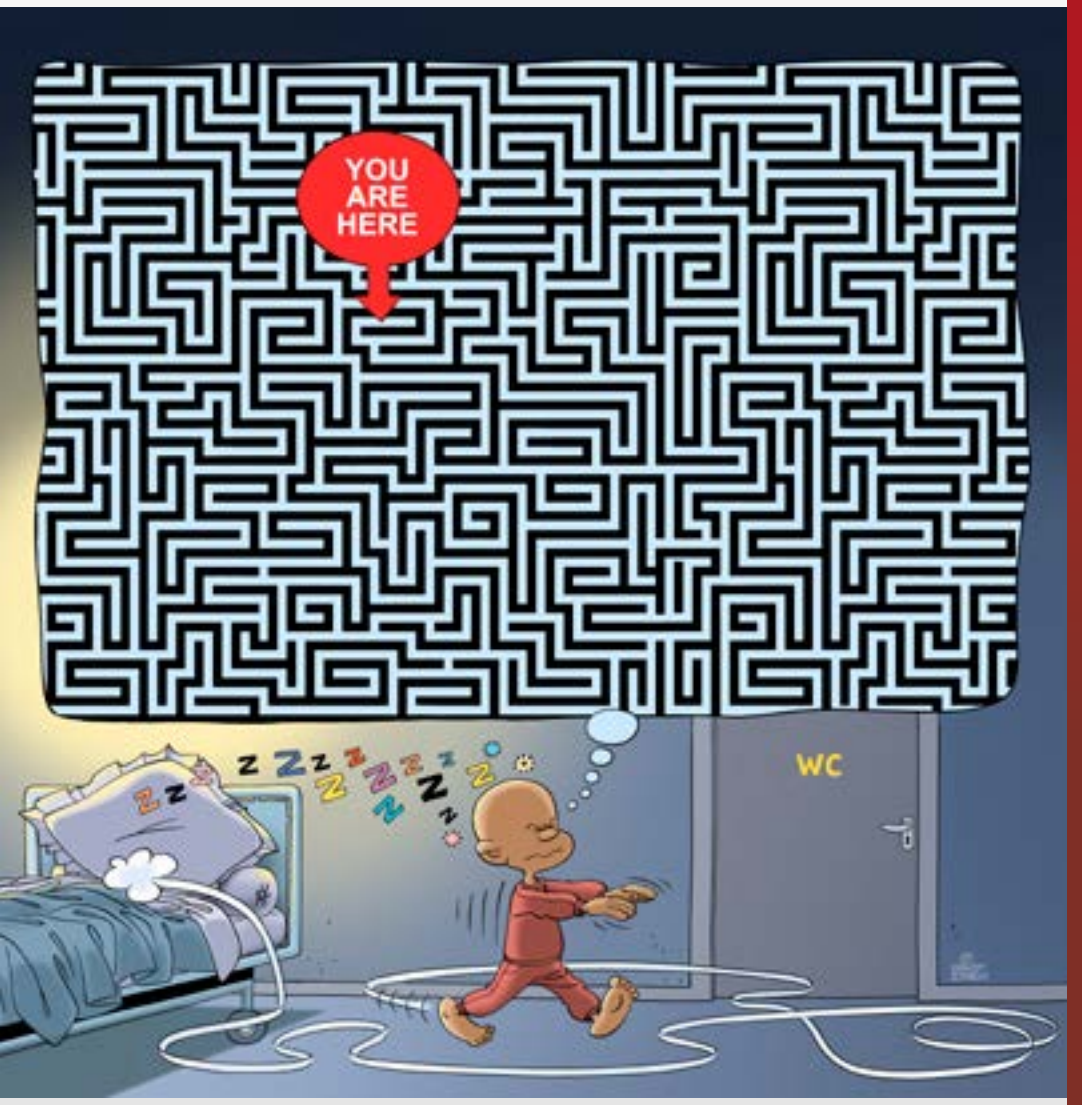
BjP
Belgian Journal of Paediatrics
Publication of the Belgian Society of Paediatrics
BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE
2021 - Volume 23 - number 3 - September



Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

QUARTERLY
ISSN 2466-8907 (printed version)
ISSN 2566-1558 (digital version)

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Editorial

This issue of the Belgian Journal of Pediatrics deals with sleep and sleep disorders in children. As Belgian, pediatric sleep clinicians and researchers, we have to acknowledge the pivotal role of Professor Kahn, a pioneer in the field. Approximately 40 years ago, motivated by his passion for research, professor Kahn set up the pediatric sleep laboratory at the HUDERF, with the primary aim to research SIDS. Since then, sleep research and sleep medicine in the pediatric field has changed focus, as SIDS research drastically helped reduce the SIDS rate. Pediatric sleep medicine expanded with the setup of more sleep centers to investigate sleep in children both healthy and with co-morbidities. Sleep in children is particular in that up to the age of 5 years, children spend more time asleep than awake. It could therefore be considered the child's most important activity. And an activity it is: sleep in children has been proven essential for consolidating memory and insuring proper cognitive development.

In the newborn child, sleep reflects brain maturation that is rapidly taking place from birth to 6 months. At first there is very little quiet or NREM sleep; Then over a period of a few months the amount of deep sleep increases, as the amount of active or REM sleep decreases. Typical markers of certain sleep stages, such as spindles for stage II, start appearing.

Heart and breathing rates, which both decrease as the child matures, reflect the developing autonomic nervous system. Sleep also becomes more consolidated, allowing most infants to be able to sleep through the night by the age of 6 months.

The study of sleep in the prematurely born infant allowed for the identification of markers of cardio-respiratory immaturity, which are discussed in one of the papers presented in this special edition.

The impact on sleep of typical affections of the newborn, such as laryngomalacia and Pierre Robin sequence is discussed in this issue. Sleep is a state that favors hypoventilation, as muscle tone is decreased, especially during REM sleep. Affections that further increase resistance to airflow will result in the appearance of obstructive apnea with all the repercussions associated with them. The study of sleep in these cases allow for the quantification of the problem, as severe cases can lead to respiratory insufficiency. A sleep study can therefore optimize the way the infants with laryngomalacia and Pierre Robin sequence are taken care of. Two articles in this edition will discuss these topics.

As the child grows, parasomnia can become evident. They are frequent, and mostly benign, but they have to be differentiated from epilepsy. These subjects are also discussed in this issue, as they are a frequent reason for consultation.

Daytime sleepiness is rare in children but needs proper investigation when present, as academic performances and social development will be impacted. A sleepy child is also an irritable child, with the obvious effect on family life.

Narcolepsy is a rare but treatable disease, which too often is not recognized early. A case report is presented here, in the hope that pediatricians will think of this possibly when faced with a sleepy child during the day.

Of course, there are many other possible causes for daytime sleepiness (DTS) in children, the main one being obstructive breathing during sleep linked to hypertrophy of tonsils and adenoids. This particular subject is not treated in this issue as it is well known and extensively described in the literature.

However, restless legs are a much less known affection in children, and can be the cause of DTS. This subject is treated in this issue, to familiarize the reader with this pathology.

Another cause of DTS, delayed sleep phase syndrome, is discussed in this issue as it is a typical affection often observed in adolescents.

The final paper in this issue gives the pediatrician a complete and practical overview for the indications of a polysomnography in children.

It is our hope that these various subjects, investigating sleep from birth to adolescence, will inspire you to consider the study of sleep in children as an integral part of pediatrics.

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Sleep of the prematurely born infant

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Keywords

Prematurity, apnea of prematurity, polysomnography, positive pressure respiratory support, maturation

Abstract

Introduction
Prematurely born infants (PBI) very often present apnea during sleep. These events can still be detected at term equivalent age (TEA), with variable impact on ventilation. An immature respiratory control is responsible for these events, which disappear as the infant matures. This observational study describes polysomnographic results for a cohort of 12 PBI who were examined at TEA and again 11 weeks later.

Method
A cohort of 12 extreme preterm (average gestational age of 27 weeks) infants were followed by the HUDERF sleep unit as they received a cardio-respiratory monitor for home uses during sleep.
Polysomnography 1 (PSG1) was performed at TEA for the 12 infants. 10 of these 12 infants had another PSG (PSG2) 11 weeks later.

Results
All infants presented with apnea of prematurity at TEA, which significantly decreased at PSG2. Respiratory rates and heart rates both decreased significantly, while saturation in oxygen was not significantly different when compared between PSG1 and PSG2.

Discussion
Poorly tuned chemo and mechanoreceptors together with a highly pliable thorax, immature lungs and suboptimal central respiratory control are responsible for the apnea. These respiratory events disappear as the child matures.
Lower heart and respiratory rates at PSG2 reflect the maturing parasympathetic system.

Conclusion
Apnea in PBI result from suboptimal respiratory central control. They can result in a vicious cycle where hypoxia increases, thereby further destabilizing respiratory control. Further studies are necessary to investigate the feasibility of home use of respiratory support in the case of oxygen dependency in PBI.

Introduction

There is compelling evidence that sleep in children is essential to consolidate learning and memory . It is a time of rest for the body which allows for processing of daytime experiences. The conscious is disconnected and all vital functions are taken care of by the autonomic nervous system (ANS).

For the PBI, taking care of the vital functions poses a major problem : all systems are immature and still developing, including the ANS. The PBI spends most of his time in the state of sleep, which itself looks very different to what we understand by « sleep ».

The continuous period of sleep during night time that we have come to cherish as a refuge after the busy daytime hours is for the PBI fragmented and filled with cardiorespiratory events. Sleep is said to be unconsolidated (figure 1).

Perhaps this particular sleep architecture, littered with arousals and awakenings is necessary to allow for the preservation of vital functions : stimulants such as caffeine has saved many PBI just as it has saved many weary vehicle drivers at night. The awake state allows for better control of breathing, a key function often compromised during sleep of the PBI. Thus, the fragmented sleep observed in the PBI could be a necessary condition to help maintain adequate oxygenation.

The study of sleep using polysomnography informs about the state of vital functions. It is a very complete tool to evaluate both cerebral and ventilatory activities. The electroencephalogram (EEG) reflects the sleep state, and the eventual reaction to a potentially dangerous cardio-respiratory event. All other sensors measure ventilation directly or indirectly. Thus, the impact of sleep disordered breathing can be observed, and the ANS can be evaluated in its response to the many cardiorespiratory challenges faced by the PBI.

Apnea of prematurity are frequent, and their number increases as the gestational age decreases. These apnea can be central (no respiratory effort observed), obstructive (respiratory effort visible on the thoracic and abdominal belts) or mixed. The airflow measurements complete the information obtained by the thoracic and abdominal belts to identify the type of apnea observed.

All are apnea of immaturity, as they arise from suboptimal central responses to poorly tuned chemo and baro-receptors.

The upper airways have to be maintained open by the ANS, which can be almost non-operational in the PBI. Physiological hypercapnia during sleep maintains breathing movements. These movements disappear if chemoreceptors are not fine-tuned enough to maintain this relative hypercapnia, hence the frequent central apnea that can be observed in sleep of the PBI.

The obstructive respiratory events result from the periodic collapse of the upper airways that an immature ANS is not able to maintain open in a continuous manner.

These respiratory events can be more or less well tolerated. Often, they do not have any observable repercussions but sometimes they are accompanied by bradycardia and deep desaturation in oxygen.

The only way for the PBI to resolve a badly tolerated respiratory event is to have an arousal or an awakening. But again, these arousal reactions, which can be lifesaving, are sometimes inexistent, or very late in coming, creating a dangerous vicious circle (1). The late arousal response increases the hypoxia, which impacts negatively on central control, thereby increasing its instability (figure 2).

Figure 1: *hypnogram showing unconsolidated sleep at Term Corrected Age (TCA).*

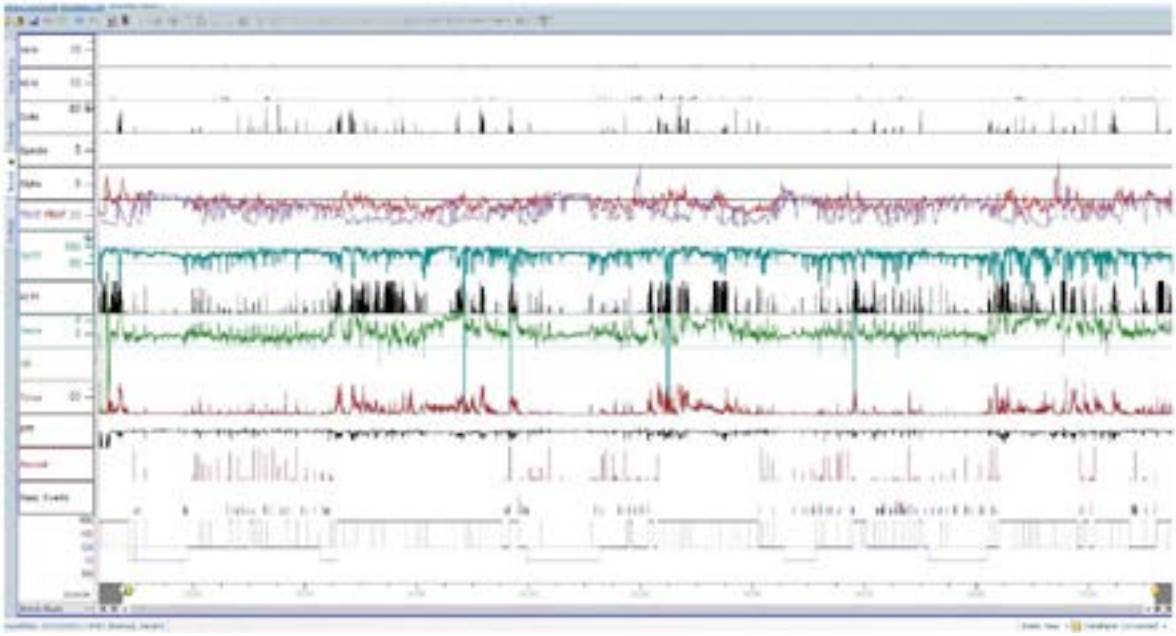
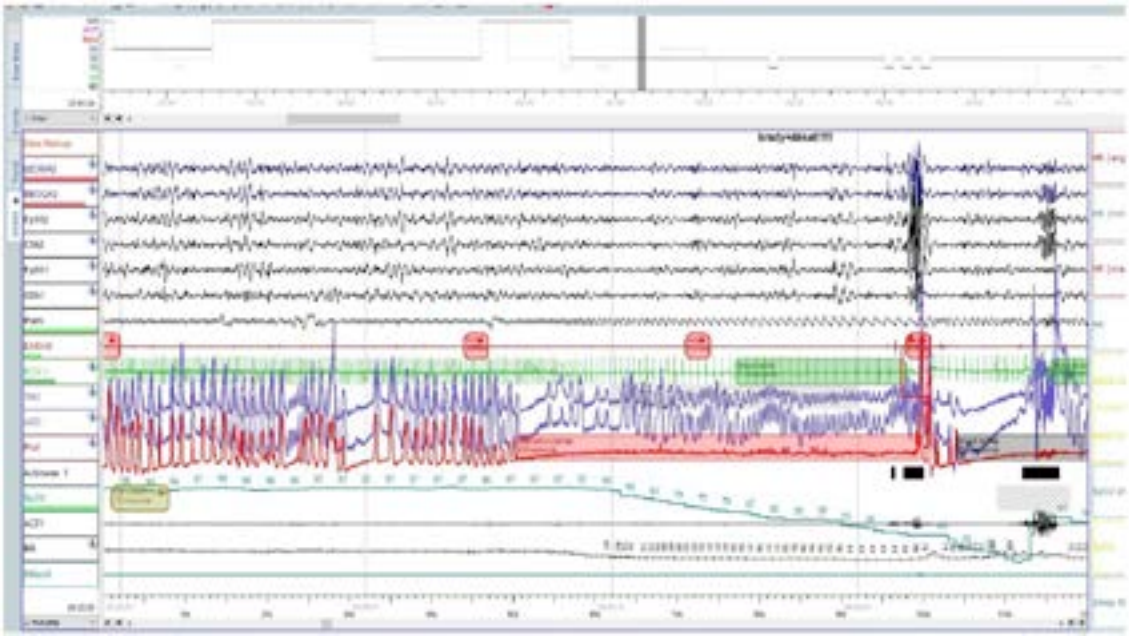


Figure 2: *A poorly tolerated obstructive apnea (OA) at TCA. The OA lasted 50 seconds and was accompanied by deep desaturation (minimum 23%) and a bradycardia (44 beats/minute) before the child finally reacted.*



The use of oxygen, CPAP (continuous positive airway pressure) and caffeine all help in maintaining proper oxygenation during sleep, providing optimal conditions for immature control centers.

Polysomnographic studies have shown that supplemental oxygen significantly decreases the amount of apnea of prematurity, suggesting that reducing hypoxemia optimizes central respiratory control (3).

Recently, NIV (noninvasive ventilation) in the form of BIPAP (bilevel positive airway pressure) has been used with promising results to allow discharge from the neonatal unit without supplementary oxygen. This method both keeps the upper airways open, and recruits pulmonary function that may otherwise be underused, thus optimizing breathing (2).

Discussion on home use of NIV during sleep of the PBI is outside the scope of this article, but there is evidence that it has a normalizing effect on sleep, as is demonstrated in figure 3, where the use of BIPAP results in the disappearance of the apnea.

Apnea of prematurity should therefore not be ignored, as they are a manifestation of central control instability.

Knowing when this instability becomes unmanageable for the PBI is impossible to predict, but outside stressors such as viral infections could very well tip the scale to a life threatening situation. Intermittent hypoxia associated with these apnea could also have long term effects on cognitive development, long after they have disappeared from sleep. Thus, their detection and treatment should be a priority (4).

This study describes the polysomnographic features of 12 infants born between June 2019 and November 2020 after an average of 27 weeks of gestation. The recordings were done at term equivalent age upon request from the neonatal unit (NICU), which corresponded to the time of discharge from the NICU (PSG1). Ten of these infants had another polysomnography 2 to 3 months after the first one (PSG2). It is usual for the sleep unit to program a PSG on average 21/2 months after the one performed at TEA to monitor maturation. The results of the PSG2 help guide the decision to maintain or not the surveillance by cardio-respiratory monitor during sleep. The population characteristics are shown in table 1.

Figure 3A: *PSG performed in a PBI re-admitted one week after discharge from the neonatal unit for alarms on the CR home monitor and a suspicion of viral infection: mean oxygen saturation during sleep 90%, with 48 minutes spent <90%. She has periodic breathing (figure 4) with an index of central apnea of 80.6 central apnea/hour of sleep (maximum length of the central apnea: 11 seconds) and a high number of obstructive and mixed apnea, with a combined index of 49.6/hour.*

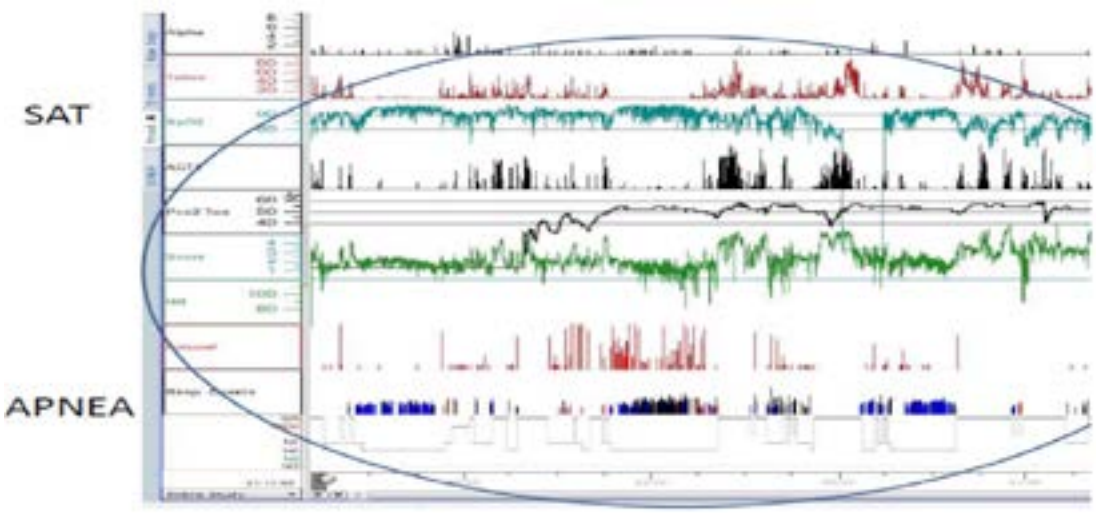


Figure 3B: *Same child with BIPAP (6 days after the PSG described in figure 3A): normalisation of the oxygen saturation (mean :96%) and the disappearance of the apnea. The child went home with the NIV, and used it during sleep for one month.*

