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Sleep and respiration in children: time to wake up!

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Summary

The interest in paediatric sleep disorders over the last few decades has had its main focus on the sudden infant death syndrome (SIDS) – healthy infants who go to sleep and never wake up again. Overall, this is the most dramatic form of paediatric sleep disordered breathing. By contrast, classical presentations of sleep disordered breathing in children, such as snoring and obstructive sleep apnoea as well as their clinical implications have been greatly neglected and underestimated in the past. In contrast to snoring in adults, snoring in children has so far generally been regarded as noisy breathing with no significant impact on the general health of children. This is also to a lesser extent true for obstructive sleep apnoea syndrome (OSAS). The sometimes dramatic complications of OSAS, such as *cor pulmonale* and developmental retardation have at least indicated that OSAS in children is important and may have a great impact on the general health of children. This has led to an increased interest from a clinical as well as a scientific point of view with some important findings, mainly that sleep disordered breathing in childhood varies from sleep disordered breathing in adulthood and that even mild to moderate disease has a huge impact on the general health of children, mainly on neurocognitive development.

Key words: sleep disorders; OSAS; sudden infant death syndrome; upper airway resistance syndrome; snoring

Sudden infant death syndrome

Sudden infant death syndrome (SIDS) comprises deaths which remain unexplained after thorough examination. Epidemiological findings of risk factors for SIDS have led to national preventive campaigns worldwide with a huge impact on the reduction of SIDS. The "Back to Sleep" campaign in the early 90s in particular was very successful with the SIDS mortality being more than halved. Campaigns on SIDS prevention confuse recommendations specifically aimed at SIDS with those targeting general health. Both have an impact on infant mortality. A recent review on SIDS-specific prevention messages has addressed this confusion and discussed the evidence for preventive SIDS-specific measures [1]:

Sleeping position
- Causal relationship between prone sleeping position and SIDS. There is a close temporal relationship between the "Back to Sleep" recommendation and the fall in SIDS and total post-neonatal mortality.
- Most studies find also an association between side sleeping and SIDS (doubles the risk).

Maternal smoking in pregnancy
- More than 60 studies have shown that maternal smoking in pregnancy is associated with an increased risk of SIDS. The magnitude of the effect seems even larger since the reduction in SIDS.
- The greatest benefit is achieved by getting light smokers to stop smoking rather than heavy smokers to reduce the amount smoked.
- The recommendation that partners should not smoke near the mother when she is pregnant is based on limited evidence.

Environmental tobacco smoke exposure
- The odds ratio (OR) has been estimated at 1.47, which is considerably less than for maternal smoking in pregnancy, suggesting the predominant effect is *in utero*.

Thermal factors
- The increased risk with thermal factors is predominantly among infants sleeping in the prone position.

No financial support declared.

Head covering
- Case series have reported that 25–40% of infants found dead have their heads covered by bedding. However, whether this is an agonal event or part of the causative pathway has never been established.

Bed sharing
- Bed sharing increases the risk of SIDS, however, this increased risk in infants of maternal non-smokers is quite small compared with bed-sharing infants of maternal smokers.
- Sleeping with older siblings is especially dangerous.

Sofa
- Infants sleeping on a sofa have been shown to be at risk. This is also the case when sharing the sofa with an adult.

Illness and infection
- Illness has been shown to interact with sleeping position, so that infection is only a risk for SIDS in prone-sleeping infants.

Immunisation
- As immunisations in the first year of life are given around the same time of peak incidence of SIDS, it is not unexpected that some deaths will occur in close temporal relationship with immunisation, which has led to the suggestion that immunisation may cause SIDS.

Sleeping environment
- Infants using an adult pillow seem to be at increased risk of SIDS.

Bottle feeding
- Almost all studies show that breast feeding is associated with a reduced risk of SIDS.

