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REVIEW ARTICLE

Sleep apnea in infants

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Infancy is a developmental period characterized by instability of the control of breathing. Apneas of short duration are common, mostly central, and more frequent during rapid-eye-movement (REM) sleep. Obstructive apneas are rare in healthy control infants. Triggering factors such as respiratory syncitial virus infection can increase the frequency and the duration of apneas. Upper airway problems related to bone malformations, soft tissue infiltration, and neurologic lesions are responsible for obstructive apneas, but also for episodes of partial airway obstruction or upper airway resistance syndrome. In certain infants, an apparent-life-threatening event has been related to upper airway anomalies. Congenital central hypoventilation syndrome, a rare respiratory control disorder, may be presented by apneas. Polysomnography is the gold standard for the diagnosis of sleep-disordered-breathing in infants. Early diagnosis of abnormal breathing during sleep is of critical importance for the neurocognitive development in infants.

Key words: development, breathing, upper airways, polysomnography, congenital central hypoventilation syndrome, continuous positive airway pressure

Introduction

Instability of the breathing pattern is an inherent characteristic of the normal healthy infant during sleep. Occurrence of apneas of short duration is a physiological phenomenon that declines with advancing postnatal age. However, paediatricians have to be aware of triggering or predisposing factors that can suddenly turn a physiological phenomenon to a pathological one. Furthermore, apneas especially of the obstructive type may be related to upper airway problems that need to be treated. In some infants, upper airway problems may be responsible for apparent-life-threatening event or sudden infant death. Finally a rare respiratory control disorder, the congenital central hypoventilation syndrome, may be presented with apneas. Polysomnography should be performed as soon as the diagnosis of sleep-disordered-breathing in infants is suspected. Early diagnosis and treatment allows the protection of infants against poor growth, cardiorespiratory failure, or even sudden death. Furthermore, undiagnosed sleep-disordered-breathing disturbs sleep architecture and therefore the neurocognitive development of the infants.

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Infancy, a developmental period

The control of breathing during infancy undergoes dramatic changes with the maturation of neurophysiological, metabolic, and mechanical components of the respiratory system [1]. The profound influence of states of alertness on respiratory control has been the focus of intense scrutiny during the last decade. The effect of rapid-eye-movement (REM) sleep on various mechanisms involved in respiratory control are of particular importance during the postnatal period. In full-term newborns, REM sleep occupies more than 50% of total sleep time, and this percentage is even greater in preterm newborns [2].

From term to 6 months of age, the proportion of REM sleep decreases to approximately 25% of total sleep time. Respiratory instability in REM sleep is greater than in NREM sleep during the early period of life [3–5]. Potential mechanisms include the association of overall immaturity of the brain stem centers and phasic inhibitory-excitatory mechanisms inherent to REM sleep. Irregular phasic respiratory patterns of REM sleep occur in synchrony with other brain stem phasic activity, such as rapid eye movements [6]. Inhibitory mechanisms during REM sleep affect upper airway muscles. Upper airway muscle inhibition may make upper airway obstruction more likely to occur especially in infants with narrow upper airways. Ventilatory responses to chemical stimuli (hypoxia and hypercapnia) are lower in REM sleep than in NREM sleep [7–10]. Lower ventilatory responses to chemical stimuli in REM sleep may favor more frequent and longer apneas than in NREM sleep.

Many studies have documented the occurrence and duration of apnea during the first months or the first year of life in healthy control infants [11]. However, there was no uniformity among studies in regard to measuring conditions, including testing methods, duration of testing, identification of the type of apnea, central, mixed, and obstructive. Apneas of short duration (less than 10 s) are common during the early period of life. Apneas are more frequent in REM sleep than in NREM sleep. Apneas are mostly central (Table 1) [3,4]. The central apnea index (number of apneas per hour of total sleep time) decreases with advancing postnatal age (Table 1) [4]. Episodes of periodic breathing (defined as two central apneas shorter than 10 s occurring in less than 20 s) are observed in healthy control infants (Table 1) [4,12]. Mixed or obstructive apneas are rare in healthy control infants. Table 1 shows the combined mixed-obstructive apnea index reported 20 years ago by Guilleminault *et al.* [4].