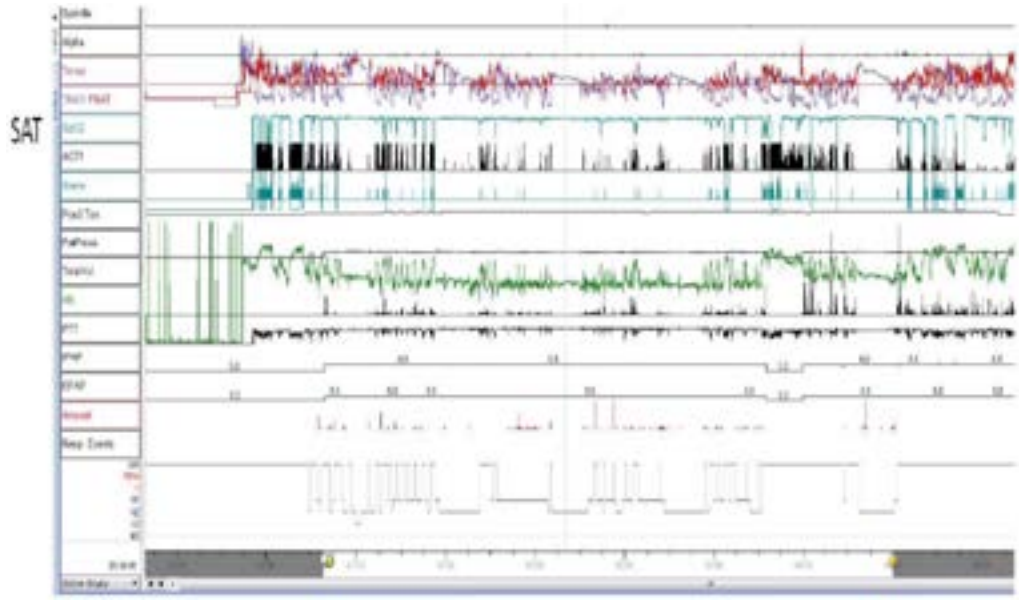
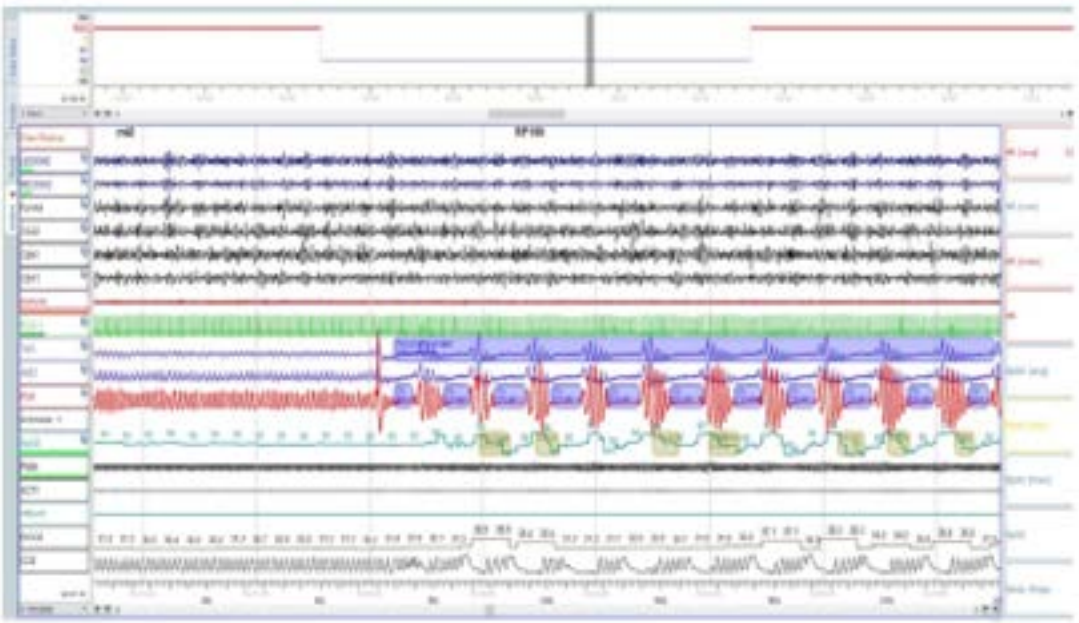


Figure 4: *Periodic breathing*



Results

All 12 infants were discharged from the neonatal unit with a cardio-respiratory monitor to be used at home during sleep. One infant also received a CPAP for home use, which she used one month, then did not tolerate it any longer. A second polysomnography (PSG2) was performed one month after she stopped using it.

Another infant was re-admitted one week after discharge from the neonatal unit for alarms on the home cardio-respiratory monitor and a suspicion of viral infection. No germs were identified, but as she could not be weaned off the supplemental oxygen, she left the hospital with an NIV.

During the hospitalization, she had a polysomnography to evaluate her ventilation during sleep, as the PSG performed at discharge from the neonatal unit (PSG1) did not show major signs of respiratory insufficiency. Another one was also performed to titrate her NIV (figure 3).

Again, the devise was used for a month, then the child did not tolerate it any longer. A final PSG (PSG2) was performed one month after that.

PSG2 was scheduled on average 2 and ½ months after PSG1 for all infants, but 2 infants left the cohort and handed their cardio-respiratory monitor before the scheduled date. Thus, the statistical analysis was performed on 10 infants.

The PSG results for the 12 infants performed at TEA at a mean corrected age of 39.3 weeks (PSG1) and those for the 10 of the 12 infants at a mean corrected age of 50.6 weeks (PSG2) are presented in table 2.

Table 1: characteristics for the 12 infants at PSG1 and the 10 infants at PSG2

	Mean	Median (min – max)
Gestational age (weeks)	26.8	26.5 (24 – 31)
Weight at birth (gr)	849	805 (494 – 1380)
Corrected age at PSG1(weeks)	39.3	39.5 (36 – 41)
Weight at PSG1 (gr)	2894	2840 (2355 – 3610)
Corrected age at PSG2 (weeks)	50.6	49.6 (45 – 57)
Weight at PSG2 (gr)	5400	5372 (4180 – 6600)

Table 2

	PSG1 Mean (min-max)	PSG 2	P (Student T-test, paired) 10 pairs
N (N° of infants)	12	10	
Sleep efficiency (SE)	71.8 (44-86)	74.8 (34-99)	0.189 (NS)
Saturation in oxygen (NREM)			
Mean	97.3 (95-100)	97.6 (95-99)	0.313
Lowest	73.3 (65-89)	78.4(69-87)	<0.01
% TST spent <90%	1.2 (0-3.2)	0.7 (0-2)	0.150
% TST spent between 91- 94%	6.6 (0.1-14)	4.8 (0-14)	0.270
Breathing rate (cycles/min) (RR)			
Min	58 (35-82)	39 (25-56)	<0.01
Max	76 (42-110)	45 (29-72)	<0.01
Delta RR	18 (3-36)	6.5(2-16)	0.010
Mean heart rate (beats/min)	147 (134-160)	126 (111-142)	<0.01
Min	81 (48-116)	84 (46-114)	0.056
Apnea			
Central (number/hour of sleep)*	8.7 (2.5-26.2)	5.2 (0-12)	0.016
Obstructive (number/hour of sleep)	6.8 (0-17.4)	2.4 (0-10)	<0.01

NREM: non-rem sleep or quiet sleep; TST: total sleep time

*Data on central apnea (CA) indices for one child who presented at PSG1 a large amount of periodic breathing (resulting in a CA index of 92.3 CA/hour of sleep) is not included, as none of the other infants presented with such a large amount periodic breathing at PSG1. That infant was discharged from the neonatal unit with a CPAP. The statistical analysis of CA data is therefore performed on 9 paired infants and not 10.

Discussion

There is a significant decrease in the number of both central apnea and obstructive apnea between PSG1 (performed at term equivalent age or TEA) and PSG2 (performed on average 2 1/2 months after PSG1).

Apnea of prematurity are well known in the neonatal units and attributed to the immature control of the respiratory system, combined with immature lungs and soft pliable thorax. Several treatments are routinely used to counteract their effect, such as prone positioning, oxygen supplementation, CPAP and xanthine use.

Most neonatal units monitor these apneic events using pulse oximeter, as they are often accompanied by intermittent oxygen desaturations and bradycardia. A polysomnography examination at the time of discharge from the neonatal unit, at term equivalent age (TEA), allows for in detail analysis of different cardio-respiratory parameters, thereby evaluating the infant's capacity for adequate response to the various apneic events that may occur during sleep.

In one case, the infant was discharged with a CPAP treatment, as he presented with an abnormally high amount of both central and obstructive events during sleep. These events were short, and were associated with intermittent hypoxia (during periodic breathing, figure 4), even though the overall average saturation during sleep time remained within normal values. It has been proposed that episodic hypoxia/reoxygenation cycles have the potential to sustain a pro-inflammatory cascade with resultant multisystem morbidity (4).

The use of CPAP diminished greatly the appearance of these apneic events, both central and obstructive, treating the intermittent hypoxia (IH). This suggests that CPAP treatment improves overall oxygenation, thereby optimizing central respiratory control.

All infants at PSG1 exhibited apnea of prematurity, some more than others. And all infants showed a significant decrease in these events at PSG2 ($p<0.05$), reflecting the maturation of respiratory control.

It is noteworthy that one infant was rehospitalized just one week after discharge, for a suspicion of viral infection, but no germs were identified. The child remaining oxygen dependent, a PSG was requested (figure 3A), which showed a marked increase in the apneic events when compared with PSG1 at discharge. It is proposed that in this case the infant had entered a vicious cycle of respiratory control destabilization, brought about by some inflammatory event (1). The use of oxygen stabilized the situation somewhat, but the use of NIV completely resolved the problem, resulting in the disappearance of the apneic events and the regularization of the oxygen saturation (fig 3B). The child was discharged with NIV, which was used for a period of one month.

This case raises the question whether apnea of prematurity are as benign as is generally thought. Certainly all premature infants will exhibit them, but when exactly must they be considered potentially dangerous? The answer perhaps lies in the way the infant is able to respond to the event. Figure 2 illustrates one obstructive respiratory event which lasted a very long time (50 seconds) before the child responded with an arousal, lifting the obstructive apnea. The deep desaturation and bradycardia that accompanied the event reflects the inability for this child to deal with such events.

So, it is not the number of apnea per se that can be worrisome, but rather how the child responds to the event that determines his ability to deal with an immature respiratory control.

As the infants mature from PSG1 to PSG2 the heart and respiratory rates significantly diminishes, as expected with the maturation of respiratory

control centers in the brain stem and the development of the autonomous nervous center (ANC).

A typical feature of respiratory rates (RR) at PSG1 is their increased variability, when compared with variability at PSG2 (delta RR, p=0.01), reflecting cardio-respiratory instability.

Heart rate variability studies have proven to be an important tool in the study of the ANC in term and preterm born infants (5). It was shown that an increasing postnatal age is associated with an increase in parasympathetic activity.

Moreover, gestational age at birth influences maturation of autonomic cardiovascular control, as preterm born infants exhibit less heart rate variability at TEA when compared with term born infants. The authors proposed that this increased immaturity of cardiovascular control when compared with term born infants could contribute to the increased risk of SIDS that premature infants face (6).

The significantly lower heart rate observed at PSG2 when compared to values observed at PSG1 can therefore be interpreted as reflecting the increased parasympathetic activity that establishes itself in the first months of life.

Sleep efficiency (SE) is a parameter that reflects the amount of time the child is actually asleep during the recording of the PSG. To obtain this parameter, the EEG during the recording has to be scored (active, quiet sleep or awake) and a ratio is established between the time spent asleep versus awake. During the first months of life infants do not have consolidated sleep, as they sleep a lot but not in a continuous manner. The sleep efficiency at PSG1 (72%) was not very different to that observed at PSG2 (75%) indicating that they were still unable to sleep through the night at 50 weeks corrected age.

There is some evidence that term babies are already able to sleep through the night at 2 months of age, but there is a lack of serious studies on the subject. Moreover, PSG sleep studies in the laboratory promote uncomfortable conditions for sleep, that may or may not be well tolerated by the infant, thus influencing the sleep efficiency results. A SE above 70% in sleep laboratory conditions can therefore be considered normal for preterm born infants at PSG1 and PSG2.

The oxygen saturation results are also not very different between PSG1 and PSG2 : this is to be expected, as this is a parameter which will determine the infant's ability to leave the neonatal unit. The value shown in table 2 are only those obtained during NREM (or quiet) sleep, which are short periods of uninterrupted sleep with few or no apnea. REM sleep (or active) is littered with micro-arousals and apnea, making oxygen measurements difficult and unreliable. Therefore for the sake of comparison between PSG1 and PSG2 only oxygen saturation in NREM sleep is presented.

Conclusion

Polysomnography studies are a precious tool to evaluate the cardio-respiratory immaturity that these infants invariably have when leaving the neonatal unit. And even though it is impossible to predict how a particular infant will react when confronted with an outside stressor (such as a viral infection), it is safe to presume that it will impact negatively on the infant's central respiratory control, placing the child in a potentially dangerous situation.

Further studies are necessary to evaluate noninvasive ventilation for home use during sleep as a potential treatment for infants who cannot be weaned off oxygen.

Conflict of interest

The authors have no conflict of interest to declare.

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Sleep-disordered breathing and laryngomalacia

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Keywords

obstructive apnea, central apnea, laryngomalacia, polysomnography, supraglottoplasty

Abstract

Congenital laryngomalacia, the most frequent cause of inspiratory stridor in infants, can be associated with sleep-disordered breathing. A high prevalence of obstructive sleep apnea (OSA) has been documented among infants with laryngomalacia and surgical treatment by supraglottoplasty improves OSA severity. Consequently, polysomnography plays a role in the diagnostic evaluation, therapeutic decision making and follow-up after treatment of congenital laryngomalacia. A subgroup also presents with central apneas but the effect of treatment on the central apneas is rarely reported. Sleep-dependent laryngomalacia may be the primary cause of OSA in a minority of children and is the 2nd most common cause of persistent OSA after adenotonsillectomy. Children with sleep-dependent laryngomalacia are typically older (> 2 years), present with OSA related symptoms but do not have an inspiratory stridor while awake. Sleep-dependent laryngomalacia can be readily diagnosed by sleep-endoscopy and responds to surgical intervention by supraglottoplasty.

1.Introduction

Laryngomalacia is the most common cause of congenital stridor and typically presents in infants during the first weeks of life. It is caused by a dynamic, inspiratory obstruction of the supraglottis, both during wakefulness and sleep. Supraglottic collapse during sleep may result in sleep-disordered breathing (SDB).

More recently a different clinical entity was described in children beyond the neonatal period (usually > 2 years old) in which a collapse of supraglottic structures is only observed during sleep. This phenomenon results in in increased respiratory effort and airway obstruction during sleep and causes daytime symptoms of OSA but no stridor.

Various terms have been introduced to describe laryngomalacia that only presents during sleep: state dependent laryngomalacia , occult laryngomalacia , sleep exclusive laryngomalacia , late onset laryngomalacia, or sleep-dependent laryngomalacia (1-6). For the purpose of this paper, we will use the term sleep-dependent laryngomalacia.

In the following paragraphs, I will discuss the epidemiology, the pathophysiology, the association with sleep-disordered breathing and the effect of supraglottoplasty on sleep-disordered breathing for both congenital and sleep-dependent laryngomalacia.

2. Congenital laryngomalacia.

2.1 Classification of congenital laryngomalacia

In congenital laryngomalacia, upper airway obstruction is typically attributed to short aryepiglottic folds, inspiratory collapse of redundant supra-arytenoidal mucosa and/or a collapse of the epiglottis against the posterior pharyngeal wall. Different classification systems have been developed to describe the pattern of collapse. The classification system by Olney et al. is widely adopted in clinical practice and was found helpful to guide surgical treatment (7, 8). Video 1 provides an example of a type 1 and 2 laryngomalacia with short aryepiglottic folds and inspiratory prolapse of supra-arytenoidal mucosa blocking the laryngeal inlet.

Video 1: *Type 1 and type 2 laryngomalacia co-occurring in an infant presenting with inspiratory stridor and OSA*

2.2. Pathophysiology of congenital laryngomalacia

The pathophysiology of congenital laryngomalacia is not yet fully understood. The anatomical theory dates back to 1897 when Sutherland and Lack proposed that laryngomalacia results from a congenital malformed larynx with immaturity of the tissues – a so called infantile appearing epiglottis (9). However, histological proof of an abnormal laryngeal cartilage or soft tissue is lacking (10). In addition, the anatomical theory does not account for the varying degrees of symptoms among infants with laryngomalacia. Based upon extensive clinical research in infants with laryngomalacia of varying severity and a wide range of clinical presentation,

D. Thompson formulated a neurological theory (11). According to this neurological theory, laryngomalacia is caused by an abnormal sensorimotor function of the larynx related to immaturity or abnormal integration of peripheral nerves such as the posterior laryngeal nerve, the brainstem nuclei and central pathways involved in maintenance of upper airway patency.

The neurological theory is in accordance with several clinical observations:

1) symptoms worsen during sleep in a subgroup of infants with laryngomalacia, causing obstructive sleep apnea;
2) maturation of the peripheral and central nervous system may explain a spontaneous resolution by age 2 in the majority of infants;
3) laryngomalacia may develop after a neurological insult;
4) outcomes of treatment are worse in children with underlying neurological conditions or comorbidities for whom a correction of the "anatomical" abnormality is insufficient.

2.3 Symptoms of congenital laryngomalacia

Inspiratory stridor, which starts within the first few days of life, is the main symptom in infants presenting with congenital stridor caused by laryngomalacia. Other symptoms may be present in varying degrees such as feeding difficulties, choking, apneas, regurgitation, cyanosis, weight loss. Children with moderate disease may present with inconsequential brief apneic episodes whereas those with severe disease may have life-threatening apneic episodes and consequences of obstructive breathing such as failure to thrive, pulmonary hypertension and cor pulmonale (11, 12).

2.4 Treatment of congenital laryngomalacia

Congenital laryngomalacia is commonly described as a condition that present shortly after birth, worsens in the first months of life, gradually improves thereafter

and resolves by age 18 months (11). As such, most patients can be managed with a non-surgical approach including feeding modification and treatment of gastro-esophageal reflux. It is widely accepted that about 10 to 20% of patients with congenital laryngomalacia would require surgical intervention because of severe symptoms (11).

Surgical intervention is advocated in children with feeding difficulties and failure to thrive, cor pumonale and episodes of cyanosis and apnea. Factors that are associated with an indication for surgery are prematurity, younger age at presentation and emergent evaluation in the hospital (13).

Endoscopic treatment of laryngomalacia by supraglottoplasty aims to trim the aryepiglottic folds, to remove redundant supra-arytenoidal mucosa and is the first line surgical treatment modality (6). Epiglottopexy is performed in cases of type 3 laryngomalacia with retroflexion of the epiglottis against the posterior pharyngeal wall completely covering the laryngeal inlet (14).

Tracheotomy is reserved for supraglottoplasty failures or infants with multiple comorbidities requiring tracheotomy for additional reasons other than airway obstruction (14).

Only few authors report on their experience with continuous positive airway pressure (CPAP) as a treatment modality for congenital laryngomalacia associated with obstructive sleep apnea (OSA). Zwacka et al reported on successful CPAP treatment in 10 infants with congenital laryngomalacia (15). Application of CPAP pressures between 4 and 7 mbar resulted in an immediate clinical improvement with a decrease of heart and breathing rate, an improvement in oxygen saturations and relief of inspiratory stridor. The effect of CPAP on the laryngeal appearance was documented by flexible endoscopy performed under chloral hydrate sedation.

In infants with laryngomalacia associated OSA that are deemed unfit for surgical intervention or when parents decline surgery, CPAP treatment may be considered a valuable non-invasive treatment option.

2.5 Sleep-disordered breathing and congenital laryngomalacia

Although apneas during sleep are recognized as a symptom of congenital laryngomalacia, only a few studies investigated the prevalence of SDB in children with congenital laryngomalacia.

Thanphaichitr et al. investigated the prevalence SDB in infants with congenital laryngomalacia (16). Data were available for 54 patients of whom 33.3% presented with an underlying neurologic disease, hypotonia or syndrome and 14,8% had a history of prematurity. A diagnosis of OSA (obstructive apnea/hypopnea index 1 event per hour) was made in 92.6%. Central sleep apnea syndrome (CSA),

defined as central apnea index 5/hr, was identified in 46.3%. Interestingly, 38.9% of children without risk factors had CSA. In a study by Fard et al, 108 patients had confirmed laryngomalacia and nearly half (52%) underwent a polysomnography (PSG) (17). Among them, 44 out of 56 (79%) were diagnosed with OSA. There were only 3 patients with a central apnea index (CAI) > 1/hour. Important to note is that this study included not only infants but also older children with sleep-dependent laryngomalacia. The mean age of the study population was 1.36 (range 0.65-3.18).

In a more recent study by Verkest et al. OSA, defined as obstructive apnea/hypopnea index 2/hr, was diagnosed in 77% of the 44 patients with laryngomalacia. An elevated central apnea index 1/hr, was found in 57% and 7 % had a CAI >5/hr (18).

2.6 Value of polysomnography in the diagnostic approach to congenital laryngomalacia

The role of polysomnography in the diagnostic work-up for infants with congenital laryngomalacia is poorly defined. In a recent paper published by IPOG (International Pediatric Otorhinolaryngology Group) on diagnosis and management of laryngomalacia, PSG was considered and adjunct and the authors recommended oximetry or PSG in cases with significant apneas (12). The study by Verkest et al. illustrated the potential value of PSG in the decision - making process for infants with laryngomalacia. In this paper, the severity score of laryngomalacia was altered in nine patients from mild to moderate and in 13 from moderate to severe. Polysomnography was found to be a useful non-invasive tool in the assessment and follow-up of infants with laryngomalacia. However, treatment decisions should be based upon the whole clinical picture, PSG and endoscopic findings (18). This conclusion is also supported by Cortes et al. who investigated the presence of OSA and sleep disturbances in children with severe laryngomalacia and the effect of supraglottoplasty on PSG parameters (19). In this study 11 patients with severe laryngomalacia based upon clinical symptoms and confirmed by flexible or rigid endoscopy underwent a polysomnography. All patients were diagnosed with severe OSA. The authors considered PSG as a non-invasive tool to identify OSA in children with severe laryngomalacia and to support surgical decision making.

Tawfik and colleagues investigated trends in indications for polysomnography in a large tertiary care hospital over a nine year period (from 2003 till 2012). The frequency of laryngomalacia as an indication for PSG increased from 2.5% to 14.3% and this difference was statistically significant. The authors assumed that this would reflect the increasing awareness among clinicians on the high prevalence of sleep disorders among infants with laryngomalacia (20).