Aside from the scientific focus on the epidemiology of risk factors for SIDS, a great deal of research has focused on the possible pathophysiological mechanisms of SIDS. Since the first year of life is characterised by a significant maturation of the organism in general, there is also a significant maturation in autonomic control of the cardiovascular as well as respiratory system. The respiratory system in the first year of life has age-specific structural and functional characteristics. Airway diameter is small, airway muscles contain fewer type I fibres, the rib cage is horizontal, round and compliant and the diaphragm is in a horizontal position with a smaller extent of rib cage contribution to respiration. These structural characteristics lead to physiological, functional changes such as increased airway resistance, reduced functional residual capacity, reduced compliance and airway flow. These functional characteristics are further influenced by the sleep stage. In quiet sleep, abdominal and thoracic respiratory movements are largely synchronous. In active sleep, reduced muscle tone and the compliant chest wall produce paradoxical movements. Paradoxical breathing is associated with a 30% reduction in thoracic gas volume, higher oxygen consumption, lower and more variable oxygen levels, higher and more variable respiratory rate and higher minute ventilation. These findings may explain SIDS as a result of respiratory inadequacy. In addition, the centrally mediated modulation of ventilation and alterations in excitatory carotid body chemoreceptor input lead to an age-specific biphasic hypoxic ventilatory response (augmented phase, depressive phase) [2]. Infants arouse more readily under hypoxic conditions than spontaneously, whereas the level of hypoxia affects arousal responses. Arousal may be more important in active sleep with greater oxygen consumption. Infants habituate to repeated tactile stimuli. A decrease in arousability is seen with increasing postnatal age in quiet sleep. Maternal smoking leads to a lower respiratory drive and decreased ventilatory response to hypoxia, which is explained by nicotinic cholinergic receptors being involved in cardio-respiratory control. In addition, a decreased arousability in infants is also seen in broncho-pulmonary dysplasia (BPD), history of apnoea, apparent life treatening events (ALTE) and cocaine exposure [3]. In addition, breast-fed infants are more easily aroused from active sleep than formula-fed infants [4]. These findings may explain SIDS as a consequence of changes in arousability with arousability being an important survival mechanism.

Table 1

Recommendations for preventing the risks for SIDS.

Place your baby on its back to sleep
Do not let anyone smoke in the same room as your baby
Cut smoking in pregnancy – fathers too!
Do not let your baby get too hot
Keep your baby's head uncovered – place your baby in the "feet to foot" position
Do not share a bed with your baby if you have been drinking alcohol, have taken drugs or if you are a smoker
The safest place for your baby to sleep is in a cot in your room for the first months of life
If your baby is unwell, seek prompt advice

Figure 1

Polysomnography of a child with OSAS with frequent obstructive apnoea and desaturations. There are four obstructive apnoeas with absent oral/nasal flow detected by a thermistor but ongoing thoraco-abdominal effort. Between the single obstructive apnoeas there is evident paradoxical breathing with thoracic wall movements being discordant to the abdominal wall movements. A period of significant desaturation is indicated by a purple square.

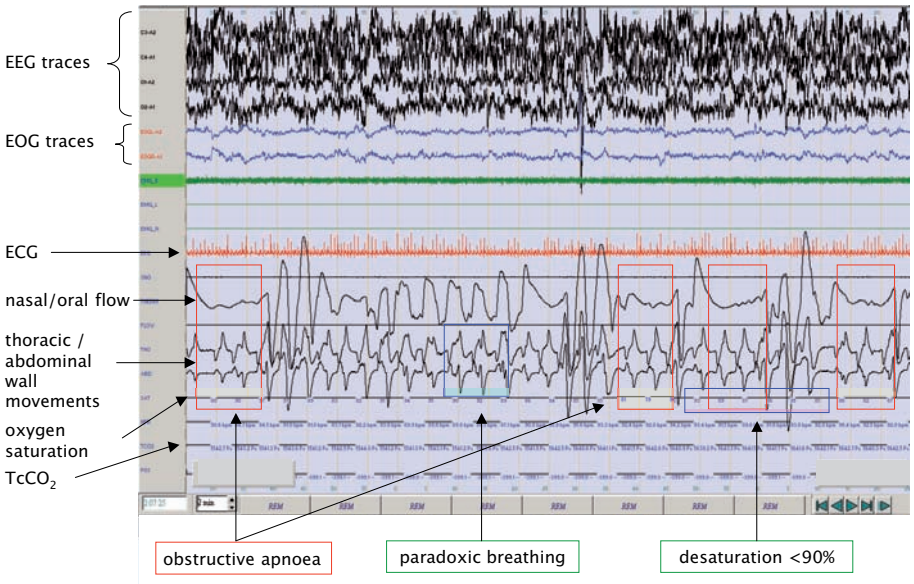


Figure 2

Polysomnography of a child with primary snoring. There is paradoxical breathing as an indication of increased work of breathing due to upper airway obstruction. In the nasal flow trace airflow limitation is recognisable. Obvious snoring, synchronous to breathing. Note that there is no desaturation.