Healthy control infants from 3 weeks to 6 months of age were tested during 24 h. It can be seen that, on average, the mixed-obstructive apnea index calculated as the sum of indices for mixed and obstructive apneas longer than 3 s was less than 1. However, a large variability is observed as indicated by the large standard deviation for all indices. The more recent study showed an increase in the mixed-obstructive apnea index between 3 and 6 weeks [12]. Three other more recent studies [13–15] including obstructive apnea counting gave values in the range of values reported by Guilleminault *et al.* [4]. Florez-Guevara *et al.* reported an obstructive apnea index of 0.56 between 2–3 months of age [13]. Hoppenbrouwers *et al.* found slighty higher values than Guilleminault *et al.* [4], however the methodology was not identical between both studies [15]. The recent experience of the collaborative home monitoring evaluation (CHIME) study group in North America is not yet available with regard to publication of obstructive apnea index in healthy control infants [16].

Table 1 Apnea index[a] in full-term infants

Age	>3–6 s			6–10 s			>10 s	
	C	M-O	PR	C	M-O	PR	C	M-O
3 weeks (10)[b]	6.97±2.44	0.31±0.18	7.43±7.05	2.87±0.45	0.24±0.26	3.69±5.08	0.73±0.72	0.07±0.09
6 weeks (10)	7.10±1.57	0.66±0.66	6.11±7.15	2.46±1.15	0.38±0.61	3.26±6.45	0.36±0.66	0.10±0.21
3 months (9)	6.08±2.28	0.28±0.46	3.43±1.08	2.18±1.49	0.13±0.13	0.93±0.58	0.16±0.19	0.02±0.05
4.5 months (10)	4.80±1.53	0.15±0.21	2.67±1.76	1.31±0.93	0.07±0.11	0.57±0.45	0.24±0.32	0.00±0.00
6 months (9)	4.77±1.35	0.17±0.24	4.16±2.96	2.34±0.93	0.03±0.05	1.01±0.65	0.25±0.30	0.00±0.00

C=central apnea (A); M=mixed apnea; O=obstructive apnea; PR=periodic breathing defined as two central apneas shorter than 10 s occurring in less than 20 s; [a] Index equals the number of respiratory events (apnea, periodic breathing, or both), divided by sleep time, multiplied by sleep time in hours; [b] Number of infants studied. From reference 4.

"Triggering" and predisposing factors for apneas in infants

A number of factors may suddenly "trigger" apneas in infants. Medications such as phenothiazine increase the number of apneas especially of the obstructive type [17]. Increase in body temperature enhances breathing instability especially during REM sleep with more periodic breathing episodes [18]. Short time sleep deprivation increases the number of short obstructive apneas [19]. In infants whose homeostasis is disturbed, the risk of increased respiratory instability appears to be greater in REM than in NREM sleep [17–19].

In infants, reflexes originating in the upper airways can induce apneas. The laryngeal chemoreflex has been shown to be enhanced by upper airway infection, and infection by the respiratory syncitial virus (RSV). RSV infection has been shown to be associated with central and obstructive apneas during sleep in human infants [20]. Hypoxia dramatically increases the apneas and bradycardia elicited by the laryngeal chemoreflex [21]. This is produced by eliciting a cardio-inhibitory effect of peripheral chemoreceptors during apnea with suppression of the pulmonary stretch receptors.

Conflicting data were reported on the relationship between the occurrence of apneas and gastroesophageal reflux (GER). In small series of infants, a temporal relation between obstructive apnea, regurgitation, and drop in esophageal pH has been reported [22–25]. Obstructive apneas can occur while infants are awake or asleep, but both reflex and the obstructive apnea related to reflux usually occur awake [25]. However, large series of infants conclude that obstructive and central apnea are not related to reflux episodes [26–28].