Whereas only a few studies investigated the prevalence of SDB in cases of congenital laryngomalacia, several studies investigated the effect of treatment on polysomnographic parameters. These studies documented an improvement in PSG parameters after supraglottoplasty and concluded that PSG is an effective method to assess the efficacy of supraglottoplasty (19, 21-23).

2.7 Natural history of congenital laryngomalacia.

Symptoms of congenital laryngomalacia and especially stridor and respiratory distress resolve by 12-18 months of age (24). The natural evolution of other clinical manifestations such as OSA and endoscopic findings of laryngomalacia is yet unclear. Fard et al. investigated whether there is a spontaneous improvement in OSA in those children presenting with laryngomalacia and OSA whose laryngomalacia improves spontaneously (17). In the report by Fard et al, 34 out of 44 children with OSA and laryngomalacia and a mean age of 1.9 years, did not undergo a surgical intervention (17). They had a mean apnea/hypopnea index (AHI) of 2.1/h, nine underwent repeat PSG with a mean AHI of 1.5/h. The authors suggested that OSA may resolve with spontaneously improving laryngomalacia but the exact resolution rate could not be extrapolated given the limited number of patients that underwent a repeat PSG.

Moreover, the recognition of so called laryngomalacia variants presenting primarily with sleep-disordered breathing or swallowing disfunction in children beyond 18 months has challenged the evidence that laryngomalacia is characterized by spontaneous resolution in a vast majority of the cases. Isaac et al performed a systematic review on the natural history of laryngomalacia in otherwise healthy newborns without comorbidities or secondary airway lesions. These authors concluded that there is limited, level IV evidence for a spontaneous resolution of stridor and respiratory distress but that other endpoints such as endoscopic resolution or resolution of OSA have not been studied (1).

3. Sleep-dependent laryngomalacia

3.1 Clinical findings in sleep-dependent laryngomalacia

As an introduction to sleep-dependent laryngomalacia, I will first present a clinical case.

A 14 month old boy was admitted at the pediatric ENT department upon referral by the pediatrician. Pregnancy and birth were unremarkable, but the parents noticed noisy breathing and snoring since birth. He sleeps restless and awakens four to five times each night. The parents also noticed apneas during sleep. There are no other health related issues, growth and weight gain are age appropriate. Flexible upper airway endoscopy at another hospital was reported as normal. At the age of eleven months, a polysomnography was performed and showed moderate OSA: OAHI 5.5/h, CAI 1.8/h, Mean oxygen saturation 96.8% and lowest oxygen saturation 90%. Video recording during PSG showed noisy breathing, no snoring and frequent coughing during the night. A direct laryngoscopy was performed at the age of 14 months under general anesthesia with spontaneous breathing. This examination

showed mild adenoidhypertrophy (< 50% obstruction of the rhinopharynx) and laryngomalacia with inspiratory collapse of redundant supra-arytenoidal mucosa. The endoscopic findings are illustrated in Video 2.

Video 2: *Sleep-dependent laryngomalacia in a 14 month old boy presenting with OSA*

In 1997, Amin and Isaacson were the first authors to describe a condition called state-dependent laryngomalacia (10). These authors published a series of five infants (seven weeks to eight months of age) who presented normal breathing during wakefulness but had stridor and increased respiratory effort during sleep (10). Flexible endoscopy under anesthesia revealed a diagnosis of laryngomalacia. Follow-up was conducted by telephone interview and a resolution was reported between 6 and 15 months of age. In 2005, Smith et al. described a series of four children, aged 3-4 years, presenting with a primary complaint of noisy breathing during sleep. A diagnosis of laryngomalacia was established through an endoscopic examination under general anesthesia. Because the findings of laryngomalacia were only present in a hypotonic neuromuscular state and not during wakefulness, the term state-dependent laryngomalacia was coined and a neuromuscular system immaturity or disfunction for the observations was proposed.

In 2008, Richter et al defined sleep-dependent laryngomalacia as a clinical entity causing OSA in children beyond the neonatal period or first year of life (6). In line with earlier reports, the authors emphasized that these children do not present with inspiratory stridor but rather exhibit OSA related symptom such as snoring, restless sleep and apneas during sleep.

3.2 Pathophysiology of sleep-dependent laryngomalacia

The neurological theory of laryngomalacia could also explain sleep-dependent laryngomalacia, a condition only present during sleep when the neurological dysfunction is exacerbated by a reduction of neuromuscular tone which characterizes sleep onset. However, other factors such as gastro-esophageal reflux are thought to play a role (6). In addition, in cases where another obstructive lesion coexist with laryngomalacia, the malacia may be the result of a central mechanism affecting laryngeal muscle tone after a period of chronic hypoxia or CO_2 retention related to SDB (6, 25).

It is not yet fully elucidated whether sleep-dependent laryngomalacia represents a distinct clinical entity or rather a continuum of a disease process starting early on in life (1). Revell and Clarke hypothesized that some infants with laryngomalacia might never have been properly diagnosed. A delay in diagnosis may be related to several causes: atypical and non-alarming complaints, underreporting of symptoms by parents, insurance issues or limited access to medical care amongst others. Thevasagyam et al. found that, upon active inquiry, half of the children with late onset laryngomalacia had swallowing or airway problems during infancy (25). Under these conditions, laryngomalacia would represent a re-emergence or recurrence of laryngomalacia at an older age rather than a true late-onset condition (4).

Other authors such as Richter et al. considered late onset laryngomalacia as a different entity from congenital laryngomalacia being more commonly than reported at the time their paper was published (6). Moreover, in their series, these older children had no previous symptoms or diagnosis of laryngomalacia.

3.3 Diagnosis of sleep-dependent laryngomalacia

Sleep-dependent laryngomalacia is typically diagnosed during drug-induced sleep endoscopy (DISE) and is commonly caused by inspiratory collapse of redundant supra-arytenoidal mucosa (type 1 laryngomalacia).

Drug-induced sleep endoscopy allows for a dynamic evaluation of the upper airway during drug-induced sleep and aims to reveal the site(s) of upper airway obstruction in children with OSA. Suspicion of sleep-dependent laryngomalacia is a well-established indication for DISE (26).

Figure 1: *Type 1 Laryngomalacia: inspiratory collapse of mucosa overlying the arytenoid cartilages. This is the most common type found in about 60% of infants and is typical for sleep-dependent laryngomalacia. A combination of types (ex type 1 and 2) may be present in the same infant.*

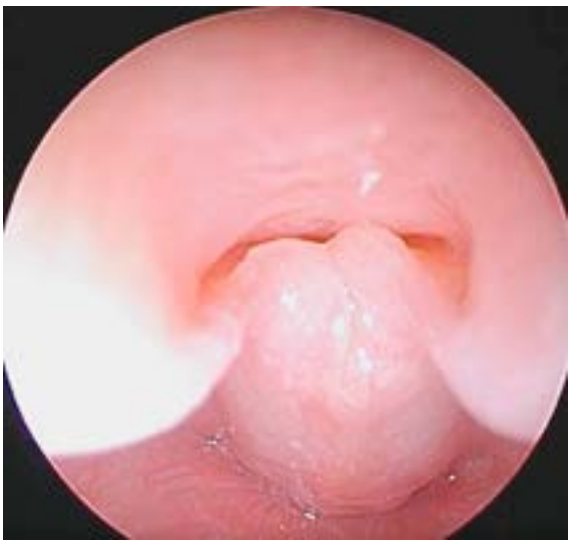


Figure 2: *Type 2: latero-lateral collapse of the epiglottis with short-aryepiglottic folds, present in about 20% of infants*

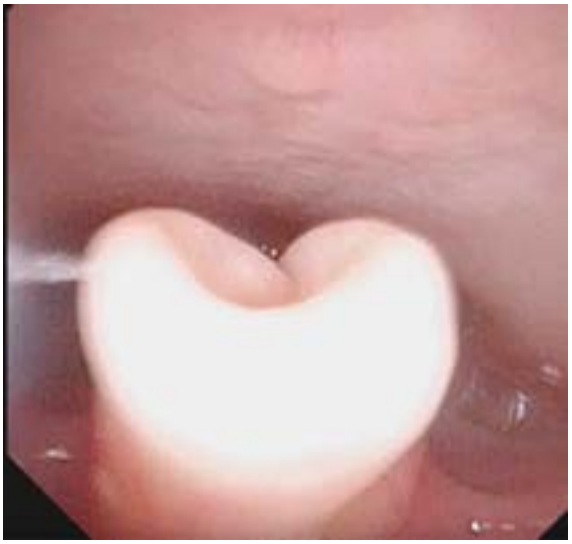
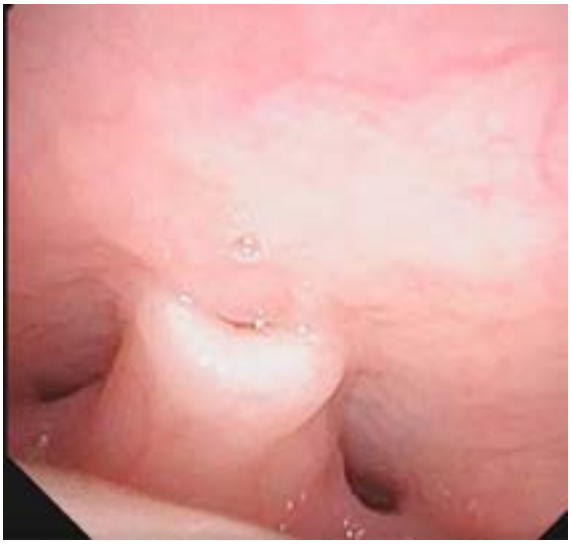


Figure 3: *Type 3: collapse of the epiglottis against the posterior wall, present in another 20% of infants.*



The case presentation above is in accordance with a disease continuum since upon careful history taking, symptoms were noticed shortly after birth. This case also points toward the role of polysomnography in young children with unexplained obstructive breathing during the night and the importance of endoscopic examination under general anesthesia in those cases were PGS is abnormal but not explained by clinical features.

3.4 Sleep-dependent laryngomalacia and obstructive sleep apnea

The prevalence of laryngomalacia among children presenting with sleep-disordered breathing identified by sleep nasopharyngoscopy is 3.9% (25). Sleep-dependent laryngomalacia has been recognized as the second most common cause of persistent OSA following adenotonsillectomy (27).

In their first paper on sleep-dependent laryngomalacia, Richter et al. presented seven patients, mean age of 6.3 years in whom a diagnosis of sleep-dependent laryngomalacia was established by flexible and rigid bronchoscopy during spontaneous breathing under general anesthesia (6). They all presented with symptoms consistent with OSA and five of them had a history of prior adenotonsillectomy. Polysomnography confirmed a diagnosis of OSA with a mean apnea/hypopnea index of 6/hr.

A few years later, Revell and Clarke reported on sleep-dependent laryngomalacia as a cause of OSA (4). The authors describe 19 children with OSA in whom a diagnosis of laryngomalacia was established by airway endoscopy. These children presented with snoring, apneas, daytime somnolence and difficulties awakening as the most common symptoms. Over 2/3 patients had adenotonsillar hypertrophy on clinical examination and the youngest was three years and nine months old (beyond the age range of congenital laryngomalacia).

Digoy et al. investigated the contribution of laryngomalacia to OSA in children over 12 months of age (28). The authors reported on 43 children with OSA on polysomnography and sleep-dependent laryngomalacia confirmed by sleep endoscopy. The majority, 32 patients, had a history of prior adenotonsillectomy. Nine patients had an underlying syndrome and five had cerebral palsy.

Laryngomalacia is increasingly reported as a cause of treatment failure after adenotonsillectomy. Chan et al. analyzed the data of 24 children, mean age

7. 3 ± 0. 8 years with persistent OSA who underwent supraglottoplasty, 50% of them had a comorbidity and 29.2% were obese (2). A greater postoperative improvement in AHI was observed in children without comorbidities (16.1 /h versus 2.6/h) compared to those with comorbidities (13.8/h versus 7.3/h) after supraglottoplasty. The authors suggested that the presence of comorbidities is a risk factor for poor outcome after supraglottoplasty (2). The children in this study all presented with sleep dependent laryngomalacia identified through sleep endoscopy and were overall younger than those presenting with lingual tonsillar hypertrophy as a cause of persistent OSA. The younger age of these patients and the high percentage of children with medical comorbidities characterized with generalized hypotonia, lead the authors to suggest that a deficiency in supraglottic tone is the cause of occult laryngomalacia.

3.4 Treatment of sleep-dependent laryngomalacia

When sleep-dependent laryngomalacia co-exists with a fixed upper airway obstruction such as adenotonsillar hypertrophy the clinician is facing a dilemma with respect to treatment. In some cases, the dynamic collapse of supraglottic tissues (laryngomalacia) is a secondary phenomenon caused by increased inspiratory negative pressure required to overcome the obstruction caused by adenotonsillar hypertrophy. In such cases with primarily adenotonsillar hypertrophy and mild laryngomalacia, the latter may resolve after adenotonsillectomy and supraglottoplasty may not always be necessary (4).

On the other hand, in meta-analysis by Camacho et al, 77.4% of children with laryngomalacia identified through DISE, had persistent OSA following adenotonsillectomy.(3)

Love and colleagues investigated the outcome of OSA treatment in surgically naïve young (< 2 year old) children with and without DISE identified laryngomalacia (29). The authors included 41 children with OSA and laryngomalacia (LM+) and 38 with OSA but no laryngomalacia (LM-). DISE directed treatment in the LM+ group consisted of supraglottoplasty in 92.3%, adenoidectomy in 46.2%, tonsillectomy in 26.3%. By contrast, in the LM- group DISE directed treatment consisted of adenoidectomy in 84.2%, tonsillectomy in 52.6% and 15.8% underwent no surgical intervention. Based upon post-operative PSG data, the authors concluded that DISE directed surgery reduced OSA severity in both groups.

Interestingly, children with OSA and laryngomalacia presented earlier in life and had worse quality of life by parental report.

Mase and colleagues investigated the impact of supraglottoplasty on OSA severity in patients with sleep-dependent laryngomalacia (5). Data were available for nine patients who underwent supraglottoplasty for sleep-dependent laryngomalacia and in whom pre-and post-treatment PSG data were available. The authors documented a significant improvement in AHI along with an improvement in weight to length percentiles and caregivers reported an improvement in sleep quality. A higher pre-operative AHI was associated with a greater postoperative improvement.

Both studies by Love et al. and Mase et al. underscore the role of sleep endoscopy to identify supraglottic obstruction, to avoid unnecessary adenotonsillar surgery and the role of supraglottoplasty as a treatment option for sleep-dependent laryngomalacia (5, 29).

Effect of supraglottoplasty on OSA in congenital and sleep-dependent laryngomalacia

Farhoud et al. performed a systematic review on the effect of supraglottoplasty for infants with congenital laryngomalacia and OSA (30). The authors included four studies, all level four evidence and could analyze data for 44 patients. Each study showed a statistically significant improvement in AHI. For patients with a pre- operative AHI greater than 12/h, the mean difference after supraglottoplasty was -30.7 and in those with a preoperative AHI less than 12/h, the mean difference after supraglottoplasty was -3.7. Both differences were statistically significant. In addition, there was a significant improvement in oxygen saturation nadir. The authors concluded that supraglottoplasty is a beneficial treatment option for infants with congenital laryngomalacia and OSA although patients may have persistent disease. A more marked improvement was observed in those with more severe disease at baseline and in younger patients (< 7 months).

Camacho et al. performed a systematic review on the outcome of supraglottoplasty for laryngomalacia associated with OSA (3). The authors analyzed data from 138 patients, 74 with congenital and 64 with sleep-dependent laryngomalacia. About 77% of the children with sleep-dependent laryngomalacia had failed adenotonsillectomy.

In children with sleep-dependent laryngomalacia, AHI decreased from a mean of 14.0 ± 16.5 to 3.3 ± 4.0 events per hour and the lowest oxygen saturation improved from 84.8% ± 8.4 to 87.6 ± 4.4% after supraglottoplasty. In cases with congenital laryngomalacia, AHI decreased from 20.4 ± 23.9 to 4.0 ± 4.5 events/hour and the lowest oxygen saturation improved from 74.5 ± 11.9 % to 88.4 ± 6.6%. Based upon individual data available from 9 studies, it was derived that 10.5% of the patients with sleep-dependent laryngomalacia were cured after supraglottoplasty (AHI <1/h) whereas 26.5% of patients with congenital laryngomalacia were cured.

The outcome of supraglottoplasty on central apneas is reported in only a few papers. Verkest et al. presented data on pre-and post-treatment polysomnography in 17 patients (18). The central apnea index decreased from 1.8/h (0.7-3.5) at baseline to 1.3/h (0.3-2.5) after supraglottoplasty but this change was not significant. Similar findings were reported by Cortes et al. (20). These authors did not find a significant improvement in CAI one month after surgery in nine infants with severe laryngomalacia who underwent supraglottoplasty. Thanphaichitr et al. warned that some infants with laryngomalacia and CSA may require additional treatment beyond surgery such oxygen therapy or respiratory stimulants (16).

A summary of the main findings and areas for future research are listed in Table 1 and 2.

Conflict of interest

The author has no conflict of interest to declare.

Table 1: Main findings on laryngomalacia and sleep-disordered breathing

Congenital laryngomalacia	Sleep-dependent laryngomalacia
A high prevalence of sleep-disordered breathing has been documented by PSG	Identified as the cause of OSA in nearly 4% of children.
Polysomnography is a useful non-invasive tool to assess disease severity, guide therapeutic decision making and evaluate treatment outcome	Represents the second most common cause of persistent OSA after adenotonsillectomy.
Infants present with inspiratory stridor during wakefulness, apneas and increased work of breathing may be noticed during sleep.	Most cases are > 2 years old, present with symptoms of OSA but do not have an inspiratory stridor during wakefulness Supraglottic collapse is only present during sleep.
A diagnosis of congenital laryngomalacia is established during awake flexible endoscopy and/or direct laryngoscopy under general anesthesia	Diagnosis established by drug induced sleep endoscopy.
Different types of laryngomalacia are described according to the pattern of supraglottic collapse	The typical feature is that of a type 1 laryngomalacia with inspiratory collapse of redundant supra-arythenoidal mucosae.
Supraglottoplasty improves polysomnographic parameters	Supraglottoplasty improves polysomnographic parameters but to a lesser extent than in congenital laryngomalacia

Table 2: Areas for future research

Congenital laryngomalacia	Sleep-dependent laryngomalacia
Is spontaneous resolution of inspiratory stridor associated with improvement of endoscopic findings and PSG parameters	What is the spontaneous evolution if left untreated?
What is the effect of supraglottoplasty on central apneas and what are treatment options if central apneas persist after surgery?	Is there a continuum in supraglottic collapse starting in infancy or is sleep-dependent laryngomalacia a different disease entity?

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Management of infants with Pierre Robin sequence

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Keywords

Pierre Robin sequence, upper airway obstruction, feeding difficulties, polysomnography

Abstract

Pierre Robin sequence is a congenital disorder classically characterized by retrognathia, glossoptosis and upper airway obstruction with or without cleft palate. This condition affects neonates and can cause serious respiratory and feeding difficulties requiring prompt intervention.

Currently there are no standardized management algorithms for neonates with Pierre Robin sequence and management of the condition remains a challenge. Assuring adequate breathing and feeding should always be the first point of concern.

Early diagnosis, sequential planning of treatment, adequate monitoring and multidisciplinary approach are essential for infants referred with Pierre Robin sequence.

We discuss here the full scope of the disease and the various management options.

Introduction

Pierre Robin sequence (PRS) is a clinical triad first described in 1923 by Pierre Robin and characterized by underdevelopment of the mandible (micro- and/or retrognathia), backwards placement of the tongue (glossoptosis) and respiratory obstruction. The term sequence is used, as each morphological anomaly is believed to arise from a cascade of events, retrognathia being considered as the triggering event. Although the presence of a cleft palate is not essential to the diagnosis, nearly 90% of infants also present with a cleft palate (1). The severity of cleft palate varies from simple bifid uvula, or occult submucosal cleft, to full palatal U-shaped or V-shaped cleft.

PRS has an estimated incidence of about 1 in 8000 newborns with a sex ratio of 1:1.

The condition can be isolated or associated with other malformations or syndromes, the latter being present in about 25-50% of the cases. The cause of this condition is not clearly identified, though different developmental theories coexist.

Prenatal diagnosis is quite challenging and the condition is most often established after birth, when the neonate presents with breathing or feeding difficulties.

Severity of PRS is often assessed by anatomical evaluation, however a functional classification scheme is more adapted for evaluating respiratory and feeding difficulties (2). The spectrum of the clinical presentation ranges from isolated episodes of upper airway obstruction and feeding difficulties to severe obstructive sleep apnea (OSA) and failure to thrive.

There are considerable differences in both definition and management of PRS between care centers and standardized treatment protocols are lacking (3).

Despite the significant initial respiratory and feeding difficulties, the evolution of Pierre Robin sequence is generally positive in isolated forms having benefited from adequate initial management.

Airway obstruction

The diagnosis of PRS is mainly clinical and somewhat subjective. Although retrognathia is defined as a 10-12 mm retraction of the inferior dental arc behind the superior arch, mandibular size is mainly assessed by clinical sight. Its diagnosis and that of glossoptosis remains subjective. *In fine*, the only objective sign in PRS is the respiratory obstruction.

The airway obstruction in infants with PRS is primarily caused by posterior placement of the tongue into the hypopharynx. Polysomnography (PSG) is a noninvasive and objective investigation tool to assess the severity of upper airway obstruction as there is a poor correlation between anatomical features and functional severity (4). PSG allows measurements of obstructive sleep apnea in terms of apnea index but also length and impact of the obstruction on the heart rate and oxygen saturation. PSG is therefore an effective tool to guide decision making for adequate treatment and for quantitatively measuring the efficacy of a given intervention. Controversy around the role of PSG is undoubtedly influenced by access to PSG and home monitoring devices (5).

