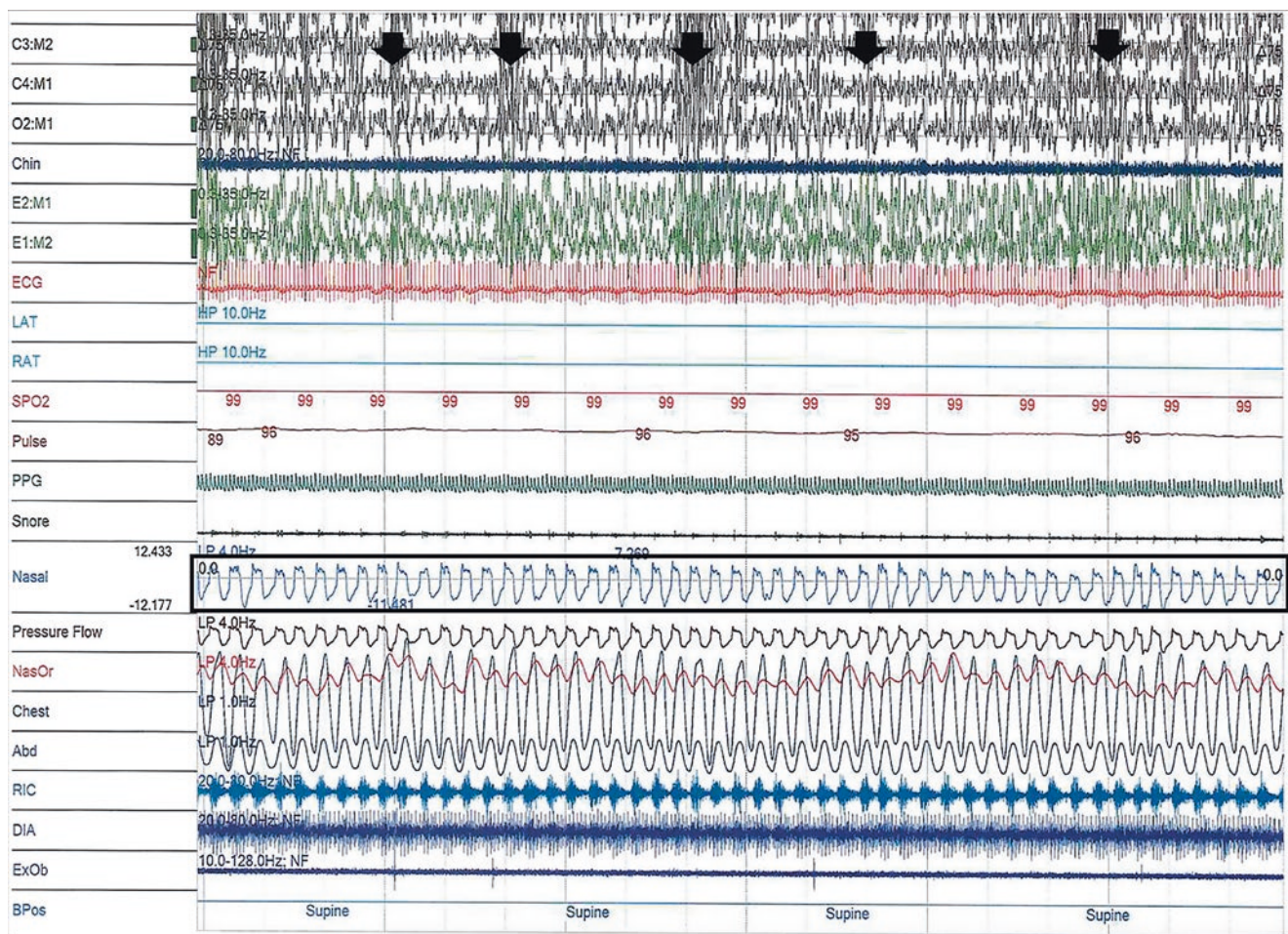Division of Sleep Medicine, Stanford University,
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Fig. 34.1 Nasal flow limitation in a 10-year-old symptomatic child. There is sustained flattening of the inspiratory portion of the nasal waveform. Snoring is absent. Arrows indicate cyclic alternating pattern. (From Guilleminault et al. [19]. Reprinted with permission from Elsevier)

nea has undergone several iterations in the last 20 years, leading to substantial diagnostic impact. For example, in 2007, the AASM made a key change in terms of scoring hypopneas, altering the threshold for reduction in airflow (30 vs. 50%), which resulted in overall lower OAHIs and putatively reduced OSA severity by approximately 24% of cases in one study, and up to fivefold in another study of 209 children [6, 7].

- *Respiratory effort-related arousals,* or *RERA*s, defined as a sequence of at least two breaths that do not meet criteria for apnea or hypopnea, but are characterized by increasing respiratory effort (classically measured quantitatively by esophageal manometry, as other measures of respiratory effort are not quantitative); inspiratory nasal flow limitation; snoring; of an elevated end-tidal PCO2 above pre-event baseline, in association with an EEG arousal. Inspiratory flow limitation in children with abnormal nocturnal breathing has been shown to be associated with increased respiratory driving pressure (i.e., respiratory effort, as measured by esophageal manometry) and there-

fore elevated upper airway resistance in both NREM and REM sleep [8]. In fact by 1982, it was already recognized that apneas and hypopneas were inadequate to define the syndrome of OSA seen in children, and defining breathing abnormalities using snoring and "sleep-related respiratory resistive load" had been proposed [9]. Still, even now RERAs are not included in the calculation of *apnea-hypopnea index* (AHI), which represents the average of apneas and hypopneas recorded hourly over a single night recording. The *Respiratory Disturbance Index* (RDI) is more broadly defined, and represents the average of apneas, hypopneas, and RERAs recorded hourly over a single night recording. The presence of RERAs per se, in the absence of overt hypopneas and apneas, and with or without snoring, may give rise to the entity of upper airway resistance syndrome (UARS), in which clinical symptoms of sleep disturbance are associated with increased effort, sleep disturbances, respiratory arrhythmia, altered heart rate variability with altered parasympathetic activity. UARS was described in children over 20

years ago and remains relevant for understanding the clinical manifestations of, and developmental evolution of, sleep breathing disorders [10–12].