Epileptic seizures can be associated with apnea [29]. In rare occasions, apnea has been reported as the primary manifestation of epileptic seizure [30].

Intrinsic vulnerability of the infant may predispose to obstructive apneas. An abnormally increased number of short obstructive apneas has been reported in asymptomatic overweight infants [31]. Prenatal smoking by mothers correlated with an increase in frequency and length of obstructive apneas [32].

Apnea and narrow upper airways

Infants with narrow upper airways are at risk of obstructive apneas during sleep. Clinical symptoms during sleep are heavy and laborious breathing, noisy breathing (including but not limited to snoring), and profuse night sweating [33,34]. During wakefulness, infants may have breath-holding spells [35]. Failure to thrive may also develop. Among a group of 54 infants suffering from sleep disordered breathing due to narrow upper airways, 33 exhibited poor growth [34]. An acute cardiorespiratory failure may be the presenting complaint. Otitis and/or upper airway infection are frequent and accompanied by enhancement of nocturnal clinical symptoms.

In infants, obstructive apneas are considered to be most frequently associated with anatomic abnormalities that reduce the patency of the upper airways. Anatomic abnormalities may involve bone malformations, soft tissue infiltration, and neurologic lesions. Causes of narrow upper airways in infants include craniofacial abnormalities, micrognathia, cleft palate, glossoptosis, Pierre Robin syndrome, adenotonsillar hypertrophy, mucopolysaccharide storage disease, hypothyroidism, Down's syndrome [36–37]. Other contributing factors include choanal atresia, nasal obstruction that may be related to allergic reactions. Spinal cord compression such as those

associated with Chiari malformations type I or II, or myelomeningocele [38] can also concur to obstructive apneas. Severe laryngomalacia can be associated with obstructive apneas in infants [39]. Infants with neuromuscular disorders are also at risk of obstructive apneas.

However, it must be noted that obstructive apneas are in fact infrequent in infants with narrow upper airways. Respiratory events during sleep are more often episodes of partial upper airway obstruction leading to obstructive hypopneas or obstructive hypoventilation episodes [40]. Furthermore, these events may be rare in sleep-disordered breathing related to upper airway resistance syndrome (UARS). The UARS is characterized by increasing respiratory efforts during sleep. The diagnosis of UARS needs esophageal pressure recordings during polysomnography. Guilleminault *et al.* described the functional criteria to diagnose UARS in infants [34,41]. A characteristic pattern is called a "crescendo" indicated by a progressive increase in the end inspiratory esophageal pressure oscillations. These episodes of "crescendo" increased inspiratory efforts terminate by EEG arousals [41]. "Crescendo" episodes may cover more than 10% of total sleep time [42]. According to Guilleminault *et al.*'s report [34], clinical symptoms are not useful in distinguishing UARS from obstructive sleep apnea syndrome. Therefore, when obstructive apneas are not found on polysomnographic evaluation, physicians may assume an absence of sleep-disordered breathing. The analysis of esophageal pressure patterns during sleep has to be performed in infants with clinical symptoms suggestive of upper airway problems despite the absence of typical obstructive apneas.