In Belgium, where PSG is readily available, all infants with PRS should be rapidly assessed by PSG to evaluate the degree of airway obstruction. In our experience, we recommend PSG around the age of 3-4 weeks.

Once the degree of OSA is evaluated, the first priority of treatment is to relieve respiratory difficulties. Treatment of upper airway obstruction differs considerably between countries. Several methods have been used ranging from adapted positioning to invasive surgery (6).

Most physicians agree that prone positioning is the treatment of choice for mild PRS. There is however debate over the management of moderate and severe cases in which prone positioning alone is not sufficient.

There is still debate over the optimal criteria to determine conservative versus surgical management for patients with PRS. Neonates with severe airway obstruction at birth or soon after birth need more interventional treatment although there is a lack of clear-cut OSA criteria to define neonates requiring more than just conservative treatment, hindering development of standardized management guidelines.

Prone sleep positioning in widely used as first-line treatment in PRS and most are successfully managed by positioning alone (7).

Placing the infant in a prone position allows for forward movement of the mandible and the tongue by gravity. The tongue falling forward instead of backward in the pharynx increases the oropharyngeal space and reduces airway obstruction.

Prone sleeping position resolves airway obstruction in 40 to 70% of infants, although there are very few published studies documenting this effect of positioning on upper airway obstruction by PSG (1,8). However, there is great debate over recommending prone position in particular in infants with breathing difficulties as non supine positioning is clearly associated with increased risk of sudden infant death.

Again, in Belgium, we have easy access to home cardiovascular monitoring devices allowing us to benefit from prone positioning without endangering the infant.

Choosing the best intervention for a neonate with PRS should be individually tailored. In our institutional practice we recommend comparative PSG or at least oximetry in different positions to define the best sleep position for each child. We generally associate prone positioning with raised position (reverse Trendelenburg) and elevate shoulders. At discharge, when prone positioning is indicated, we equip the infant with a home monitoring device. When positioning alone is not sufficient, a nasopharyngeal tube is generally our second option (3). This is a flexible rubber tube inserted through the nose and ending at base of tongue to prevent the tongue from covering the epiglottis and therefore helping to keep the airway open.

In a retrospective cohort study from 1997 to 2014 of 172 infants with PRS treated in our center 91% were successfully managed by positioning alone and 9% required nasopharyngeal tube (9).

Conservative management (defined as prone positioning) is considered to be successful if the patients demonstrate stable airway (confirmed by PSG), absence of significant apnea and bradycardia on monitoring device and sustainable weight gain.

When conservative measures fail, there is need to resort to other nonsurgical or surgical practices. Depending on local expertise, the second line of treatment is often using a nasopharyngeal tube. Main difficulties with the nasopharyngeal tube are excessive secretions and obstruction of the tube itself.

A valid alternative is the use of noninvasive ventilation (most commonly continuous positive airway pressure). Nevertheless, this can be challenging in infants with PRS.

Although nonsurgical management is sufficient for many infants with PRS, those who fail will require surgical management.

Surgical options to relieve upper airway obstruction include the following techniques.

Glossopexy, also known as tongue-lip adhesion; in this procedure, the tongue is anchored to the lower lip and mandible, securing the tongue in an anterior lingual position and preventing occlusion of the upper airway (10). This technique has been somewhat abandoned because it prevents the tongue from moving correctly and makes feeding quite a challenge. The success rate is low and the risk of dehiscence not negligible.

Subperiosteal release of the floor of the mouth musculature is another surgical technique to partially relieve the excessive tension creating the glossoptosis theoretically allowing the tongue base to fall down to the floor of the mouth.

Mandibular distraction osteogenesis has been adopted by many centers as the primary surgical intervention for obstruction in PRS patients, though not in very young infants. Lengthening of the mandible addresses both retrognathia and glossoptosis by creating more space for the tongue and bringing the tongue forward through its attachments to the lingual surface of the mandible. The results are evidently not immediate, as the mandible is lengthened by progressive distraction. Complications include scarring, infection, facial nerve damage, dental and orthodontic complications.

Finally, tracheostomy, which was historically the only option for airway stabilization, is a definite and rapid option when upper airway obstruction is severe and requires immediate treatment. This technique can be associated with significant morbidity including delays in language development.

Studies comparing different treatment options are difficult to interpret as the discrepancies in expertise in performing each intervention between centers can impact treatment outcome.

It is important to keep in mind that most of these treatments serve as a temporizing measure while awaiting natural mandibular growth. Although there is controversy on this subject, findings support the hypothesis of (partial) mandibular catch-up growth in the PRS infant (11). Furthermore, infants exhibit improvement in OSA severity on sequentially performed PSG tests with advancing age (12).

The natural history of OSA in Pierre Robin patients treated conservatively shows improvement over the first 6-8 months of life with resolution by the age of 15 months. Factors potentially explaining this progress include craniofacial and airway growth and maturation of respiratory control (12).

Feeding difficulties

Feeding difficulties are very common and should be addressed rapidly to avoid major weight loss during the first days of life and to insure proper growth during the first months. Adequate feeding is essential to growth and to general well-being of the infant and the parent-infant relationship. Feeding and growth issues are generally consequential to multiple factors. They can be due to poor-quality sucking, dysfunctional swallowing, tendency to aspiration or acid gastro-esophageal reflux. They can also be secondary to respiratory problems causing elevated energy requirements or to associated anomalies or underlying syndrome (13).

Breastfeeding *per se* is generally not feasible due to the fact that the cleft palate makes it particularly hard to create a vacuum in the mouth, which is necessary to induce suction. Breastfeeding can be proposed for short periods, as appetizer or desert, to stimulate lactation and maternal contact, while avoiding fatigue. Maternal milk remains highly recommended and should be given with adapted bottle and positioning. When artificial milk is necessary, hypoallergenic milk is recommended as children with cleft palate present a higher rate of allergies, particularly to milk products, because these allergens come in direct contact with nasal mucosa.

Correct positioning during feeding is crucial. The best position for bottle feeding is an upright sitting position to limit milk flowing into the nasal cavity and aspiration. One hand is used to hold the infant's head (neck elongation) and the other to handle the bottle in order to apply pressure if needed to help suction and a finger under the jaw applying an upright movement to help advance the mandible (chin traction).

Use of a specialized cleft palate bottle such as Haberman nipple can help but is generally not necessary. In our center, we use classical disposable bottles (which are slightly suppler) with soft nipples and widened opening. Oro-facial physiotherapy is also used to stimulate the proper movement.

Feedings should be completed in 30 minutes or less, more time suggests the baby is working too hard and spending too much energy. Infants with PRS can benefit from more frequent but shorter feeding sessions to avoid fatigue. Calories might need to be added if volume intake is not optimal. Early intervention by a dietitian is recommended to reduce impacts of feeding difficulties.

Infants with PRS express to some extent glosso-pharyngo-laryngo-esophageal dysmotility. Gastro-esophageal reflux is therefore frequent and should also be taken into consideration and addressed by thickening the milk, offering adequate positioning during and after milk intake and if necessary use of proton pump inhibitors.

If failure to thrive persists despite these measures, feeding through a nasogastric tube (or in fewer cases gastrostomy) might be indicated. Some studies describe up to 40-70% of PRS cases that require nasogastric tube feeding for up to several months and may even require gastrostomy (1). Generally, 70% achieve full oral feeds by one month of age (12). Feeding difficulties correlate with longer length of hospitalization and are more frequent and more severe in patients with associated anomalies or syndromes (13,14). Poor weight gain can also be responsible for delaying surgical correction.

Growth and feeding should be routinely monitored during the first weeks or months of life and diet adapted accordingly. Growing and gaining weight will allow a better growth of the mandible, therefore a better positioning of the tongue, and in turn, less respiratory obstruction.

Malformative assessment

PRS is frequently associated with other anomalies or syndromes. Most studies conclude that 50% are isolated findings while the other 50% are associated with other malformations or genetic syndromes. Routine screening for associated malformations is recommended with cardiac, cerebral and renal ultrasounds.

The two most common syndromes associated with PRS are Stickler syndrome and 22q11 deletion syndrome. A molecular karyotype is performed and a genetic consult offered. An ophthalmological evaluation is recommended around the age of 12 months.

Otitis media is quite often (occurring in over 80% of the time) and is due to inadequate pneumatization of the mastoid cavity and poor middle ear drainage. This can lead to conductive hearing loss. Evoked auditory potentials need to be performed to exclude other causes of hearing loss.

Cleft palate repair

In our center, patients with isolated cleft palate (so without PRS), benefit from early closure of the palate around the age of 3 months. Early reconstruction of the oral cavity allows the tongue to regain a normal position, to restore normal deglutition, to reduce regurgitations and to prevent otological complications. Closure of the cleft palate also plays an important role in speech acquisition.

The limiting factor for early surgery is respiratory obstruction as this can be amplified by closing the palate. Depending on the degree of OSA measured by PSG, surgery might need to be delayed up to 6 months of age or even later in more severe cases of PRS.

Trans-tympanic tubes are placed in practically all children during the closure of the cleft palate to prevent serous otitis media, with the hearing impairment and infectious complications (15).

The mandible does generally not require surgery as its natural course is to grow with age to a normal size.

Multidisciplinary follow-up

Both feeding and airway obstruction are routinely evaluated during the first months of life and improve over time. This is attributable to normal developmental growth allowing craniofacial and airway growth and maturational changes of respiratory control.

The main complications observed in patients after cleft palate repair are ear and hearing complications, speech disorders, swallowing disturbances and infections of the upper respiratory tract. After staphylorraphy, children can present speech disorders with hypernasality generally due to velopharyngeal insufficiency. Speech therapy is often required. Corrective surgery can be offered in cases with poor response to therapy.

Growth and neurocognitive development are closely linked to underlying OSA. Our observations match those of previous publications demonstrating a generally normal long-term development in children with an isolated Pierre Robin sequence (16).

Long term follow-up should be offered by a trained multidisciplinary team including a pediatrician with expertise in developmental and sleep medicine, a plastic surgeon, a maxillo-facial surgeon, an otolaryngologist, a geneticist, a dentist, an orthodontist, an orofacial physiotherapist and speech pathology experts. The purpose of the follow-up is to prevent and correct these complications (15).

Conclusion

In infants referred for PRS, our primary goal is to offer effective and safe treatment until they have grown out of their respiratory and feeding difficulties. Objective assessment of OSA severity is essential.

There is a long list of options for management of airway obstruction in infants with PRS and a lack in standardizing treatment protocols. Rigorously comparing outcomes following a treatment plan remains difficult due to variations in the cohorts, in the severity of the phenotype and the experience of the care giving center.

Nevertheless, choosing the best intervention for a neonate with PRS should be individually tailored as there is great heterogeneity among this group of patients. The primary goal being to choose the less invasive effective treatment to minimize morbidity.

Future prospective work is needed to evaluate long-term neurodevelopmental outcomes in this population.

Conflict of interest

The authors have no conflict of interest to declare.

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Parasomnias in Children

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Keywords

Childhood – parasomnias - Arousal disorders - NREM sleep – REM sleep

Abstract

The International Classification of Sleep Disorders (ICSD-3) defines parasomnias as "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep." The term parasomnia derives from the Greek word para meaning around and the Latin somnus meaning sleep. Parasomnias in childhood are common, more often benign, self-limited and typically resolving in adolescence; they occur either in slow sleep (non-REM) or in paradoxical sleep (REM). To make a diagnosis, it is necessary to clearly identify their characteristics, first by a history as precise as possible and then, if necessary, by a video-polysomnography. Indeed, the differential diagnosis with other events, including epilepsy, is essential. Polysomnography is not always sufficient for the diagnosis and video polysomnography may be indicated to assist in the definition of parasomnias or other sleep disruption, especially when it is not possible for the clinician to identify the etiology of the motor activity in sleep. Misdiagnosis should be avoided and appropriate treatment chosen, if necessary. In this article, we will only review the most common NREM and REM sleep parasomnias in pediatrics; other parasomnias, such as enuresis, will not be discussed. We will attempt to describe their characteristics, pathophysiology and triggering factors, as well as their management.

Introduction

somnias are physical events - or unwanted experiences that occur during sleep (slow or paradoxical), or during sleep-wake transitions (when falling asleep or waking up). According to the 2014 International Classification of Sleep Pathology (ICSD3), parasomnias are classified according to the time of their appearance during sleep (Table1). They can be motor (the subject moves), verbal (he speaks) or sensory (emotions, perceptions, dreams) (1). Most parasomnias occur almost exclusively in childhood and become pathological during this period only if they are too frequent.

Table 1 : Parasomnias categorized according to the International Classification of Sleep Disorders 3rd edition.

I . Disorders of arousals (NREM parasomnias)
- Confusional Arousals
- Sleepwalking
- Night Terrors
- (Sleep Food Disorder)

II. Parasomnias associated with REM sleep
- REM Sleep Behavioural Disorder (RBD)
- Recurrent Isolated Sleep Paralysis
- Nightmare Disease (or disorder)

III. Other parasomnias
- Exploding Head syndrome
- Sleep-related hallucinations
- Sleep enuresis
- Parasomnia due to medical conditions
- Parasomnia due to drug or substance
- Parasomnia, unspecified

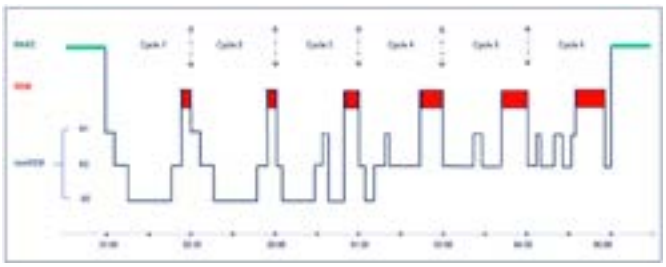
IV. Isolated symptoms and normal Variants
- Somniloquy (sleep talking)

The state of human consciousness is broken down into three stages: awakening - slow wave sleep (SWS) or non-rapid eye movement (NREM) sleep – rapid eye movement (REM) sleep. The process of the appearance of these different states is modulated by a multitude of factors at the level of our central nervous system (CNS) which receives and decodes all related stimuli, internal or external, via very complex neural and neurochemical circuits between the brainstem, the thalamus and the cortex. The method of study of these stages is done classically by the electroencephalography (EEG) which is the reference tool for functional exploration of cortical and subcortical activities. Each stage of consciousness has its own characteristics that allow us to identify them (1).

Thanks to the homeostatic and circadian control of sleep and wakefulness, the process of onset of a particular sleep-wake state is expected and maintained in a stable and predictable manner throughout the 24 hours. A classic night consists of several cycles of sleep that follow one another. Each cycle lasts approximately 90 to 120 minutes. As the night progresses, very deep slow sleep (NREM sleep) decreases in favour of REM sleep (Figure 1).

NREM parasomnias are therefore more common in the first part of the night, while parasomnias of REM sleep are more common later in the night. This article will review the most common parasomnias in paediatrics - their classification, epidemiology, clinical characteristics - differential diagnoses to be considered - their evaluation and management.

Figure 1: *Classic hypnogram showing the succession of sleep cycles (about 90 min.). At the start of the night, sleep is dominated by the 3 stages of NREM sleep and in particular by slow-wave N3 deep sleep. Later, in the second part of the night, the incidence of REM sleep gradually increases.*



Evaluation and diagnosis

1. Description of the sleep disorder

The diagnosis of parasomnias is mostly based on clinical data and therefore detailed information on the events is necessary. Parents are the first source of information, but often they are unable to report the exact description of the events because they were asleep or because the event is often sudden, violent and can represent an intense emotional experience for them.

In view of this, it is very important to have a detailed parents /caregivers history regarding the characteristics of the events, with a description of the details of the movements and behaviours. To complete their descriptions, parents very often make a video with their smartphone which can be very helpful, even crucial in some cases.

2. Clinical examination

It is also essential to carry out a clinical / neurological examination in search of disorders likely to influence sleep (for example adenotonsillary hypertrophy, retro-micrognathia, other abnormalities of the face which may lead to disorders of sleep breathing). The presence of breathing disorders during sleep can reinforce the occurrence of parasomnias (2).

3. Questioning of parents / witnesses

1. At what time during the night do the events occur? How long after falling asleep? Does the episode also take place during naps? Were similar events observed during the days before?
2. What is their duration? (seconds, minutes, hours?)
3. What is the child's level of consciousness during the events? (is the child fully awake? does he recognize his parents? is he able to relate what is happening?)
4. Consequence of the intervention or efforts of the parents to console the child (do they worsen the episode?)
5. Recollection or complete amnesia of the event the next morning ?
6. Semiological description of the event: stereotypical complex motor movements? or semi-intentional behaviour?
7. Number (if any) of events per night?
8. Are there other sleep disorders at the same time : snoring, apnea?

I. NREM-SLEEP PARASOMNIAS or DISORDERS OF AROUSAL (DoAs)

NREM sleep is characterized by a cyclical synchronization of brain activity and an overall but heterogeneous decline in brain metabolism. Gradual synchronization of brain activity defines 3 stages of slow sleep (NREM sleep) : very light SWS, when falling asleep : N1, light SWS (with sleep fuses or spindles) : N2, and deep SWS : N3. DoAs include Sleep terrors, confusional arousals and sleepwalking which are very common disorders in children. Sleep-related eating disorders are only seen in adults, and will not be detailed in this article.

Common features

Those parasomnias correspond to a phenomenon of partial awakening in the deep SWS (N3) (80%), but sometimes in N2 (20 %) (3,4). In fact, one could say that the musculoskeletal system and the autonomic nervous system activate themselves when the brain is still sleeping. Cognitive abilities are greatly impaired or even non-existent, while motor skills, for the most part, are maintained. The subjects therefore have a very altered perception of the environment, and are difficult to wake up during the event (especially not to provoke!). Activation of the autonomic nervous system, semi-automatic behaviour, varying degrees of confusion, disorientation and amnesia of the facts are characteristic (Table 2).

a. Time of occurrence

Because of the association with slow wave sleep, NREM parasomnias (DoAs) tend to arise during the first third (or even the first half) of the night, when SWS is most important. They can occur during other times when deep slow sleep is increased, such as during recovery sleep after sleep deprivation, and rarely during a daytime nap.

Table 2 : Common features of NREM parasomnias

Characteristics	Confusional arousals	Sleepwalking	Night terrors
Age (years)	2-10	4-12	1,5 -10
Family history	++	+++	++
Onset	First part of the night (often 1 to 3 hours after falling asleep)		
Agitation	Poor/mild	Poor/mild	marked
Autonomic activity	Low	Low	High
Behaviour	automatic behaviour but not stereotypical - seem haggard - cognitive functioning minimal or absent		
	Sitting in bed Sometimes talking or moaning	Walking around Unresponsive to verbal orders	Screaming – agitation flushed face - sweating reject potential interveners
Amnesia the next day	++	++	++
Contributing factors	Stress, fever, anxiety, sleep deprivation, irregular sleep schedules …		

b. Epidemiology

No gender difference has been reported in sleepwalking, sleep terrors or confusional arousals. DoAs are common in childhood in preschool children (3 to 6 years of age) : sleepwalking 14.5%, sleep terrors 39.8% and in 14.4% of preadolescent children (5,6). A Quebec study, carried out over 12 years, studied the prevalence of sleep terrors and sleepwalking from 18 months to 13 years. For sleep terrors, the prevalence, was 34.5% at 18 months, rapidly decreased to 13.4% at the age of 5 and gradually decreased to 5.3% at 13 years.

Sleepwalking generally appears a little later in childhood (2.5 years), with a peak of prevalence (13%) at 10-13 years (7). Confusional arousals occur in 17.3% of children 3–13 years of age ; the prevalence drops to 6.9 % in those more than 15 years and to 2.9%–4.2% in adults (8,9). Arousal disorders can persist into adulthood, but their frequency is much lower.

c. Pathophysiology

The high prevalence of arousal disorders in childhood is well recognized. This specific parasomnia-child link depends on certain ontogenetic characteristics of sleep: the importance of deep slow sleep that increases significantly between the first and the tenth year of life, the immaturity of transitions from one state of alertness to another, or the immaturity of certain functions, such as bladder control in the case of enuresis. Even minor changes in the child's habits may lead to desynchronization of its normal rhythms and cause internal arousal stimuli, occurring at "the wrong time", cause an incomplete arousal from very deep sleep. As development continues, these mechanisms mature, synchronization occurs, and the symptoms resolve, unless an underlying pathology, such as sleep apnea, exists (10). The decrease in these parasomnias of NREM sleep in adolescence is linked to the physiological decrease in the amount of SWS at night with aging. This decrease in slow sleep and slow wave activity (delta, ~ 0.5–4.5 Hz) is secondary to underlying changes in the structure and organization of the brain; it is the decrease in synaptic density that probably results in the reduction of high amplitude slow waves (11,12).

The activation of the serotonergic system is partially responsible for arousal and is involved in triggering motor activity. In NREM parasomnias the abnormal excitability of the serotonergic system exists, which, when activated independent of other neurotransmitters involved in arousal, results in motor behaviours but incomplete arousal (10,13).

c.1. Genetic factors

Many factors can influence the mechanisms by which parasomnias arise and are clinically expressed. Genetic predisposition plays a very important role in DoAs, specifically in sleepwalking. The prevalence of childhood sleepwalking: 22.5% for children without a parental history of sleepwalking, 47.4% for

children who had 1 parent with a history of sleepwalking, and 61.5% in those with two affected parents (7). Population-based studies of monozygotic and dizygotic twins suggest that genetic factors are involved in 65 % of cases of sleepwalking (14). A family study, carried out by a Franco-Swiss team, found a positive association between the HLA-DQB1 * 05 subtype and sleepwalking, suggesting a possible additional interaction between the immune system and sleep (15).

c.2. Favouring / precipitating factors

Besides genetic influence, there are several contributing / triggering factors of parasomnias, such as age, sleep deprivation (which causes a rebound in SWS), irregular sleep schedule, fever, occurrence of stressful events, such as family conflicts, separation anxiety, problems related to work or school and changes in the sleeping environment (for children: moving, changing rooms, etc.) (5,16). DoAs can also be triggered by environmental stimuli such as phone calls, text messages, pagers, messages from electronic devices, and several other stimuli (1).