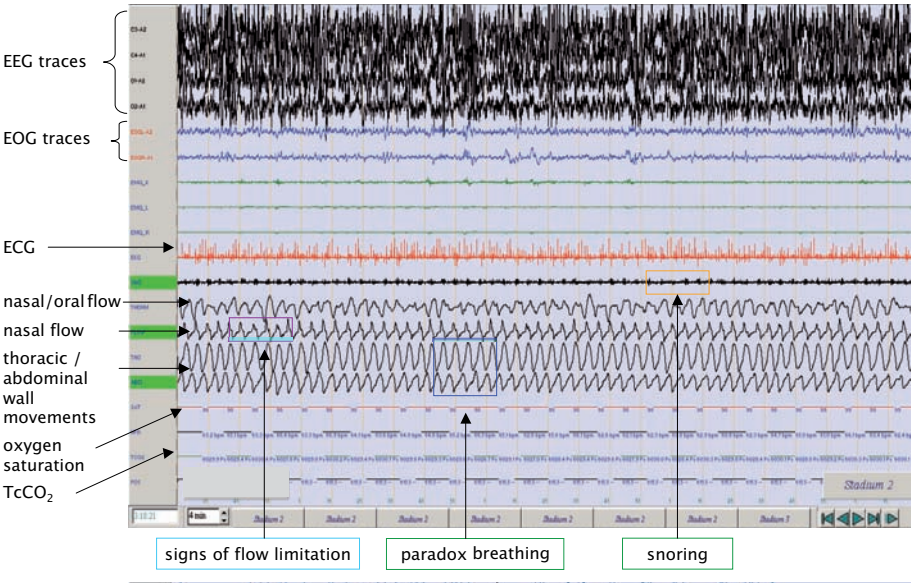
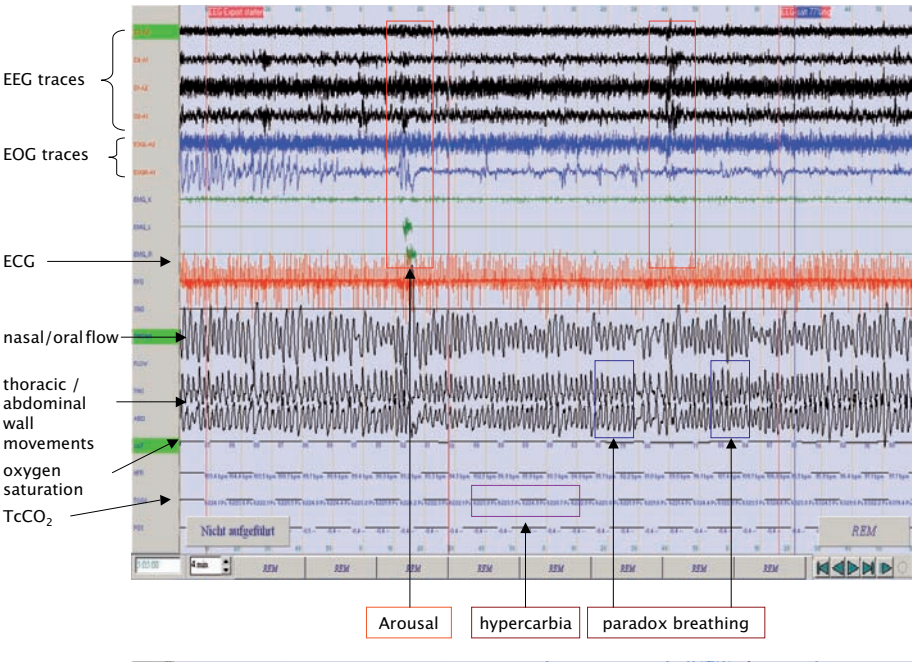


Figure 3

Polysomnography of a child with upper airway resistance syndrome with frequent arousals. There is continuing paradoxical breathing and low oxygen saturations between 76–88%. Transcutaneous CO_2 is elevated with values around 6.2–6.3 kPa. Two arousal episodes are noticed.