Apnea and congenital central hypoventilation syndrome

Congenital Central Hypoventilation Syndrome (CCHS) is defined as the failure of autonomic control of breathing [43]. Since the initial description in 1970 [44] less than 200 cases have been reported (unpublished personal review). Clinical symptoms occur during the first month of life in most of the cases. They are variable and dependent on the severity of the disorder. Some newborns will not breath at birth or during the first hours of life and will require assisted ventilation. Other infants will appear asymptomatic during the first weeks of life, but will present repetitive episodes of apneas or an apparent life-threatening event later on. The diagnosis of CCHS needs polysomnographic examination including end-tidal CO_2 partial pressure measurements during different behavioral states. The criteria for CCHS diagnosis include hypoventilation during sleep especially during NREM sleep and decrease in minute ventilation [45]. Long central apneas are common, but obstructive apneas related to abnormal upper airway muscle control may occur during sleep [46]. When possible hypercapnic ventilatory challenges are an essential component for the diagnosis of CCHS. CCHS infants are lacking ventilatory response to hypercapnic stimulus [43,45]. In the most severe cases, CCHS infants hypoventilate during wakefulness. Increased awareness of this rare respiratory control disorder, and a comprehensive evaluation of every CCHS infant are critical for early diagnosis and appropriate treatment.

CCHS is a lifelong condition. Adequacy of treatment and quality of follow-up are the guarantee of the neurocognitive development of the infant and protect the infant against acute cardiorespiratory failure triggered by mild events especially respiratory infection.

Apnea and apparent-life-threatening-event (ALTE) and sudden infant death syndrome (SIDS)

The relationship between SIDS and upper airway obstruction during sleep has been questioned for two decades [4]. Studies have occasionally been done in infants who subsequently died of SIDS [4,14]. These studies provided documented evidence of more frequent obstructive apneas in future SIDS victims [4,14]. Guilleminault *et al.* reported clinical symptoms of obstructive apneas among parents or grandparents of SIDS or near-miss SIDS cases in the same families [47]. The risk was apparently related to the presence of a small posterior airway, which was found in several family members including young children [47]. More recently Tishler *et al*. reported data from a community-based study of obstructive sleep apnea (OSA) that demonstrated a relationship between OSA and SIDS or ALTE [48]. The SIDS/ALTE families were more frequently brachycephalic, and had reduced dimensions of the oral-pharyngeal airways [48]. Guilleminault *et al*. reported data from a core investigative protocol over 297 infants referred for ALTE [42]. Fifty-seven percent of these ALTE infants had abnormal breathing during sleep. They had obstructive sleep apnea or evidence of UARS during sleep at polysomnographic recording. These infants presented mild facial dysmorphia. Familial sleep-disordered breathing was common in these ALTE infants. This important study points out that ALTE may be an indication of a sleep-disordered breathing syndrome. Infants with ALTE may have an unrecognized increase in upper airway resistance long before having mixed and/or obstructive apneas [49]. Home nasal continuous positive airway pressure (CPAP) may be required in ALTE infants with upper airway problems [50]. In clinical practice, infants presenting with ALTE should have clinical evaluation of craniofacial features and upper airway patency [34]. A careful family history should be performed. Infants with ALTE should benefit from polysomnographic examination. Recognition of upper airway problems in infants with ALTE may need esophageal pressure recordings during polysomnographic examination.

Consequences of apneas in infants

Apneas may induce hypoxemia. The degree of hypoxemia and the resulting fall in oxygen saturation as measured by pulse oximetry is in general related to the duration of apnea. However, other factors interfere such as stages of sleep and type of apnea. Apneas may be accompanied by a transient episode of bradycardia. However, when apneas are terminated with a body movement, movement-induced heart rate acceleration protects the infant from heart rate deceleration [15]. Conflicting data have been reported with regards to the occurrence of arousal at the end of apneas in infants. Part of these conflicting data are related to different criteria used for arousal definition. Hoppenbrouwers *et al.* [15] defined a miniarousal on the presence of body movement after the apnea. These miniarousals were not always accompanied by EEG arousals. The majority of obstructive apneas were accompanied by movements and heart rate acceleration [15]. McNamara *et al.* [51] used the criteria for EEG arousals used for adults [52]. However, they required only 1 s duration for EEG arousals in infants instead of the 3 s required in adults. They found that less than 8% of respiratory events either apnea or hypopnea ended by an EEG arousal and that EEG arousal occurred more frequently after obstructive than after central events [51]. An important study in