Other sleep disorders (hypersomnia, insomnia, circadian rhythm disturbances) and intrinsic sleep disorders (obstructive sleep apnoea syndrome (OSAS) and periodic limb movements during sleep (PLMS)) can trigger parasomnias that can disappear after their treatment (2).On the contrary, infantile psychopathology is not frequently associated with parasomnias (17). There are other co-morbid factors: migraine, hyperthyroidism, head trauma, use of certain drugs (e.g. neuroleptics, sedative hypnotics, stimulants, antihistamines, etc.) and consumption and abuse of coffee or alcohol.

Clinical features

The three clinical entities (confusional arousals, sleepwalking, and sleep terrors) have common characteristics such that they could represent 3 clinical variants of the same pathophysiological entity (18).

Confusional arousals

These are characterized by sudden arousal with disorientation, confusion, movements and moaning, sometimes associated with semi-purposeful behaviours like calling out (screaming), crying or thrashing. The subject, who sleeps peacefully, suddenly sits up in his bed, but does not ambulate away, does not walk around the room; he looks around confusedly, his eyes haggard. They typically occur in the first part of the night, but can also occur later in the night or even in daytime naps. The events may be brief, lasting 1 or 2 minutes or longer (19,20). Some forms of confusional arousals can evolve into sleepwalking in adolescence. The differential diagnosis includes nocturnal partial seizures, which could trigger or mimic confusional arousal, sleepwalking and sleep terrors, and also REM sleep behaviour disorders (Table 3).

Somnambulism or sleepwalking

Somnambulism is defined as "a series of complex behaviours that are usually initiated during arousal from slow wave sleep and culminate in walking around with an altered state of consciousness" (1). It most often occurs in the first third or the first half of the sleep period, usually during SWS (N3) at the end of the first or second sleep cycle.

Sleepwalking can start as soon as a child is able to walk, but may start at almost any point in the life cycle. It usually goes away on its own around puberty but can persist into adulthood. Episodes occur with varying frequency (once to several times per week or per month), but usually once per night; however, more rarely, several episodes per night have been reported.

Sleepwalking attacks can be calm or restless with varying degrees of complexity and duration (21). Patients often start by sitting in bed and looking around in a confused manner with haggard eyes before getting up and walking, but sometimes may immediately leave the room, walk or run, or get out of the house, talk (often absurdly), dress, eat and drink. They also may exhibit absurd or abnormal behaviours (urinating in a trash can, rearranging furniture, or climbing out a window.). It can be dangerous to try to wake a sleepwalker, he can have an "escape reflex": either he can flee and risk being injured, or behave violently or aggressively against the observers who try to wake him up, hold him back or redirect. Violent features are more common in men (9).

The agitated form of sleepwalking occurs more often in the older child. The episodes may last from a few minutes to more than half an hour, and usually end with the patient returning to bed, lying down and continuing to sleep. There is usually amnesia for the episode. Affected individuals usually find their way through familiar environments but are prone to falls and injuries. These patients may exhibit a high tolerance for pain, such as burns or lacerations that may not awaken them. The frequency is highly variable, ranging from an isolated occurrence to several per night. There is a reported association between higher sleepwalking frequency and earlier age of onset (22).

Sometimes it is difficult to distinguish restless sleepwalking from sleep terror, as both conditions can manifest as screaming, bed hopping and running, and violence. However, in sleepwalking there is usually no autonomic activation or expression of fear. The eyes are often open with a confused "glassy" gaze, while in behavioural disorders in REM sleep, the eyes are generally closed.

Sleep terrors

Sleep terrors are distinguished from other DoAs by their prominent autonomic activation. Events are characterized by vocalizations such as screaming, with associated manifestations of terror and excessive sweating, tachycardia, tachypnoea, and mydriasis. Affected children appear agitated, usually

Table 3 : Comparison of paediatric parasomnias and nocturnal seizures

Characteristics	Conf. arousals	Sleepwalking	Night terrors	Nightmares	Seizures
Age (years)	2-10	4-12	1,5-10	3-10	Any age
Timing during sleep	1st third (or half)			2nd half	any
Number/night (average)	≥1	1	1	≤ 1	>> 1
EEG states	N3 (N2) NREM			REM	any
EEG abnormalities	No			No	Yes
Episode duration	2-30 min.		1-10 min.	-	< 1 min.
Behaviour (video) Autonomic activation Agitation	Moderate Moderate	None/mild None/mild	Marked Severe	Mild (before awake)	Variable Variable
Movement semiology	Variable complexity- not highly stereotyped (on video)			-	stereotypic
Confusion	+	+	+	No	+
Mental content	Poor or absent			rich, elaborate, scripted	rarely present
Reassurance (effect of)	No	No	No	Good	No
Family history	Yes			No	Rare
Clinical evolution	Trends to disappear with age (teenager)			Variable	Often stable

According to Mason (3), Derry (10) Stores (20).

sit up in their bed and are unresponsive to external stimuli, may exhibit prolonged inconsolability without awareness and, like confusional arousals, the behavioural manifestations typically take place while sitting up in bed. Episodes typically last several minutes and are followed by the individual calmly and quietly returning to sleep (9). The episodes emerge in the first third of the sleep period (first part of the night) and may last up to 10 minutes or longer. Typically, they do not remember the events and do not report dreams or nightmares but might have a vague sense of frightening images. One of the main problems of the disorders of arousal is to differentiate them from nocturnal complex partial seizures or frontal lobe seizures (Table 3).

Management and therapy

The treatment of disorders of arousals in NREM involves first reassuring parents that parasomnias are common in childhood and can be effectively managed (3). A comprehensive explanation of the nature of these parasomnias and reassurance that the children are mentally and developmentally normal should be provided (23). First and foremost, the most important care is to remove the noisy and disturbing environment, the sources of stress, recognized as triggers of parasomnias and treat any sleep disorders such as obstructive sleep apnea (OSA) (2). A period of quiet activity or relaxation techniques should be instituted before bedtime (23).

General guidelines for the management of these DoAs include education, prophylaxis, safety precautions, and clear and specific intervention instructions for parents / witnesses (Table 4). Specific treatment approaches include early arousal, psychotherapy, hypnosis, and pharmacotherapy (9).

Table 4 : NREM parasomnia management.

Parents information first !	**Prophylaxis measures**
· Reassure and explain parasomnia · Usually benign, self-limited · Genetic predisposition · No association with psychiatric condition * · Safety is one key in treatment * in adults only	· Avoid sleep deprivation · Avoid stress factors · Avoid stimulation (emotional or physical) before bedtime · Avoid caffeinated drinks ** · Practice good sleep hygiene · Prevent environmental stimulation (i.e., light, sound, beeper smartphone, touch) · Treat co-morbid factors (OSA ,GERD, pain..) · Minimize medications (including psychotropic drugs) ** and alcohol in teenagers
Safety measures	**Parents/Bystander guidelines**
· Remove potentially dangerous items near the bed · Lock doors and windows · Security alarm to alert family members if the subject leaves his room · Stairwell gates and night light to prevent falls / injuries	· Observe in silence · Allow the subject to move and follow him · Don't wake him up · Intervene only to avoid injury · Avoid physically restraining the patient - this could cause violent behaviour or an escape reflex

General guidelines

1. Safety measures, important to advise parents are: place the mattress on the floor, secure windows and exterior doors, use alarm systems and bells informing parents that the child is leaving his room. It is very important to inform the parents not to try restraining or awakening the child during an episode because this might worsen (escape reflex and risk of injury) or prolong it.

2. Education – prophylaxis : It is also imperative to remember the rules of sleep hygiene, and the importance of a regular sleep schedule that avoids sleep deprivation. To do this, we can ask parents (and children) to keep a sleep diary, to become aware of the child's real sleep schedule and time; this can help them reduce sleep deprivation and therefore also reduce the frequency and duration of parasomnias. Caffeine or theine- containing beverages must be eliminated because they may contribute to decrease sleep efficiency and may predispose to the episode. It is also very important to inform parents not to try to restrain or wake the child during an episode as this could make it worse (escape reflex and risk of injury) or prolong it. As the child usually has no recollection of the episode, then there is no point in telling him the next day, as this can promote anxiety.

3. Specific treatment approaches

*3.a. The behavioural method of "programmed awakenings"***:** may be useful only in children whose parasomnias occur frequently and at a predictable time, and also before parents go to bed (3,24).

Parents should keep a diary of when episodes occurred for about 2-3 weeks to determine the average time these episodes occur. Then they will need to wake the child up every night about 15 to 30 minutes before their usual parasomnia time for about a month - and make sure to wake the child up for about 5 minutes before letting him go back to sleep. The cessation of episodes is maintained even after the cessation of forced arousals (Table 5).

Table 5 : Method of programmed awakening in the treatment of somnambulism and sleep terrors.

1.	Keep a diary of when episodes started for about three weeks (increase this period if episodes are infrequent).
2.	Establish the average time of onset of episodes.
3.	Wake the child up every night 15 to 30 minutes before the average time of onset of episodes for a period of about a month.
4.	Make sure the child is awake for about five minutes and let him fall back to sleep.

According to Petit D. and Zadra A. (24)

3.b. psychotherapy – hypnosis - relaxation

Other non-pharmacological interventions such as hypnosis, relaxation and psychotherapy have been proposed for the treatment of DoAs ,with controversial results (4). Some studies (adult patients) have shown a complete disappearance or a very great improvement in 45% of patients after one month of hypnotherapy but little evolution afterwards. One or two hypnotherapy sessions could therefore be useful as a first-line treatment for patients with certain types of parasomnias (25).

3.c. Drug treatment, often reserved for adults

Drug therapy is only indicated when parasomnias are frequent, prolonged and / or causing injury to patients. Benzodiazepines are often effective: low dose clonazepam, starting with 0.25 mg one hour before bedtime, increasing slowly if necessary (watch out for possible daytime sedation). Generally 3–6 weeks of treatment may be curative for a long time (21). However, in children the use of psychotropic drugs is generally not recommended because: a) they are thought to mask the symptoms rather than to treat the causes of partial arousals; b) the drug-induced decrease in slow-wave sleep might have detrimental effects; c) tolerance and rebound effects occur frequently and cause severe increase in parasomnias (19).

3.d. L-5-hydroxytryptophan (L-5-HT)

According to a physiopathological hypothesis (put forward by Jacobs in 1992), DoAs could be due to a conflict between the mechanism which induces slow sleep and that which causes wakefulness, via a dysfunction of the serotoninergic system. Based on this hypothesis, the administration of L-5-hydroxytryptophan (L-5-HTP), a precursor of serotonin and capable of increasing the levels of cerebral serotonin, could exert beneficial effects on the disorders of arousal such as sleep terrors (26).

II . PARASOMNIAS associated with REM sleep

REM sleep behaviour disorder, sleep paralysis and hypnagogic hallucinations are reported in adults but very rare in children. When present in childhood, sleep paralysis and hypnagogic hallucinations are classically associated with narcolepsy, but can occur in very rare cases of familial sleep paralysis or sporadically with a rebound in REM sleep. The most well-known REM sleep disorder in children is, of course, the nightmare.

REM sleep behaviour disorder (RBD)

RBD is characterized by the loss of the physiological atony characteristic of

REM sleep; on the contrary, there is an increase in phasic muscle activity in REM, resulting in the acting out of dream content. These patients have complex movements that can be vigorous and even violent, may injure themselves or the bed-partner by punching, grabbing or kicking. Episodes seem to occur more often during the first phase of REM sleep at night (23).

Childhood RBD is very rare and appears to occur in children: 1. who have narcolepsy or sometimes idiopathic hypersomnia, 2. who have received pharmacological agents that increase muscle tone during REM sleep, such as selective serotonin reuptake inhibitors (SSRI) antidepressants drugs, or 3. who suffer from neurodevelopmental disorders or brainstem abnormalities such as autism, Smith-Magenis syndrome, Moebius syndrome, Chiari malformations, and midline tumours. In the short term, in the paediatric population, it seems to be modestly responsive to low dose benzodiazepines (clonazepam 0.125 to 0.25 mg) or melatonin (27).

Polysomnographic studies with multiple electromyography (EMG) channels are essential for the diagnosis, in order to demonstrate the loss of muscle atonia . There is an intermittent loss of REM atony with an excessive phasic muscle contraction activity of EMGs (submental - upper or lower limb) during REM sleep (28).

Recurrent isolated sleep paralysis

Recurrent isolated sleep paralysis (RISP) not occurring in association with narcolepsy is defined as isolated sleep paralysis. It characterized by a transient inability to perform voluntary movements when falling asleep (hypnagogic) or upon awakening (hypnopompic): the patient is unable to speak or move limbs, trunk and head. Breathing is usually affected. Consciousness is preserved, and the memory is complete. Each episode lasts seconds to a few minutes and causes clinically significant distress, including bedtime anxiety or fear of sleep. It usually goes away spontaneously, but can be interrupted by sensory stimulation (tactile or sound) or when the person quickly moves its eyes or makes intense efforts to move its limbs or body (29,30).

The pathogenesis of this disorder is linked to the persistence of REM atonia into wakefulness : normal mental activity occurs in the presence of body paralysis ! Severe anxiety is usually present, at least during the first few episodes. In EEG polysomnography (PSG), there is a typical sequence, with the intrusion of an alpha EEG rhythm in REM sleep, followed by an arousal response, then the persistence of REM atony in the waking state.

RISP may be accompanied, in approximately 25% to 75% of patients, by very intense and vivid hallucinations, auditory, visual, tactile or a sense of presence in the room. These paralyzes are rare in children (apart from narcolepsy) and do not often occur before adolescence but always in young people (generally less than 30 years old). Some studies report a prevalence of at least one episode of sleep paralysis in 15 to 40% of the general population, while recurrence is less common.

Support - treatment. First-line treatment is reassurance that the episodes are benign**.** Apart from narcolepsy, in healthy patients, the main contributing factors are sleep deprivation, irregular sleep-wake schedules and jet lag. The most effective therapy is to avoid these factors (29).

Nightmare disorder

Nightmare disorder is characterized by repeated nightmares, which are most often frightening dreams that usually involve threats to survival, security, or physical integrity, and usually wake the sleeper up. They usually involve negative experiences such as anxiety, fear, terror but also anger, rage, embarrassment, so the children may appear anxious after awakening but can detail the nightmare's contents (23,29,30).

Occasional nightmares are common in children, ranging from 60% to 75%, but the prevalence of nightmare disorder is estimated to be 1.8% to 6%. Typically nightmares start between the ages of 2.5 and 6 years, with a peak around 6 to 10 years and decreases thereafter. In children aged 3 to 5 years, it is reported that 10–50 % have nightmares severe enough to disturb their parents, without gender differences. However, adolescent and adult females report these episodes more frequently (31).

Anxiety or psychiatric disorders are more frequent in children with nightmares than without. Exposure to violent content in video games or television programs can contribute to nightmares and should be avoided as part of routine sleep hygiene and bedtime education. Monsters or other fantastic images often characterize the dreams of young children, while adolescents may experience more realistic images related to daytime stressors or traumatic events. Nightmare disorder can also be a specific marker of post-traumatic stress disorder (PTSD) or a history of sexual abuse or maltreatment in children and adolescents (3,32).

Support - treatment In the case of simple, ordinary nightmares, the child should be listened to and reassured so that he can fall back to sleep peacefully. Cases of psychological distress and cases of psychological or physical abuse require appropriate and psychotherapeutic care. For the treatment of repeated nightmares, the most effective method in children is mental imagery rehearsal therapy (IRT), which has been adapted from that used in adults. In this cognitive-behavioural approach, the child having nightmares learns to modify the content of their bad dream as they wish and mentally (or by drawing) revise it at certain times of the day or week. Results from recent clinical studies in children show a decrease in the frequency of nightmares and associated distress (24,33).

Conclusions

Childhood parasomnias are common, mostly benign and self-limited in time. Their assessment should begin with a full history, careful listening (attention to psychological suffering and possible abuse of children) and a physical examination; this is often enough for the clinician to identify the problem. In some cases, however, the clinician must resort to video-PSG-EEG to identify the exact aetiology of motor activity during sleep and to differentiate a common parasomnia from sleep-related seizures. These PSG recordings may also be needed to identify certain precipitating factors for parasomnias, such as obstructive sleep apnea syndrome or the presence of PLMS for example, the treatment of which can really help reduce or resolve parasomnias. Neglecting the care of these parasomnias can have serious consequences for children; fortunately, most of them respond favourably to behavioural methods.

Conflict of interest

The author has no conflict of interest to declare.

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Sleep and epilepsy

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Keywords

epilepsy, sleep, insomnia, SQ-SP questionnaire, childhood

Abstract

Introduction: Sleep and epilepsy have a bidirectional relationship. Children with epilepsy have a higher prevalence of sleep problems. In turn, these sleep disturbances can exacerbate seizures, contribute to cognitive and behavioral disturbances and impact the quality of life of both children and families. In this study we explored the prevalence and nature of sleep problems in children with epilepsy and its impact on parents.

Methods: A validated sleep questionnaire was presented to the parents of children with epilepsy (aged between 6 months and 18 years).

Results: Parents of 106 children (59 males, 47 females) completed the questionnaire. Mean age was 8.4 years (SD ± 5.1). Chronic insomnia was present in 21% of the patients, and an additional 37% experienced mild settling or night waking problems. Most children experienced problems maintaining sleep, while difficulties related to sleep initiation were less frequent (54% versus 13%). The prevalence of sleep problems decreased with age. Sleep difficulties have a serious impact on the parents, with 64% of the parents experiencing a negative influence from the sleep problems of their child, with daytime fatigue, concentration problems but also feelings of incompetency, irritability, or even depressive feelings.

Conclusion: One out of 5 children with epilepsy has a chronic insomnia, mainly due to problems related to waking up during the night. Settling problems are less frequent. The impact of these sleep problems for children and their parents is huge. Screening for sleep problems should be part of the integrative care of children with epilepsy.

Introduction

Sleep is an active process with varying important functions, related to brain development, synaptic plasticity, learning and attention, emotional regulation, and behavior (1). Sleep difficulties are frequent in children and adolescents, ranging between 25 and 40% in healthy children. In children with neurodevelopmental problems and / or epilepsy, the incidence of sleep difficulties is even higher (2, 3).

Sleep disturbances do not only alter sleep processes but also negatively impact cognitive functioning, behavior, emotions and may exacerbate seizures in patients with epilepsy (4-6). In addition, disruption of the sleep has a negative impact on the quality of life of patients and their caregivers (7, 8). Caregivers of children with epilepsy often already lack restful sleep due to the fear of seizures in their child's sleep or sudden unexplained death in epilepsy (SUDEP) (9).

To adequately treat the sleep problems, it is important to differentiate between the different sleep problems. Seven major sleep disorders are described in the 3rd edition of the International Classification of Sleep Disorders (ICDS-3) including insomnias, parasomnias, sleep-related movement disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders and other sleep disorders. Diagnosis of insomnia requires repeated difficulties with sleep initiation or sleep maintenance that occur despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family.

In this paper we studied the prevalence of sleep problems and more specifically insomnia and its components in children with epilepsy.

Methods

Patients with epilepsy, aged 6 months up to (and including) 18 years, followed at our outpatient pediatric epilepsy clinic at the Antwerp University Hospital could be included. The survey consisted of the Dutch translation of the '*Sleep Behavior Questionnaire by J.F. Simonds & H. Parraga (SQ-SP), modified version for use in individuals with intellectual disability (ID)*' (10, 11). This sleep questionnaire has been used in individuals with ID or genetic syndromes (12-14) and assesses several types of sleep problems with their level of severity. Completed questionnaires can be evaluated by different scores: Composite Sleep Index (CSI) and 5 different sleep factor scores (FS). The CSI reflects the level of severity of sleep problems. A CSI of ≥ 4 is an indicator of a severe sleep problem. There are 5 different factor scores; snoring, daytime sleepiness, complaints related to sleep, sleep apnea and anxiety related to sleep. The FS 'complaints related to sleep' refers to movements, excessive sweating, and episodes of confused behavior during sleep. Sleep problems were defined according to the definition of Wiggs and Stores (table 1) (15).

Table 1: definition of sleep problems according to Wiggs L et al. (15)

Sleep problem	Definition
Severe settling problem	Occurred ≥3 nights per week, whereby it took more than 1 hour to fall asleep and parents or other caregivers were disturbed during this time
Mild settling problem	Occurred 1-2 nights a week and falling asleep took >30 minutes and parents or other caregivers were disturbed during this time
Severe night waking problem	Occurred ≥3 nights per week and the child woke up for more than a few minutes and disturbed parents or other caregivers during that time
Mild night waking problem	Occurred 1-2 nights a week and the child woke up for more than a few minutes and disturbed parents or other caregivers during that time
Severe early waking problem	Waking before 5 o'clock in the morning several times per week

The digital questionnaire (Qualtrics Survey Software) was presented on an electronic device to the parents of patients with epilepsy during their ambulatory visit at the outpatient epilepsy clinic. The questionnaire could be completed during the visit. The study was approved by the ethics committee of the Antwerp University Hospital. Participation was completely voluntary. The anonymised data was extracted out of the Qualtrics Survey Software into IBM SPSS Statistics version 27 for statistical analysis. Chi square was used for comparison of group differences for categorical variables.