Snoring, upper airway resistance syndrome and obstructive sleep apnoea syndrome

Already in the late 18th century, there have been descriptions on the importance of sleep disordered breathing and its impact on the development in children:

"On some causes of backwardness and stupidity in children" (Hill 1889) and "at night the child's sleep is greatly disturbed: the respirations are long and snorting, and there are sometimes prolonged pauses, followed by deep, noisy inspirations – in long-standing cases, the child is very stupid-looking, responds slowly to questions, and may be sullen and cross" (Osler 1892) [5]. Despite this early recognition of sleep-disordered breathing in children and its health impact, the next description of sleep-disordered breathing followed only in 1976 by Guilleminault with most of the work being performed in the last decade [6].

OSAS is defined as a respiratory anomaly of sleep which disturbs normal ventilation and sleep cycles by partially or completely obstructing the airways (figure 1). Primary snoring is characterised by loud upper airway breathing, but sleep frame and saturation remain normal (figure 2). Upper airways resistance syndrome is characterised by loud snoring, frequent EEG awakenings, fragmented sleep but no flow reduction (no apnoeas) and not necessarily desaturations, although they may occur (figure 3).

8–10% of children snore, 0.7–3% of children suffer from upper airway resistance syndrome, and 2% of children suffer from OSAS with the highest incidence between the age of 2 and 6 years. There is no difference in prevalence between boys and girls. The most common reason for snoring and OSAS is adeno-tonsillar hypertrophy. Family history is often positive, mainly in Afro-American children.

Primary snoring has for a long time been considered to be a truly benign symptom. However, recent research has shown that primary snoring disrupts developmental processes [7]. In a subgroup (1%) of children with clinically diagnosed primary snoring OSAS can be found in the polygraphic assessment. This subgroup has mostly frequent daytime mouth breathing, snoring most nights, observed cyanosis or apnoea, difficulty breathing during sleep and parental concerns about the child's sleep. The differentiation between truly "benign primary snoring" and snoring leading to significant consequences such as recurrent oxygen desaturation during sleep and neurocognitive alterations is difficult. Recent reports highlight that neurocognitive consequences may arise in children with habitual snoring independent of whether they show significant OSAS or not [8]. It is not necessary to evaluate every snoring child in the sleep laboratory, however is important to closely follow up children with primary snoring regarding day time symptoms, neurocognitive functioning, and behaviour.

Obstructive sleep apnoea syndrome

Most of the attention in sleep-disordered breathing in children has been on OSAS and findings from adults have been translated for children. However, there are some pertinent questions regarding differences in the pathophysiology as well as clinical presentation of OSAS in children compared to adults:

- Which are normal values for polygraphic parameters in children?
- Are the diagnostic criteria in adults valid for children?
- Is there a difference in pathophysiology in children compared to adults?

Normal polygraphic parameters

Marcus *et al*. addressed questions of normal values and diagnostic criteria in childhood in a study in 1992 [9]. In her collective she found only 9 children with one or more episodes of obstructive apnoea with the duration of all obstructive apnoea being less than 10 seconds. 15 children had 1 to 5 central apnoea events lasting between 10 and 18 seconds, and 1 child had a fall in oxygen saturation <90% together with central apnoea. From her findings, she concluded that polygraphic criteria for adults (obstructive apnoea >10 seconds, apnoea index <5 = normal) do not apply for children and she suggested the following pathological values for children:

- apnoea index of 1 per hour,
- oxygen saturation <92% and CO_2 >45 mm Hg.

Table 2

Diagnostic criteria of OSAS.