More recently, then, it has been understood that OSAS should be defined in the broader context of a spectrum of sleep disturbances due to altered upper airway resistance and consequent altered respiration, known collectively as "sleep disordered breathing" (SDB), a term that more aptly reflects diverse presentations. This spectrum may involve habitual snoring, overt apneas and hypopneas, obstructive hypoventilation marked by alterations in surrogate measures of $PaCO_2$, or nonhypoxic increased respiratory effort associated with sleep fragmentation or autonomic nervous system alterations [13–16]. Increased respiratory effort is well-established as a way to measure to quantify the impact of increased airway resistance, but esophageal manometry, while insightful, is infrequently used in pediatric sleep laboratories, giving rise to interest in additional measures of impaired breathing in sleep.

Additional Elements of Sleep-Related Respiratory Disturbance Not in the Definitions

As noted above, apneas and hypopneas are now recognized to be an incomplete description of respiratory-related sleep disturbance. In 1985, Guilleminault and colleagues reported on 25 children who had daytime symptoms associated with sleep disturbance as well as heavy snoring. Polysomnography did not reveal OSAS or hypoxemia but did demonstrate increased respiratory resistive load during sleep associated with electrocardiographic R-R interval and esophageal pressure swings, with improvement on symptoms after upper airway surgery [9]. More recently, snoring severity itself has been found to correlate with poorer general behavioral and cognitive functional findings independent of AHI among a large cohort of community dwelling children [17].

More subtle but reliable and accessible measures of the breathing abnormalities associated with pediatric SDB exist. These include the presence of tachypnea, inspiratory nasal flow limitation measured by standard nasal pressure transducer; impairment of nasal breathing/habitual mouth breathing in sleep measured using a commercially available oral scoop, altered inspiratory-to-expiratory time ratio, accessory expiratory muscle activity measured by surface EMG, as nasal pressure transducer is an unreliable measure of expiratory flow limitation [13, 18, 19]. Whether these measures, which are generally available clinically in limited locations, can be extended into widespread practice and can be integrated into updates to the definition of pediatric sleep-disordered breathing remains to be seen.

Additionally, measures of sleep stability and fragmentation may also provide advances into defining the syndrome. The current definition of arousal from sleep, for example, is an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz for at least 3 seconds, with 10 seconds of stable sleep preceding the change [5]. Arousals described this way are the key element of defining SDB-related sleep fragmentation but may not be sensitive enough to capture important disturbance. Additional, potentially more telling, sleep microstructural changes, that is, cyclic alternating pattern (CAP) rate changes, have been described [20] in association with pediatric SDB, for example [13, 21]. Using more refined measures of the sleep encephalogram in addition to AHI may become more practical with the advent of newer technologies capable of detecting the phenomenon in a less labor intensive and more consistent manner.

Finally, the diagnosis of pediatric OSA currently requires access to a qualified pediatric sleep laboratory, which poses potential access and cost challenges. While history alone has been shown to be insufficient diagnostically, and even recently, an AASM position paper reinforced the inadequacy of home-based sleep testing for the diagnosis of sleep apnea in children, evaluation of home-based assessments of breathing and sleep, in conjunction with clinical evaluation and validated tools, have been reported and may alter the landscape of pediatric OSA definition in the future, especially in resource-limited areas [22–26].

A Look Forward: Challenges to Define Early Signals of Pediatric OSA

While these respiratory abnormalities correspond generally to events scored in OSA defined for adult populations, it should be emphasized that the sleep-disordered breathing in children differs markedly from the syndrome seen in adults, in epidemiology, underlying proximal contributing factors, clinical presentation and associations, polysomnographic and physiologic findings, and largely, in treatment. It has been argued that the spectrum of pediatric sleep breathing disorders represents the earliest manifestations of airway dysfunction that will blossom in adulthood to fully manifested OSAS, with the epidemic of obesity either hastening or initiating this process [15]. Furthermore, the risks for pediatric SDB have been argued to occur as early as in utero, gaining steam throughout early and middle childhood if not corrected [27, 28]. To the extent that this occurs, the manifestations of SDB are not static and unlikely to be defined by simple "events" described by the consensus scoring criteria and manuals, but rather a spectrum of dynamic challenges to the airway and craniofacial complex, autonomic nervous system, and sleep stability. The dynamic interplay of structure and function in pediatrics in particular has given rise to

the argument that notion of OSA defined by apneas and hypopneas, and even UARS, are historical, if not just incomplete, as there is already enough knowledge to grow beyond these definitions by recognizing manifestations of sleep respiratory challenges differently, with a focus on secondary prevention [29]. In recognition of these factors, inclusion of degree of nasal flow limitation, oral breathing in sleep, stertor, CAP frequency, and other measures may be utilized clinically in the future to better define the syndrome of sleep disturbance associated with abnormal breathing, especially in those children without associated hypoxia.

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