infants with UARS during sleep found an abnormal number of EEG arousals compared with age matched control infants [41]. EEG arousal occurred at the end of the "crescendo" of esophageal pressure recording [34,41]. Despite these conflicting data on the frequency of the occurrence of arousal at the end of apneas in infants, it clearly appears that sleep-disordered-breathing in infants may favour sleep disruption, sleep fragmentation and reduction of REM sleep [53]. Normal REM sleep structure and duration is of major importance in infancy for behavioral and neurocognitive development [54]. McNamara *et al.* showed the beneficial effects of nasal CPAP in infants with upper airway problems. Nasal CPAP dramatically improved the sleep fragmentation and increased the length of REM sleep episodes [52].

Indications for polysomnography in infants with apnea

The American Thoracic Society (ATS) produced an official statement for standards and indications for cardiopulmonary sleep studies in children [55]. Consensus recommendations stated that "polysomnography may be helpful in defining the frequency and type of apnea and the extent of cardiac, blood gas, and sleep alterations in certain infants with apnea or ALTE. These patients include infants with suspected obstructive apnea". Ongoing clinical research studies suggest to extend these indications. According to Guilleminault's reports [42], infants with ALTE associated with craniofacial feature and/or positive familial history of sleep-disordered-breathing, should be investigated not only for obstructive apneas but also for UARS. Consensus recommendations of the ATS indicate that infants suspected to have abnormal respiratory control should have polysomnography. In these infants', the major issue is to reject or to confirm a diagnosis of CCHS. As stated before, polysomnography should be performed in different behavioural states and should include hypercapnic challenges.

When indicated, polysomnography (PSG) in infants should be performed in optimal environmental conditions. The gold standard remains the PSG in a sleep laboratory during night sleep. Measurements should include variables necessary for sleep staging, airflow and respiratory movement detection, measurement of oxygenation and CO_2 partial pressure using end-tidal and/or transcutaneous samplings. ECG, actimeters, and audiovisual recording are recommended. In all cases, PSG should be performed during natural sleep without sedation or prior sleep deprivation.

Indications for nasal CPAP in infants

Infants who had abnormal breathing during sleep related to severe upper airway abnormalities have, in the past, been treated with tracheostomy. In those in whom tracheostomy seemed unjustified, no other treatment was available. In the absence of good alternative treatment approaches, home monitoring, usually cardiorespiratory monitoring, has been often recommended. Recent applications of nasal CPAP in infants have modified the therapeutic approach of infants even with severe upper airway problems [50,53]. Before recommending nasal CPAP, infants should have careful evaluation of the upper airways, and PSG including esophageal pressure measurements, if indicated [34]. Titration of nasal CPAP should be performed during PSG recording [50]. Nasal CPAP can be applied at home with a careful training of the parents. The greatest technical problem in using home nasal CPAP for infants is the production of masks

that fit well [50]. Appropriate follow-up is necessary. The level of pressure required to normalize breathing pattern during sleep changes with advancing growth [56]. Long-term evaluation allows to decide either nasal CPAP treatment discontinuation or other surgical procedures [50]. During infancy, compliance to CPAP depends on parents.

Practice Points

1. Polysomnography is the gold standard for the diagnosis of sleep-disordered-breathing in infants
2. Healthy infants rarely develop obstructive apneas
3. A number of factors can suddenly "trigger" apneas in infants
4. Infants with narrow upper airways are at risk for obstructive apneas
5. Apparent-life-threatening events may be related to upper airway anomalies
6. Infant with congenital central hypoventilation syndrome may present with unexplained apneas
7. Nasal CPAP is feasible in infants
8. Early diagnosis of abnormal breathing during sleep is of critical importance for preserving neurocognitive development

Reasearch Agenda

In the future we need to:

- collect more normative data during infancy
- evaluate home sleep studies in infants
- define criteria for arousal in infants
- develop a genetic approach in familes art risk for sleep-disordered-breathing

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