Results

Responses of 106 children with epilepsy were collected (59 males and 47 females). Questionnaires were mainly completed by the mother (80.2%). The median age was 7.4 years (SD 5.1, range 1 – 18 years). All patients had epilepsy although the etiology was heterogeneous, ranging from absence epilepsy to a Lennox-Gastaut Syndrome (a severe epileptic encephalopathy). Most of the patients had a genetic or structural etiology for their epilepsy. Almost all patients took at least one antiseizure medication (97.2%), with a median of 2 (range 0 – 5). Many patients (36.8%) used a benzodiazepine for their epilepsy. An intellectual disability (mild – severe) was present in 71.4% and a motor impairment in 60.4%. Approximately 10% was not able to turn around in bed without help.

The seizure frequency was variable, with 23.6% of the patients having ≥1 convulsive seizure per week while 39% was seizure free during the last month. Nocturnal seizures were seen in 51% although the majority of the patients (68.2%) mainly had seizures during the day. Most of the patients slept alone in their room (67%). In 20% parents used a nocturnal detection device (to detect nocturnal seizures or due to fear of SUDEP).

Without providing criteria or definitions of sleep problems, approximately 29% of the parents responded positively on the question 'Do you think your child has a sleep problem?' (figure 1). Parents identified the sleep problems mainly as problems with sleeping through the night. In 70% of the patients these sleep problems were present for >1 year.

Based on the SQ-SP questionnaire (CSI score ≥4), a serious sleep problem was present in approximately 1 out of 6 patients (17.9%). A mild or severe night waking problem was seen in 54% of the patients, a mild or severe settling problem in 13% and early waking problems in 8.5% (figure 2). With age the prevalence of sleep problems diminished, especially the night waking problems, although even in the older age groups, severe sleep problems remained present (figure 3). The prevalence of sleep problems was not significantly higher in patients with frequent nocturnal seizures (≥1 per week) or patients with mainly nocturnal seizures. Patients using a benzodiazepine, more frequently had mild night waking problems (p=0.003), but severe night waking problems (p=0.266) or settling problems were not significantly different.

Figure 1 : *Parental report of sleep problems*

*Legend. *Question ('Do you think your child has a sleep problem?') was presented to one of the parents of 106 children with epilepsy, 2 parents did not complete this question. This question was presented without definition of sleep problems.*

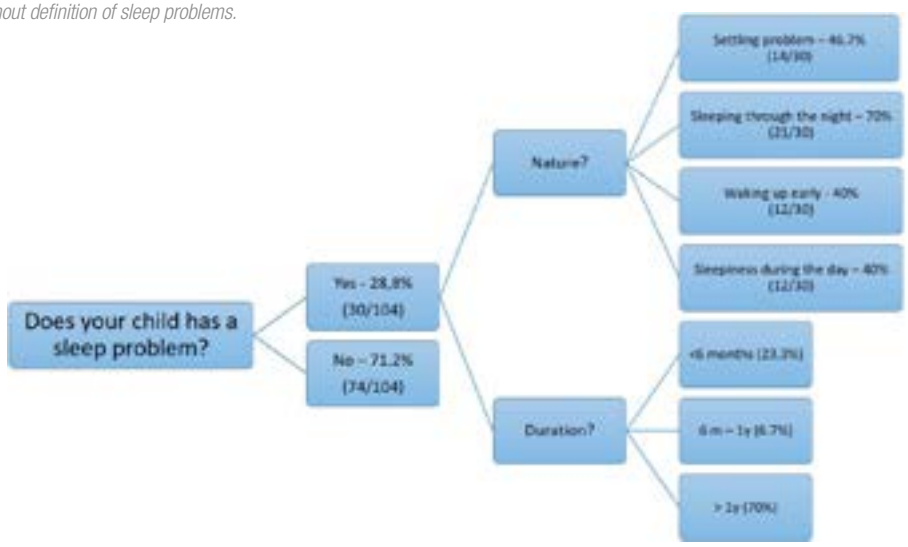


Figure 2 : *Illustration of the prevalence of sleep problems in patients with epilepsy*

*Legend. Illustration of the prevalence of sleep problems in patients with epilepsy based on the SQ-SP questionnaire and definition of Wiggs and Stores. *overall is the combination of patients with a mild or severe sleep problem. #Severe early waking problems is defined as waking up before 5am >2 times per week. Mild early waking problems is defined as waking up before 5am 1-2 times per week. °Sleep problem is the combination of night waking, settling and early waking problems. CSI, composite sleep index. A CSI of ≥4 is defined as a severe sleep problem.*

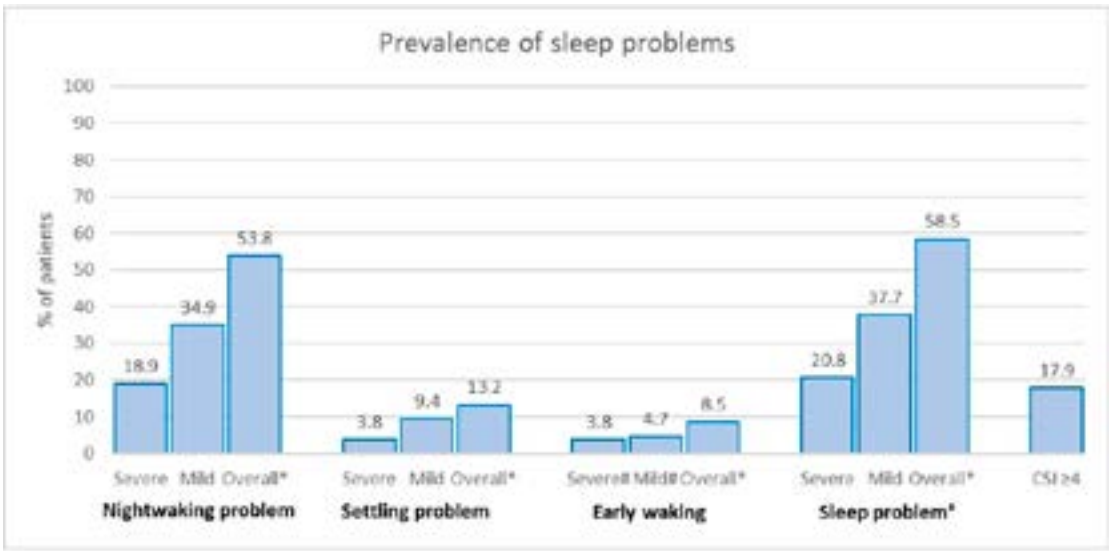
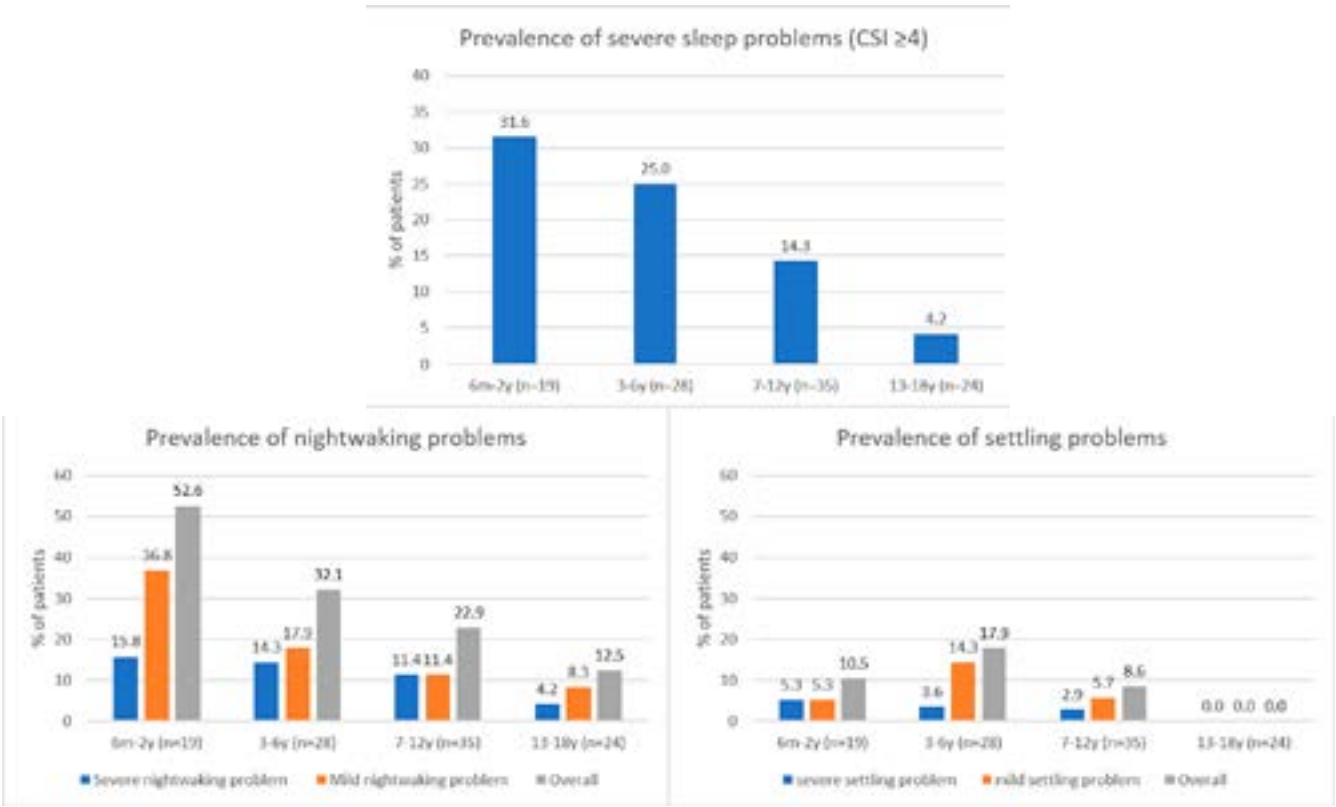


Figure 3 : *Prevalence of sleep problems according to the age.*
Legend. Illustration of sleep problems according to the age in children with epilepsy based on the SQ-SP questionnaire. CSI, composite sleep index. A CSI of ≥4 is defined as a severe sleep problem.



The factor scores (figure 4) indicate a relative higher prevalence of snoring and especially daytime sleepiness. Apnea, complaints related to the sleep and anxiety related to sleep were generally lower.

Parents tried sleep regulating medication in 20.8% (mainly melatonin or antihistamines with a sedative effect) although the efficacy was low or only temporary.

The sleep problems seriously impact the family, with 63.7% of the parents indicating a negative influence of the sleep problems on their daily life, leading among others to fatigue, concentration problems and feelings of incompetency (figure 5).

Discussion

Sleep problems are frequently reported in patients with epilepsy, especially in childhood. In our cohort of patients, chronic insomnia was present in one out of 5 patients. Most patients experienced problems with maintaining sleep, while initiation of sleep (expressed as settling disorder) was less frequent disturbed. Overall, the prevalence of sleep problems decreased with age.

Several factors contribute to the higher prevalence of sleep problems in patients with epilepsy, including the epilepsy itself, but also higher prevalence of comorbidities and environmental factors (figure 6). Due to the fear of nocturnal seizures, co-sleeping was frequent. Even between the age of 5 – 15 years, 35% of the patients did not sleep alone in their room. Co-sleeping can have a negative influence on the sleep quality of children with greater fragmentation of night sleep and might cause or sustain sleep problems. Köse et al described a 13fold increased risk to develop sleep problems in case of co-sleeping with a parent (16). In addition, parents sleeping together with their children may be more aware of sleep problems of their children and might therefore report more sleep problems. Improved and more reliable seizure detection systems will help to give parents / caregivers the confidence to leave their children with epilepsy sleep alone.

Daytime sleepiness is an important problem with a major impact on the daily functioning of the patient. Based on this study we are not able to detect whether the daytime sleepiness is related to the disturbed sleep, medication or epilepsy. Many patients receive multiple antiseizure medications (mean number of 2.2) including benzodiazepines. Antiseizure medications itself have an impact on the sleep, especially polypharmacy (17, 18).

Identification of the type of sleep problem and potential contributing factors (comorbidities and environmental factors) is important to offer the most appropriate advice and treatment.

Good sleep practices and behavioral interventions remain the first recommended treatment but are often more difficult due to the epilepsy (fear of nocturnal seizures or SUDEP) and comorbidities (behavioral problems and intellectual disability). Based on the consequences of sleep problems on the patient and family, pharmacologic treatment can be considered but should be combined with behavioral interventions. Most pharmacological treatments are used off label since they are not recognized for the treatment of insomnia in pediatric patients. For settling disorders mainly melatonin, antihistamines (with sedative effect) and benzodiazepines (mainly clonazepam) are used. For night waking problems (long-acting) melatonin can be tried although it is less successful compared to the treatment of settling problems. In addition, benzodiazepines, sedative antihistamines, atypical antipsychotics or sedative antidepressants (like trazodone) can be tried (19, 20). The presence of comorbidities can help in the choice of the most optimal treatment per patient.

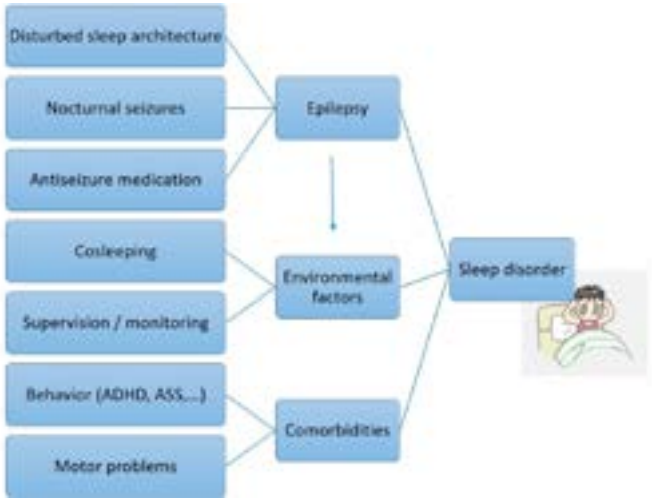
The goal of this study was to get an impression of the prevalence and type of sleep problems in our pediatric epilepsy patients. However, this study has some limitations. First the population is heterogeneous, including patients with more benign epilepsy syndromes and patients with treatment resistant developmental epileptic encephalopathies. By presenting the questionnaire to all the parents visiting the epilepsy clinic we wanted to cover the whole spectrum of epilepsy patients, instead of focussing on a specific epilepsy or genetic syndrome. Based on this study we were able to calculate the prevalence of several types of sleep problems in a broad group of patients with epilepsy. Unfortunately, due to the absence of a control group, we were not able to compare our results with the prevalence in age-matched healthy controls. Secondly, the exact response rate and reason to decline participation

Figure 4 : *Factor scores in children with epilepsy.*
Legend Illustration of factor scores based on the results from the SQ-SP questionnaire according to the age. Indication of relative scores (% of maximum). FS, factor score. The "FS_complaints" represents the refers to movements, excessive sweating and episodes of confused behavior during sleep.

Figure 5 : *Impact of sleep problems on parents*
Legend. Impact of sleep problems on parents. Percentage of parents that experience a negative emotion or effect due to the sleep difficulties of their child.

	Parents
Negative influence of sleep problems	63.7%
Daytime fatigue	34.9%
Disturbed sleep	28.3%
Concentration problems	24.5%
Feelings of incompetency	22.6%
Feelings of irritability	19.8%
Memory problems	16%
Depressive feelings	8.5%
Conflict between parents concerning approach of sleep problems	7.5%
Agressive feelings	1.9%

Figure 6 : *Etiology of sleep problems in children with epilepsy*
Legend. Schematic presentation of factors that might explain sleep problems in children with epilepsy.



were not documented. Although most parents completed the questionnaire, there might be a selection bias as parents with children with sleep problems might be more interested to participate. Since we anticipated the inclusion of patients with an intellectual disability, the SQ-SP questionnaire was used. This questionnaire has been validated in patients with intellectual disability but has no reference values for the several factor scores. In addition, the sleep problems relay on a subjective parental reporting and are not based on objective sleep studies like a polysomnography.

Assessment of sleep should be part of the care of children with epilepsy since they are more vulnerable to develop sleep problems. Simply asking whether the child has sleep problems is not enough as severe sleep problems might be missed this way. It is important to specifically question the settling (how fast children fall asleep), awakenings during sleep, waking up early and impact on parents.

Additional research is necessary to further study and understand the prevalence and etiology of sleep problems in children with epilepsy. In addition, it is important to study the effect (and limits) of behavioral and pharmacological treatment in this complex patient population. Due to the epilepsy and related fear for seizures and SUDEP, pedagogic advice is more difficult.

Conclusion

Children with epilepsy are at risk to develop sleep problems, mainly difficulties to sleep through the night. These sleep problems have an important negative effect on the daily functioning of both children and caregivers. Identification of the type of sleep disorder is important to give the most optimal support to parents.

Conflict of interest

The author has no conflict of interest to declare.

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When teenagers are out of sync. Case report teaching us what we should know about adolescents and Delayed Sleep Phase Disorder

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Keywords

Delayed Sleep Phase Disorder (DSPD), Adolescents, Case Report

Abstract

We present 2 cases of delayed sleep phase disorder (DSPD) in adolescents. DSPD is the most frequent circadian rhythm sleep disorder, which often starts in teenage years . However, it frequently goes unrecognized or is misdiagnosed as attention deficit disorder or mood disorder. Incorrect diagnoses lead to inappropriate therapy and persistence of symptoms. DSPD in adolescents often results in a wide range of secondary problems, including school problems (poor school results, concentration problems, absenteeism), behavioral problems, mood swings, and substance abuse.

With this case report, we intend to increase awareness and recognition of this disorder.

Introduction

The sleep-wake rhythm is regulated by the internal biological clock, which is located in the suprachiasmatic nuclei. In circadian rhythm sleep disorders (CRSDs), the sleep-wake rhythm is disturbed. Delayed sleep phase disorder (DSPD) is the most frequent CRSD (1-3). Adolescents appear to be particularly prone to DSPD. Approximately 90% of DSPD patients report onset of symptoms during adolescence. Prevalence of DSPD in adults is estimated around 1%. Studies in adolescents show a prevalence 3 to 4 times higher (4,5).

In DSPD, the sleep-wake rhythm is delayed, and no longer adapted to the daily school or work routine. DSPD is characterized by difficulty falling asleep at a preferred or socially acceptable time in the evening, and difficulty getting up in the morning. The delay is usually more than 2 hours. Because these patients fall asleep late, but still have to get up early in the morning to go to school, they develop a sleep deficit throughout the week. The short- and long-term consequences of sleep deprivation, both on physical as on mental health, are well known, the main concerns being poor scholastic performance and behavioral problems (6,7). Therefore, correct and early diagnosis is important. With the possibility of a DSPD in mind, a few targeted questions in the patient's history can help ensure that diagnosis is not unnecessarily delayed.

Case Reports

Case 1

A 16-year-old male presented with headaches, sleeping problems, and increased daytime fatigue.

The complaints of fatigue started 4 years ago after an infection with Epstein-Barr virus. Sleep itself was not disturbed at that time, but there was increased sleepiness during the day. Since then, fatigue complaints persisted.

Four months prior to consultation, the complaints worsened. Initiating sleep was especially difficult and took up to 3 hours. In addition, he developed sleep maintenance problems. In the morning, he did not feel rested and he felt depressed. He complained of headaches and a pronounced daytime sleepiness that required frequent naps. The complaints led to arguments with his parents, behavioral problems and school difficulties leading to important school absenteeism. There were no other systemic complaints.

The family doctor and the infectious disease specialist carried out a medical work-up with blood analysis, which did not reveal any abnormalities. He was treated with ibuprofen for headaches and valerian for sleeping problems, with unsatisfactory results.

He was referred to the sleep clinic consultation for further examination and treatment.

Further enquiries about his sleeping habits revealed the following concerns. On weekdays, he went to bed around 10pm. He often lay awake for 2 to 3 hours before falling asleep. He slept very lightly and woke up 2 to 5 times per night. He had to get up at 6am for school, but had difficulty waking and did not feel rested in the morning. He got an average of 3 to 6 hours of sleep per night. During the day he was very tired, especially in the morning. As the days progressed, he felt better and had more energy.

During school holidays, he went to sleep around 2-3am. He usually fell asleep within 10 minutes and slept until 12-13 in the afternoon. He felt better rested and had no headaches or other complaints.

Physical examination was normal. Mental neurological examination showed a cooperative young man, well oriented in time and space, without neurological deficit.

PSG showed a sleep onset latency of 30 minutes, an interrupted sleep (Wake After Sleep Onset (WASO) 247 minutes), a strongly decreased sleep efficiency (46%), and total sleep time which was too short (236 minutes). There were no arguments for other sleep pathology such as obstructive sleep apnea syndrome (OSAS) or periodic limb movement disorder.

The boy was diagnosed with DSPD with co-morbid insomnia.

Individual cognitive behavioral therapy for insomnia (CBT-I) with psychoeducation and restructuring of the sleep-wake rhythm was started. To support this, exogenous melatonin was started (Circadin® 2 mg), taken two hours before bedtime.

Over several weeks, his sleep phase was gradually and successfully shifted forward to a sleep-wake rhythm adapted to school and he became free of complaints. The data obtained from his sleep log also showed a clear improvement in sleep parameters (table 1).

Table 1: data from sleep log after start of therapy with exogenous melatonin

	Week 2	Week 3	Week 4	Week 5
Time in bed (min)	531	590	560	580
Total sleep time (min)	341	554	551	556
Sleep latency (min)	180	5.6	6.4	13
WASO (min)	10	58	2	11
Sleep efficiency (%)	64	94	98.5	96

Case 2

A 14-year-old female presented with difficulty initiating sleep, which started 5 years ago and gradually worsened. At time of consultation, it took about 2 hours to fall asleep. She subsequently developed sleep maintenance problems. At night, she often lay awake for an additional hour. She slept about 6 hours per night and did not feel rested in the morning. Throughout the day, she suffered from a high degree of fatigue, but around 8pm she had a peak of energy. On school days, she went to sleep around 9.30pm and got up at 6.45am. If she were to choose her own sleep schedule, she would go to sleep at 11pm and get up at 10.30am. During periods when she could maintain this rhythm, she did not experience any difficulty with sleep initiation, sleep maintenance, or next-day functioning. The girl had no other complaints apart from a chronic tendency to constipation treated with a laxative.