Frequent signs	Infrequent signs
Nocturnal snoring	Daytime sleepiness
Mouth breathing	Decreased appetite
Restless sleep with or without arousals	Failure to thrive
Respiratory pauses	Frequent vomiting
Respiratory infections	Swallowing dysfunction
Chronic rhinorrhea	Behavioural problems
Nocturnal sweating	Otitis media
	Enuresis

Diagnostic criteria

Whereas daytime sleepiness is common in adults with OSAS, it is not as common in children. More frequently, if any daytime symptoms are seen at all, behavioural problems are encountered in children suffering from OSAS (see table 1). In 1994, Goldstein *et al.* looked at the value of clinical history, clinical examination, and video in diagnosing OSAS in children [10]. From their study, it can be concluded that polysomnography is the gold standard for the investigation of sleep-disordered breathing in childhood but resources are very limited and demand is increasing [11]. In addition, clinical history and examination fail to differentiate children with OSAS from those with benign snoring. In children for whom there is a high pre-test probability of having OSAS, a positive overnight pulse oximetry test is highly predictive of OSAS. However, in such patients, a negative overnight pulse oximetry test does not exclude OSAS and should be followed by a more comprehensive evaluation of breathing during sleep.

Pathophysiology

Obstruction of the airways in children is more distal than in adults. In addition, in comparison to adults, children with OSAS have fewer arousals, fewer significant desaturations also during short apnoea or hypopnoea episodes, and decreased collapsibility of the upper airways due to a higher muscular tone. Adeno-tonsillar hypertrophy is the major cause of OSAS in children, but not all children with adeno-tonsillar hypertrophy have OSAS. Certain children still have symptoms of sleep-disordered breathing after adeno-tonsillectomy or have again symptoms during adolescence, most likely suggesting a pathology of the neuromuscular tone in these patients. Obese children constitute a new at risk population for OSAS in middle childhood and adolescence. Sleep-disordered breathing is common in various other chronic conditions. Examples are neuromuscular diseases such as spinal muscular atrophy (SMA) or Duchenne muscular dystrophy, neurological or neurodevelopmental disorders, hypoventilation syndromes such as the Undine syndrome and metabolic disorders, e.g., mucopolysaccharidosis. Other risk factors for OSAS are craniofacial malformations, prematurity, Down's syndrome and spina bifida. The main complications are impairment of growth, cardiovascular problems and behavioural problems (even in milder cases). Some studies reported similar behavioural characteristics in children with OSAS as found in children with attention deficit and hyperactivity disorder (ADHD). The reasons for impairment of growth are controversial with proposed mechanisms including low calorie intake, hormonal changes with reduced growth hormone and reduced growth factor receptors.

In adults, sleep-disordered breathing is associated with increased cardiovascular risk, particularly systemic hypertension and ischaemic heart disease. It is well known that arousals during sleep activate the sympathetic nervous system with a resultant pressor response. It has recently been shown that young children with SDB have measurable alterations in vascular reactivity [12]. These abnormalities are in concordance with the changes in heart rate variability that have been observed in a small group of children with SDB [13]. The long-term consequences of autonomic nervous system dysfunction associated with persistent waking due to SDB are unknown, but the risk is that these perturbations may in part be irreversible and have lifelong consequences.

Summary

Sleep disordered breathing is a common condition of childhood. There is no evidence that infants who die from SIDS suffered from sleep-disordered breathing [14]. In some cases, sleep-disordered breathing heralds an underlying abnormality of the upper airways. Importantly, it may cause disruptions of developmental processes with lasting effects. Treatment is simple and effective in most cases. Other common sleep disorders in children, such as parasomnias or inadequate sleep hygiene, may present with arousals and could be misinterpreted as SDB without polysomnographic studies. Early recognition of sleep-disordered breathing in children is likely to reduce the high economic costs and improve health outcomes and quality of life.

Open questions

Despite the increasing understanding of sleep-disordered breathing in childhood, some important questions, stressed by Nixon *et al.* [15] regarding the clinical features, the relationship with adult OSAS, the pathophysiology, and the treatment have still to be solved. There is need for longitudinal studies in larger groups of children to answer these open questions in future:

- At what level of severity of sleep-disordered breathing do consequences exist or can a benefit from treatment be expected?
- Are children with OSAS treated by adeno-

tonsillectomy at higher risk to develop OSA in adulthood?
- What is the natural history of untreated snoring or mild OSAS?
- What makes the adenoidal and tonsillar tissue of some children grow to such an extent that it impairs breathing?
- Is there an association between arousal frequency and the daytime consequences of OSAS?
- As polysomnography is currently not widely available to children, how can surgical waiting lists be prioritised and how can the peri-operative risk be adequately assessed?

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