A polysomnography showed problems with sleep initiation and maintenance. Sleep structure was disturbed with a lack of REM sleep and persistence of Slow Wave Sleep towards the morning (fig 1). There were no arguments for other sleep pathology.

Based on her history, sleep logs and polysomnography, she was diagnosed with DSPD.

Individual CBT-I with psychoeducation was started. It was also advised to postpone bedtime with 30' to reduce sleep onset latency. Simultaneously, light therapy was started. After waking in the morning, a light intensity of 1000 lux was offered for 30 minutes with Luminette® glasses. After a few days the patient already felt more refreshed and less tired during the day. At bedtime she fell asleep within 15 minutes. The patient spontaneously reported that she no longer suffered from constipation.

Discussion

Both teenagers represent clear examples of DSPD. Nevertheless, diagnosis was delayed. Failure to recognize DSPD can lead to chronic insomnia and to a range of secondary pathologies, which can be prevented when diagnosis is made in a timely manner.

During consultation, sleeping habits should be questioned in detail, and a few specific questions in the patient's history can quickly orient the physician in the right direction.

When an adolescent has difficulties initiating sleep, it is important to not only ask about his or her sleep schedule on school days, but also to enquire about sleeping habits during school holidays. If there are no complaints when circumstances permit to sleep at the teenager's self-selected sleep schedule, the patient might have DSPD.

Another clue can be found by looking at the evolution of complaints throughout the day. Most individuals with DSPD complain of excessive sleepiness mainly in the morning, and begin to feel more awake and energetic as the day progresses.

In addition to a targeted patient history, the sleep schedule should be mapped using a sleep log or an actigraphy. Although there is agreement that sleep logs can be very useful in the assessment of suspected CRSDs, the lack of widely accepted standardized sleep logs, makes their use less reliable and less valuable. An actigraphy records a sleep schedule in a more objective manner, but might not always be available in all settings.

A targeted patient history, supplemented with a sleep log and/or an actigraphy, is often sufficient for a diagnosis of DSPD. Although PSG is not routinely indicated, it can be useful when other sleep pathology is suspected, e.g. to exclude OSAS in case of snoring.

Sleep timing can mostly be shifted forward with phototherapy and/or exogenous melatonin. Both treatments are safe and, in most cases, successful in the short term (3,4,8).

Studies have shown that relatively small doses of melatonin (from 0,2mg to a maximum of 5mg for adolescents) and advance administration (3 to 4 hours prior to bedtime) are more effective for DSPD than larger doses or those given closer to sleep onset (10). Phototherapy may be of particular benefit to patients with DSPD who suffer from pronounced morning sleepiness, or in patients who are somewhat reluctant to take medication.

In more severe cases of DSPD, chronotherapy with time shifting in a delay direction can be necessary.

Long-term success is often co-determined by circumstances and requires a sustained strict sleep structure.

The authors have no conflict of interest to declare.

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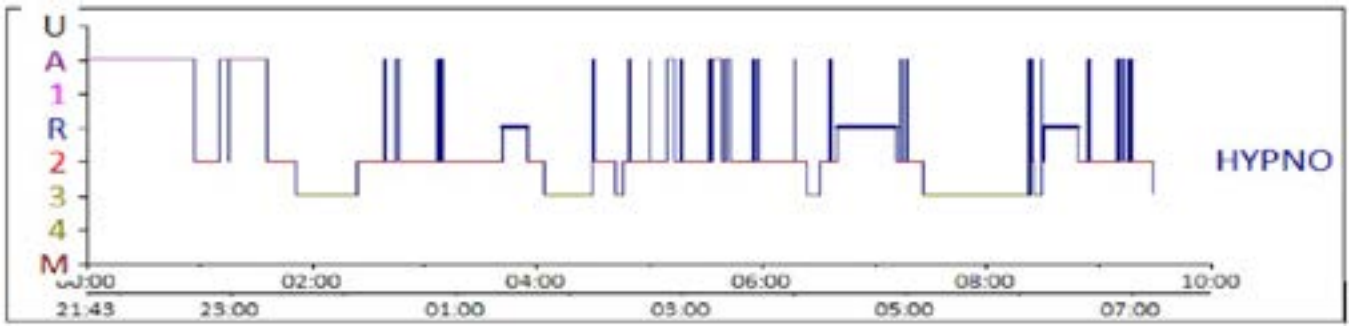
Figure 1: *hypnogram*



Narcolepsy with cataplexy in children

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Keywords

Narcolepsy, cataplexy, children, excessive somnolence

Abstract

Narcolepsy with cataplexy is a rare chronic condition without cure that can be controlled if treated adequately. The disease often starts in childhood and adolescence. Excessive daytime somnolence is the main symptom for which parents consult in somnology. Cataplexy, which corresponds to loss of tonus without loss of consciousness can appear later.

Other less specific symptoms can be identified such as hallucinations at sleep onset or at wake-up time, sleep paralysis and disturbed night time sleep.

The disease has major repercussions on school life and family life. Treatment with stimulants is required, together with good sleep/wake hygiene, treatment of the co-morbidities, psychological support of the child and his family and eventual school measures to allow for uncontrolled excessive daytime somnolence.

Rapid identification and treatment of the disease increases the chances of better integration in society as it will favor completion of studies and normalize professional life.

Introduction

Narcolepsy is one of the central hypersomnias which include type 1 narcolepsy with cataplexy, type 2 narcolepsy without cataplexy, idiopathic hypersomnia and Kleine-Levin syndrome (1). In this article, we will focus on narcolepsy with cataplexy.

It is estimated that one third of pediatric cases of narcolepsy develop the first symptoms before the age of 15, 50% before the age of 20. Narcolepsy with cataplexy is rare before the age of 4. Different studies have shown that cataplexy is present in 50 to 70% of narcoleptic children. The child has excessive daytime sleepiness and an irrepressible need to sleep, even in unusual situations, favored by inactivity and boredom. The negative consequences on social life and learning can be very significant.

Confronted with hypersomnia, differential diagnosis should be made based on the case's history, data from sleep diaries and sleep questionnaires and additional examinations. Hypersomnia secondary to neurodegeneration, more frequently found in children whose disease begins at very young age, must be excluded.

Epidemiology

Based on the number of annual births in France, the incidence of the disease is estimated at 0.05%.

Clinical case

The first consultation toke place when the girl is 6 years old. Rapid weight gain had been noted in the past year. Her BMI rose from 21 to 27. She had been complaining of fatigue during the day for two months. She was referred to the sleep consultation because she sleeps in class.

In her antecedents, allergic rhinitis treated by an antihistamine (stopped because of excessive daytime sleepiness) is mentioned. Her sleep is described as restless and of poor quality with great difficulty waking up in the morning. There is no ronchopathy. During the consultation, she falls asleep in her chair. Awake, she has sagging chin and eyelids.

The adapted somnolence scale is 20 (abnormal above 15). At this stage, a night polysomnography followed the next day by sleep onset latency tests are scheduled. The sleep registration shows a total sleep time of 397minutes, in which the child falls asleep in REM sleep in 1 minute. Sleep is divided by 4 waking periods each followed by falling asleep in REM (SOREM – Sleep Onset Rapid Eye Movement). Sleep is restless. There is no sleep apnea syndrome.

Latency tests: 5 out of 5 sleep onset are in REM sleep, in less than a minute. The medical work up is completed by HLA typing which shows the presence of the DQB10602 allele found in narcolepsy. There is no profile of neurodegeneration on MRI. The biology is normal. Lumbar puncture is not carried out.

At the 2nd consultation, the child describes loss of muscle tone, especially during laughing episodes. She describes hallucinations on falling asleep and nightmares. She continues to gain weight. The diagnosis of narcolepsy with cataplexy is retained. Treatment with modafinil is started as well as dietary management. A systematic nap on return from school is implemented.

Nine months after the start of treatment, the nights are better and getting up is spontaneous. She still exhibits drowsiness after school recess, episodes of cataplexy at laughter, and hallucinations at sleep onset. Weight gain is not stabilized. Given the persistence of drowsiness and the inability to increase modafinil, the treatment is increased by 18 mg of methylphenidate SR (sustained release) in the morning. This leads to a disappearance of drowsiness and a marked improvement in school results.

Additional work up was carried out with an endocrinology assessment that did not show any signs of early puberty, and a psychological work up that showed normal cognitive capacities. The treatment by psycho-stimulants motivated a cardiac assessment which came back normal. The weight gain motivated the prescription of an annual polysomnography in order to exclude sleep apnea syndrome.

For a few months, parents adhered to dietary monitoring and the child lost weight. Her BMI fell from 35 to 32. However, faced with the persistence of certain symptoms (hallucinations and cataplexies), an opinion was requested from the reference center for child narcolepsy in Lyon, France . On their advice, venlafaxine (an antidepressant with an effect on hallucinations and cataplexy) is added to the treatment. The overall evolution was favorable. Unfortunately, 6 months later, the dietary support was abandoned and the child regained weight.

Discussion (2)

Since the work published in the early 2000s, it has been established that narcolepsy with cataplexy is due to destruction of orexin A / hypocretin 1 neurons of the lateral hypothalamus. This neuropeptide is a mediator of the arousal system.

Early development of the disease, before puberty, is not exceptional.

Excessive daytime sleepiness is the most consistent and debilitating symptom. It is essential to differentiate between fatigue and sleepiness, which can be difficult in young children. One must think about the disease when a child falls asleep in an unusual situation and when his total sleep time over 24 hours increases compared to children of his age and / or when naps re-appear after the age of 7 or before if they had been abandoned. Unlike in adults, these naps are not necessarily refreshing. The narcoleptic child does not increase his time spent in bed.

Abnormal sleepiness can lead to behavioral and attentional disturbances and impact schooling even though these children may have normal intellectual potential. Difficulties are often encountered with the teacher who does not understand what is going on.

The negative views of other children, especially if a significant weight gain is associated, can lead to a loss of self-esteem or even depression. It is important to take these aspects into account when providing treatment.

Cataplexy is the second most common symptom of the disease. It is a sudden loss of muscle tone, often related to pleasant emotions such as laughter. The prospect of a reward can trigger the attack of cataplexy. In children, this symptom is inconstant and may not be described by parents.

It may also appear late in relation to drowsiness (several years) and present, at the onset of illness, in the form of facial hypotonia with drooping eyelids, sagging lower face, opening of the mouth and protrusion of the tongue. Facial movements can be observed. Video can help with diagnosis.

The other less frequent symptoms, such as hallucinations on falling asleep (hypnagogic) or on awakening (hypnopompic) and sleep paralysis are difficult to objectify, especially in young children. The older child will talk about nightmares and not being able to get up in the morning while awake. Only 13% of children would present the complete tetrad of narcolepsy (3)

The narcoleptic child has difficulty maintaining sleep with frequent awakenings and possible periodic leg movements.

In 60% of children under 10 years of age, the disease is associated with significant and rapid weight gain. This symptom can be a warning sign and precede the onset of excessive daytime sleepiness by several months. These children have a BMI above 25, and various studies have shown a lower basal metabolic rate than normal. A hypothesis to try to explain this weight gain calls into question the dysregulation of orexin, which plays a role in the regulation of sleep and vigilance but also in the regulation of eating behaviors (4).

There is not always an increase in food intake, but studies have shown a change in eating behavior, in an effort perhaps to control drowsiness by changing meal times and by eating at night, resulting in an unstructured diet. The inactivity associated with hypersomnia worsens the situation. Rapid weight gain could be responsible for some cases of early puberty (5).

It is in narcoleptic-obese children that we observe the most absenteeism from school: they are drowsy, their weight gain is rapid (10 to 20 kg), cataplexy attacks start earlier. 30% of them show signs of depression. It is also in these patients that one will follow the possible appearance of a syndrome of sleep apnea. However, it seems that, despite the obesity, this syndrome is not very frequent thanks to a good tonicity of the airways.

Triggering factors

Environmental factors could play a role in promoting an inflammatory process. Significant stress, H1N1 influenza vaccination, viral infection, beta-hemolytic streptococcal infection have been implicated in various studies. At the genetic level, narcolepsy with cataplexy is one of the diseases most associated with HLA class 2. There is therefore a strong autoimmune component. A study published in Nature in 2018 reinforces the hypothesis of the autoimmune origin of the disease. In this study, narcoleptic patients have an increased level of certain T lymphocytes which could attack neurons producing hypocretin (6).

Familial cases are rare, where predisposition is more likely than direct transmission. A study in France in 1994 showed 7.4% of family cases; within these, only 9% could correspond to a genetic susceptibility within the family.

Diagnosis

Diagnosis is difficult and requires a careful history to rule out sleep deprivation, phase delay, toxic substance abuse in adolescents, depression, symptoms suggesting sleep apnea syndrome. It is necessary to question the taking of drugs such as antihistamines and certain analgesics.

A sleepiness scale adapted to the child makes it possible, on the basis of 10 simple questions, to assess sleepiness in different situations. When dealing with a young child, it is important to rule out secondary narcolepsy.

Complementary examinations (7,8)

Polysomnography followed by sleep onset latency tests constitute the reference examinations making it possible to objectify the clinical criteria. A 24-hour sleep diary for 3 weeks before the polysomnography is requested in order to quantify sleep and its distribution. It is useful to exclude sleep deprivation.

During the recording of the night's sleep, narcoleptic children fall asleep with a latency of often less than 10 minutes and in REM sleep for 50% of them. Sleep is fragmented by many spontaneous awakenings or in connection with periodic movements of the legs.

The presence of a sleep apnea syndrome does not exclude the diagnosis of narcolepsy. Latency tests are carried out the day after the polysomnography: this is the recording of 5 naps of 20 minutes every 2 hours. In children, 2 sleep onsets in REM sleep or an average sleep onset latency less than or equal to 8.2 minutes are reliable markers for the diagnosis of pediatric narcolepsy (8). These characteristics may be absent at the onset of illness in children. If necessary, the latency tests will be repeated after some time.

In 85 to 100% of narcoleptic patients the HLA DQB 10602 allele is found.

An HLA DQB10602 positive patient has a high probability of developing the disease. However, this is not an absolute criterion because it is present in 20% of people without symptoms. Its absence has a negative predictive value for patients with atypical cataplexies.

HLA typing can be a good examination if we want to avoid lumbar puncture. A hypocretin-1 dosage of less than 110 pg / ml in the cerebrospinal fluid is pathognomonic for childhood narcolepsy (9). Although a specific biomarker, the dosage of hypocretin may not be conclusive at the onset of disease. It will then be necessary to re-check one to two years later.

MRI of the brain is necessary to exclude secondary narcolepsy; it is always carried out in young children.

Co-morbidities (10)

- Attention deficit with hyperactivity disorder is found to be twice as important in narcoleptic patients.
- Sudden weight gain and obesity, especially if the disease begins before 10 years.
- Sleep apnea syndrome especially in the presence of significant weight gain.
- Sleepwalking, nightmares.
- Periodic leg movements.
- Anxiety, depression: 25% have signs of depression. They have a more hallucinations and sleep paralysis. Depression has a major impact on the quality of life.

In the presence of obesity and attention deficit hyperactivity disorder, it is important to question sleep in order to exclude narcolepsy.

Management (11)

Although not curable, narcolepsy can be treated effectively with different approaches. It will be necessary, above all, to ensure a healthy lifestyle and regular sleep-wake rhythms. A nap after returning from school is essential. During school time, 1 or 2 scheduled 20-minute naps may be recommended but rarely accepted. It is essential to inform teachers and to propose arrangements for the child's working time.

Psychological support for the child and his parents is advised. It will help the child to accept his illness, his constraints and the difficulties of everyday

life. Parents may find themselves helpless when confronted with their child's disease, not knowing how to help and support.

Drug treatment (12,13)

The treatment must consider co-morbidities.

Currently, in Belgium, three molecules are available to treat narcolepsy in children. To treat excessive daytime sleepiness, psycho-stimulating drugs such as modafinil and methylphenidate can be used. Venlafaxine acts on cataplexy, hallucinations and sleep paralysis.

Other molecules are available for adults but not yet for young people under 18, sodium oxybate acts on all symptoms including weight. A study published in the Lancet Child Adolescent Health in 2018 validated sodium oxybate as a treatment for narcolepsy in children (14). It is not approved in Belgium for children and adolescents up to the age of 18.

Pitolisant which stimulates vigilance and wakefulness was approved in Belgium in 2018 as a 2nd line treatment for adult patients with narcolepsy.

A study is underway in children, and the results look promising. Well tolerated, it acts on alertness and cataplexy.

Solriamfetol is a new psychostimulant which, in January 2020, was approved by the European Commission to improve wakefulness and reduce drowsiness in adults with narcolepsy. Safety and efficacy in young people under 18 has not yet been proven.

Follow-up

- Cardiac check-up before starting the psycho-stimulating treatment, then once a year. - Blood pressure and general growth monitoring.
- Neuro-cognitive assessment and attentional tests to rule out learning problems.
- Endocrinological check-up once a year as there is a risk of early puberty especially in girls (17% especially if the disease starts early).
- Metabolic check-up once a year: obese narcoleptic children have an 18% risk of developing metabolic syndrome, hepatic steatosis or type 2 diabetes.

Finally, if some symptoms or complaints remain after correct treatment of narcolepsy, there could be an undiagnosed underlying problem such as a sleep apnea syndrome or an upper airways resistance syndrome.

Conclusion

Narcolepsy with cataplexy is a chronic and debilitating disease which begins in childhood in 30% of subjects. There is frequently a delay in the onset of symptoms, and incomplete forms of the disease are frequent in young age in both clinical manifestations and electrophysiological signs.

Cataplexy can be delayed for several years. Children may also be seen with cataplexy and normal levels of hypocretin at lumbar puncture. In this case, it will be necessary to control it at a later stage.

Excessive daytime sleepiness is usually the reason for consultation, but sudden unexplained weight gain may also be the reason. Both symptoms will need to be addressed fast, as untreated drowsiness leads to school absenteeism in 26% of cases and school failure in 36% of cases. Bullying is not uncommon.

The early diagnosis allows the establishment of treatment and family and school support.

Care should be taken to make the differential diagnosis between fatigue and drowsiness.

In young children, secondary narcolepsy should always be excluded.

Lumbar puncture is not systematic in Belgium as the sample must be sent to the Netherlands or France and the cost is not reimbursed. However, in case of doubt, it must be done.

When the symptoms are well controlled, the child will develop favorably, particularly at the level of schooling. A study carried out within the reference center for child narcolepsy in Lyon showed that there was no difference between the population of narcoleptic patients and a control population.

Conflict of interest

The authors have no conflict of interest to declare.

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Restless legs Syndrome: What a pediatrician needs to know

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Keywords

Restless Legs (RLS), Periodic limb movements in sleep (PLMS), Child, Dopamine, Sleep Disorder

Abstract

Over the last two decades, there has been increasing recognition that restless legs syndrome (RLS) occurs in children. Adults who suffer from RLS often refer to their childhood as the onset of the symptoms. Epidemiologic studies indeed report that RLS symptoms are more prevalent in children than most physicians would have expected. This article challenges pediatricians to consider what role they might play in the detection and treatment of RLS. Information is provided that should be helpful to pediatricians how to detect and how to evaluate childhood RLS. With the knowledge of pathophysiological mechanisms, the impact of pharmacological treatments, common comorbidities and other pediatric conditions, children at risk can be more easily recognized. RLS should be considered as a possible cause of growing pains and/or sleep problems and should be referred to pediatric sleep specialists if necessary, but not every child with RLS needs treatment.

Introduction

Restless legs syndrome (RLS), also called Willis-Ekbom disease (WED), is usually known as a sensorimotor disorder and is characterized by an irresistible urge to move the limbs predominantly in the evening or at night. This urge to move is usually accompanied by a specific discomfort in the lower extremities, often alluded to as a 'creepy' or 'crawly' feeling. Once thought to be a rare disorder, RLS is known now as a rather common condition with considerable clinical variability. RLS is often described in adults. A large scale population-based study in Europe and the United States reported a prevalence of RLS in 7,2% in the adult population (1). However, recent research demonstrated that RLS is also a common condition in children. It has been assumed that symptoms of RLS are more prevalent than most physicians would expect. Based on different studies, epidemiologic rates of RLS in children and adolescents ranges between 2 – 4% (2). Symptoms in children mostly appear as the inability to sit still, the experience of having growing-pain-like sensations and/or disturbed or interrupted sleep (3). Based on parent information, researchers found that RLS can manifest in early childhood, even before 2 years of age (4). However, RLS diagnosis in the pediatric population is often delayed due to unawareness of this relatively common disorder. Indeed, retrospective research, showed an average interval of 4 years between the time of consultation and the time of diagnosis (4). Furthermore, retrospective studies also indicated that many adults with RLS recall that their symptoms already started in childhood or adolescence (3). Results from the Peds REST study done by Pichietti et al. indicate a percentage of 24% and 22% for a definite diagnosis for respectively children and adolescents who consulted with specific symptoms. In addition, the authors refer to an overall percentage of 11% in the general pediatric population (3). The reasons for a diagnostic delay are rather obvious. One is a rather different clinical picture of pediatric RLS compared to the adult complaints; second might be the difficulty for (young) children to express the sensations associated resulting in a lack of verbal confirmation and third is the wrong allocation of the ache and pain symptoms to other age specific conditions, such as growing pains. Together with the unawareness of the syndrome by pediatricians, these factors can easily result in a diagnostic delay or misdiagnosis.

Based on literature and clinical experience, RLS symptoms can disrupt sleep and consequently have a potential impairment on daily functioning. However, RLS is seen as a spectrum varying from latent or subclinical to severe. The clinical presentation of the syndrome together with the severity of the complaints related to sleep disruption are therefore important to identify. In children, the impact of RLS can be significant during the day (aches and pain, mostly in the lower limbs, but in the upper limbs is also possible) and the night (sleep disruption due to the aches and pain, or to an increased motor activity experienced as a need to move the limbs). The subsequent sleep disruption may result in impairment of the cognitive, behavioral and emotional functions. Consequences as poor school performances due to hypersomnolence, inadequate concentration, a negative influence on the child's mood, a lack of energy, disturbed daily activities and hyperactivity are described (4).

Given the knowledge of underdiagnosis and secondarily the impact on cognitive and emotional functioning in children and adolescents, it is clear that RLS diagnosis should be assessed regularly in the pediatric practice whenever relevant. Clinical significance should be evaluated in order to set up a diagnostic and therapeutic protocol. This review aims to inform clinicians involved in pediatric health care about RLS by giving an overview of the clinical features, insights in the pathophysiology and by providing diagnostic and treatment tools. In addition, specific pediatric conditions in which RLS is observed more frequently are also presented.

Clinical presentation and diagnostic assessment

Clinical features of pediatric RLS

Clinicians should bear in mind that children and their parents rarely consult spontaneously for specific RLS symptoms. The most common initial burden or complaint parents refer to is the presence of a disrupted sleep. More specific descriptions include restlessness while sleeping, insomnia with difficulties in falling asleep (>30 min.) or maintaining sleep, annoying daytime fatigue or excessive sleepiness resulting in poor school performance (3). Clinically, RLS is a typical sensory-motor disorder, consisting of sensory symptoms in the legs with consequent motoric symptoms to relieve the unpleasant feeling. Information that should be helpful to primary care physicians in the detection of RLS was provided in the ped REST study, published by Picchietti et al. (3). The disturbing sensations are described by children as 'ants in the legs', 'itchy feelings', 'legs feeling heavy, with bugs', 'have to move legs', 'legs want to kick', 'need to stretch' and so on (4). These sensations are described deep inside the limbs and can occur unilaterally or bilaterally, predominantly around the ankle, knee or affecting the entire lower limb. The authors also commented that they found asking about 'growing pains' to be a useful 'lead-in' question. Nonetheless useful, the presence of growing pains however is very common and the prevalence is much greater than what was found for

Table 1: International Restless Legs-Syndrome Study Group (IRLSSG) consensus diagnostic criteria for restless legs syndrome (8).

Diagnostic criteria for Restless Legs Syndrome	
Essential diagnostic criteria (all must be met)	
1)	An urge to move the legs usually but not always accompanied by, or felt to be caused by, uncomfortable and unpleasant sensations in the legs (a) (b)
2)	Begin or worsen during periods of rest or inactivity such as lying down or sitting
3)	Partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues (c)
4)	Only occur or are worse in the evening or night than during the day (d)
5)	The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping) (e)
Specifiers for clinical course of RLS/WED (f)	
A)	Chronic-persistent RLS/WED: symptoms when not treated would occur on average at least twice weekly for the past year
B)	Intermittent RLS/WED: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events
Specifier for clinical significance of RLS/WED:	
The symptoms of RLS/WED cause significant distress or impairment in social, occupational, educational or other important areas of functioning by their impact on sleep, energy/ vitality, daily activities, behavior, cognition or mood.	

Sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs.
(α) For children, the description of these symptoms should be in the child's own words.
(β) When symptoms are very severe, relief by activity may not be noticeable but must have been previously present.
(χ) When symptoms are very severe, the worsening in the evening or night may not be noticeable but must have been previously present.
(δ) These conditions, often referred to as "RLS/WED mimics", have been commonly confused with RLS/WED particularly in surveys because they produce symptoms that meet or at least come very close to meeting criteria 1 – 4. The list here gives some examples that have been noted as particularly significant in epidemiological studies and clinical practice. RLS/WED may also occur with any of these conditions, but the RLS/WED symptoms will then be more in degree, conditions of expression or character than those usually occurring as part of the other condition.
(ε) The clinical course criteria do not apply for pediatric cases nor for some special cases of provoked RLS/WED such as pregnancy or drug-induced RLS/WED where the frequency may be high but limited to duration of the provocative condition.
RLS/WED= Restless Legs Syndrome/Willis-Ekbom-Disease

Table 2: Special considerations for the diagnosis of pediatric restless legs syndrome (2)

- The child must describe the RLS symptoms in his or her own words
- The diagnostician should be aware of the typical words children and adolescents use to describe RLS
- Language and cognitive development determine the applicability of the RLS diagnostic criteria, rather than age
- It is not known if the adult specifiers for clinical course apply to pediatric RLS
- As in adults, a significant impact on sleep, mood, cognition, and function is found. However, impairment is manifest more often in behavioral and educational domains
- Simplified and updated research criteria for probable and possible pediatric RLS are available
- Periodic limb movement disorder may precede the diagnosis of RLS in some cases

definite RLS in children (3). Growing pains have a very low positive predictive value in the sample, although the negative predictive value of 99% suggests that children who do not suffer from growing pains, mainly will not have RLS.

A certain circadian pattern of the RLS symptoms has been identified. The symptoms appear to worsen during the evening and/or night. Between 06:00 p.m. and 04:00 am with an observed peak before sleep onset, around midnight and in the morning (5). Apart from the urge to move the legs, restlessness in the arms is also reported in some (more severe) cases. The overall clinical presentation shows, in contrast to the adult population, no significant gender differences in children (3).

Nevertheless the clinical picture is highly typical, the course of the RLS symptom presentation in time can be quite variable. Adult reports of RLS frequency and severity show an increase with age (3). However, unfortunately, there is insufficient information about chronicity of the clinical course of RLS for children and adolescents (2, 4).

In addition to disturbed sleep, as mentioned above, symptoms can account for psychosocial distress as well. Cross-sectional research using the Pediatric Quality of Life inventory (PedsQL), a self-report scale for children, found RLS patients to be significant more 'feeling sad or blue', 'feeling angry', 'worrying about what will happen to me', compared to a control population (6).

Diagnostic tools and classification

Since 1960, diagnostic criteria for RLS have been published and revised by the International RLS Study Group (IRLSSG) (7). Given the concern that children <12 years of age would not be able to understand and verbally confirm the essential adult criteria, specific pediatric criteria were considered and formulated. Three diagnostic categories ("definite RLS", "probable RLS", "possible RLS") are formulated to capture the full spectrum of RLS. The two latter are mainly used in research. In 2014, a consensus was published to formulate integrated diagnostic criteria for adults, children and adolescents (Table 1) (8). In addition, special considerations for pediatric aspects of RLS were published (Table 2) (2). In particular, attention was put on their communication skills. Language and cognitive development determine the applicability of the RLS diagnostic criteria rather than age does. Moreover, physicians should be aware of the typical words children and adolescents use to describe RLS.

The International Classification of Sleep Disorders, 3rd Edition (ICSD-3) includes diagnostic criteria for RLS based on the IRLSSG criteria as shown in Table 1. To establish the ICSD-3 diagnosis of RLS, a significant impairment on daily functioning is required.

Above all, RLS is predominantly a clinical diagnosis. It is established based on the verbal confirmation of diagnostic criteria with no additional tests required per se. The presence of a positive familial history for RLS may also help to confirm the diagnosis. The patient's history and examination can be used to exclude secondary causes such as underlying diseases, risk factors or mimics. Neurologic disorders can mimic RLS symptoms such as lysosomal storage disease (Fabry), polyneuropathies, lumbosacral radiculopathies, and more common conditions such as sore leg muscles, positional discomfort or local problems (sprain, tendon, dermatitis) (2). Pharmacological side effects of prescribed medications in the pediatric population can also provoke or aggravate RLS (neuroleptics, antihistamines, beta-blockers) (9).

Besides the decisive importance of the clinical presentation in the diagnostic process, there are also some tools that can be used in the assessment of a patient with RLS symptoms. The RLS-Diagnostic Index (RLS-DI) and the international restless legs rating scale (IRLS) are validated helpful assessment tools to differentiate RLS among other sleep problems. These adult tools can be used in adolescents but are not adjusted for use in younger children. Arbuckle et. al. developed the pediatric RLS severity scale (P-RLS-SS) to properly measure RLS severity in children (10). The questionnaire items include 17 morning and 24 evening items as well as a separate parent questionnaire to asses RLS severity in children. The P-RLS-SS provides an age-appropriate tool that can contribute to the diagnostic process in pediatric RLS. However, the instrument has not been validated to date.

In addition, a positive family history among first degree relatives is frequently reported in the assessment of children with RLS. Picchietti et al. reported a biological parent with RLS in respectively 71% and 77% of cases of two different study samples (3, 4).

Another supporting feature of RLS is the presence of periodic limb movements in sleep (PLMS). PLM are described as repetitive, involuntary leg movements during sleep with a typical appearance of dorsiflexion of the toes, ankle and/or partial flexion of the knee and hip (11) (Figure 1). Polysomnographic (PSG) studies can objectify PLMS and a PLM Index (PLMI) is calculated by dividing the total number of PLMS by sleep time in hours. Studies based on PSG examination reported two-thirds of children with RLS to have a PLMI greater than 5/hour (12). However, a positive PLMI alone is not sufficient for a RLS diagnosis as it is also seen in other sleep disorders e.g. narcolepsy. Nevertheless, when a RLS diagnosis remains uncertain after rigorous clinical assessment, a PSG can be a supportive and objective additional test in the diagnostic process.

Pathophysiology

Numerous studies contributed to a better understanding of the pathophysiology of RLS. Today, there is evidence that iron as well as the neurotransmitter dopamine play a role in the pathophysiology of RLS. Additionally, a genetic susceptibility has recently been discovered as well.

The dopaminergic pathway

Prior therapeutic trials with dopaminergic agents in RLS patients provided pharmacological evidence that supports a dopaminergic mediation in RLS. Randomized, double-blind trials of dopamine (DA) agonists, such as pramipexole and ropinirole, showed a significant decrease of symptoms in RLS patients (13, 14). In contrast, DA antagonists, such as neuroleptics, worsen RLS symptoms. However, today, the precise physiological mechanism underlying the dopaminergic dysfunction in RLS patients, still remains partially unrevealed. To get more insight in the involvement of DA in RLS, we have to take a detailed look at the central and peripheral DA neurotransmitter system.

DA is known to play a central role in affecting mood, executive functions as well as locomotor activity. Central dopaminergic pathways are complex and the system includes 5 different receptors classified as D1-like (D1-D5) and D2-like (D2-D3-D4) with inhibitory and excitatory dose specific actions (15). Dysfunctions in DA activity are hard to investigate since there is no reliable manner to directly measure DA levels or activity in the brain. Recent research was able to demonstrate increased presynaptic dopamine production. Increased 3-O-Methyldopa (3-OMD) and homovanillic acid, major DA-metabolites, were found on CSF measurements in RLS patients (16). Autopsy studies in RLS patients demonstrated significant elevations in striatal tyrosine hydroxylase (TH), the rapidly limiting enzyme in DA biosynthesis, as well as a decrease in total dopamine D2 receptor expression (17). These results might most likely be caused by an increased level of intrasynaptic DA.

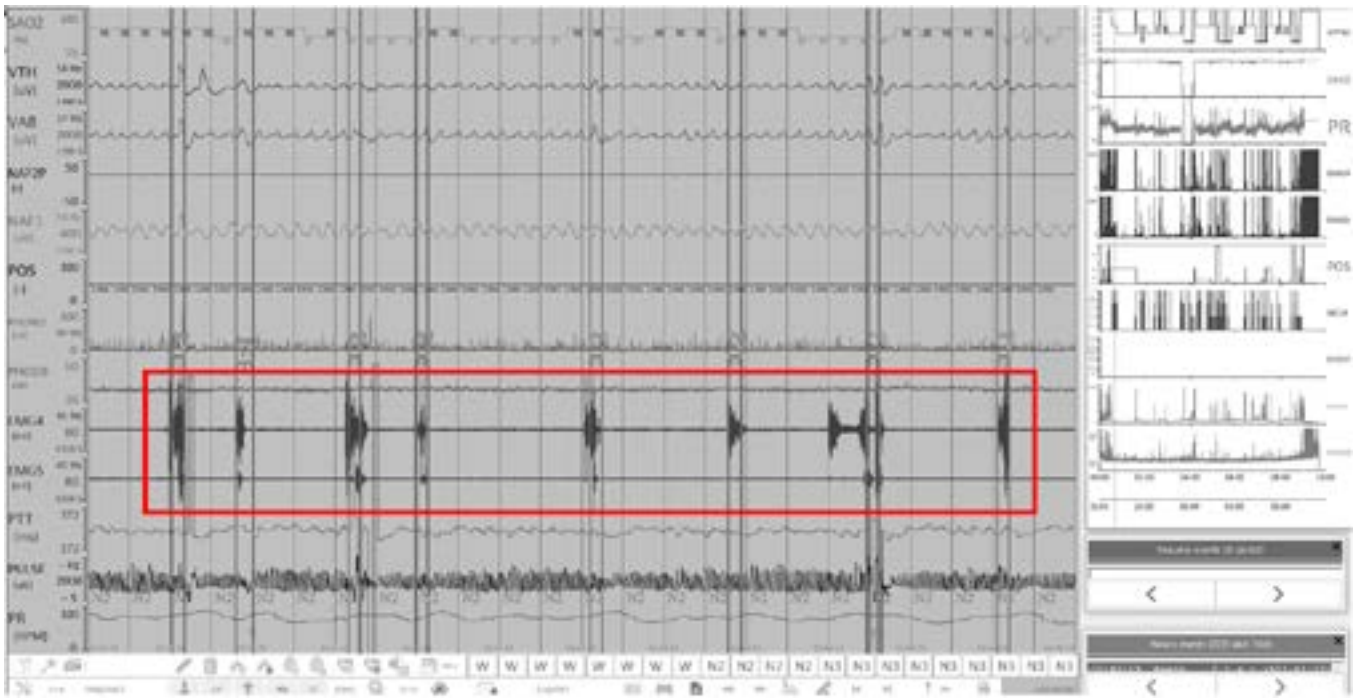
From the spinal cord perspective, DA projections from the hypothalamic A11 regions go to the dorsal (sensory) horn and ventral (motor) horn of the spinal cord and to the intermediolateral nucleus of the spinal grey matter, the final common output of the spinal sympathetic system (15). This pathway exercises an inhibitory role on the neuron excitability. According to the research of Clemens et al. an impairment of this descending control might have two consequences that are of interest in RLS: 1/ a reduced inhibitory modulation of the sensory and motor input and 2/ an increase in the sympathetic output resulting in higher blood pressure and heart rate (15). Both are reflected in the patient's complaints (higher sensory and motor activity) and/or in polysomnographic characteristics (increased heart rhythm). The urge to move the legs as well as the sensory symptoms can be understood as a dysfunctional 'gate control' mechanism that inhibits the increased sensory input due to a dopaminergic hypofunction.

The complex findings for the putative role of dopamine in RLS may also indicate different phases or expressions of RLS, different underlying disease processes and complex neurophysiological interactions.

Iron deficiency and the dopaminergic neurotransmission

From a clinical perspective, secondary causes for RLS such as anemia, renal failure and pregnancy lead to the assumption of iron deficiency as a contributing factor in RLS symptoms. Indeed, MRI studies showed reduced iron in the striatum of RLS patient's brains (18). Since no neurodegenerative abnormalities could be detected in RLS patients, a dysfunctional iron uptake is plausible. In addition, the found similarities in dopaminergic abnormalities in RLS patients as well as in iron deficient conditions are tantalizing. Significant increases in tyrosine hydroxylase (TH) and phosphorylated TH (known to be the rate limiting enzyme in the biosynthesis of DA) were seen together with decreased extracellular levels of dopamine and dopamine transporter functioning. These findings indicate the potential role of iron deficiency in the impaired dopaminergic transmission in RLS.

Figure 1 : *Periodic limb movements in sleep, a marker of restless legs in polysomnography*



Genetic susceptibility

At the turn of the century, a twin study described a concordant rate of 83% for RLS in monozygotic twins (19). A genetic susceptibility was further elaborated by a genome wide association study that confirmed genetic risk factors within six loci: *MEIS1*, *BTBD9*, *PTPRD*, *MAP2K5/SKOR1* and *PTPRD* (20). Single nucleotide polymorphisms in these six loci were shown to increase the risk of RLS and were strongly linked to increased PLMS, the polysomnographic hallmark of RLS. Interestingly the locus *BTBD9* encodes a protein domain related to the circadian rhythm genes which might explain the circadian pattern of the RLS condition. These findings contribute to a gene-environment interaction hypothesis underlying the pathophysiology of RLS and strengthen the clinical suspicion of a hereditary cause.

Co-phenomenal conditions

Primary RLS is an isolated syndrome, however a few co-occurring conditions are described in literature. The most commonly are chronic kidney disease and attention-deficit/ hyperactivity disorder (ADHD).

A systematic literature review shows consistent evidence of an increased prevalence of sleep disorders in children with chronic kidney disease (CKD), with a prevalence of 10-35% for RLS (21). The exact pathophysiology of RLS in CKD patients remains unclear; there doesn't seem to be any correlation between RLS and iron deficiency in CKD patients. This suggests a different pathogenesis of RLS in these patients (22). Symptoms of RLS especially increase during periods of rest, for example during dialysis. Adjustment of the dialysis schedule earlier in the day, short daily hemodialysis, distraction tasks during dialysis and intradialytic exercise programs are described as successful interventions that ameliorate RLS symptoms (23).

A higher prevalence of RLS in children and adolescents with ADHD was demonstrated with rates of 11.5% to 44% (24). Here, iron deficiency was described as playing a role in both ADHD and RLS (24). The mechanism of dopamine hypo-activity, in which iron is an important co-factor for dopamine synthesis, as well as a common genetic determinant may be considered as a common pathophysiology for ADHD and RLS.

In addition, there are a few other diseases in which a higher prevalence of RLS has been shown compared to the general population. These include Tourette syndrome and nocturnal enuresis (25, 26). However, extensive evidence for these associations remains limited. Furthermore, RLS frequently co-occurs with psychiatric disorders. Among these, ADHD, mood and anxiety disorder were the most common with a prevalence of respectively 25%, 29.1% and 11.5% (27). The authors emphasize the mutual impact of disturbed sleep, mood and attention difficulties. When RLS is present in patients with comorbid psychiatric conditions, it is important to consider the enhancing effect of antipsychotics and the possible amplifying effect of selective serotonin reuptake inhibitors on RLS symptoms.

Treatment

Before deciding on a therapeutic approach, some factors should be taken into account. First, since clinical implications with impact on daily life are rather variable, one should always consider treatment only when the burden on daytime functioning (mood, school performance, hypersomnolence) is significant. Second, triggering factors such as medication, poor sleep hygiene, lack of physical condition, lack of healthy nutrition must be acknowledged and third, co-phenomenal conditions should be treated first, if possible.

According to the proposed pathophysiology and pharmacological evidence, iron supplementation and dopamine agonists are the most commonly used therapeutic agents. All pharmacological interventions in children and adolescents are off-label use. A flow chart was drawn to give an overview of the recommended therapeutic options (Figure 2).

Evidence-based guidelines conducted by the IRLSSG task force recommend iron as the first -line treatment option in RLS in children and adolescents with proven iron deficiency (28). Serum ferritin below 50µg/L is considered an indication for iron supplementation. Initially, oral iron supplementation is recommended. Ferrous sulfate at a dose of 3mg/kg/day can be given with a daily maximum of 130 mg. However, the possibility of an interfering systemic problem with iron malabsorption should be taken into account. In addition, gastro-intestinal side effects (bad taste, nausea and constipation) can be challenging for children to comply an oral iron treatment (28). When oral iron treatment for 3 months does not provide adequate benefit or has to be discontinued due to side effects, IV iron may be considered. IV iron sucrose (Venofer®) is reported as a safe and effective treatment option in children (28). The recommended dose is 3 -6 mg/kg IV iron sucrose with a maximum of 120mg. The therapeutic target is to obtain a serum ferritin level ≥ 50 µg/L. The IRLSSG Working Group emphasizes that there are no studies demonstrating the long-term benefit or safety of iron treatment. Therefore, follow-up monitoring is recommended. In absence of an iron deficiency, other pharmacological treatment options should be considered.

Guidelines for the treatment of RLS in adults reported dopamine agonists, pramipexole and ropinirole, as standard level of recommended treatment (29). No recommendations for children were made. However, some randomized, double-blind studies, are described with significant improvement of RLS symptoms with dopamine agonists (30).

When using dopamine agonists, adverse side effects (aggression) and drug augmentation can appear. The latter is due to increased dopamine resulting in postsynaptic down-regulation of dopaminergic receptors, thus possibly enhancing the underlying RLS mechanism (29). Pediatric dose should start and stay low with the main aim to restore daytime functioning and sleep. After a treatment period of 6 months, a discontinuation is advised to reevaluate symptom severity (30).

In case of augmentation, the RLS guidelines recommend an alpha-2-delta-1 ligand anti-epileptic such as gabapentin as an alternative option (29). DelRosso et.al. described a few case reports suggesting RLS-symptom relief with gabapentin therapy (30).

Due to its muscle relaxing activity, clonazepam is proposed as treatment option in RLS as well. There is however limited data on its use for pediatric RLS. Moreover, important side effects can appear in children (aggression) and benzodiazepines have a bad reputation on sleep architecture when it comes to chronic use.

Other treatment options such as melatonin, vitamin D, magnesium are not retained as there is little or no scientific evidence.

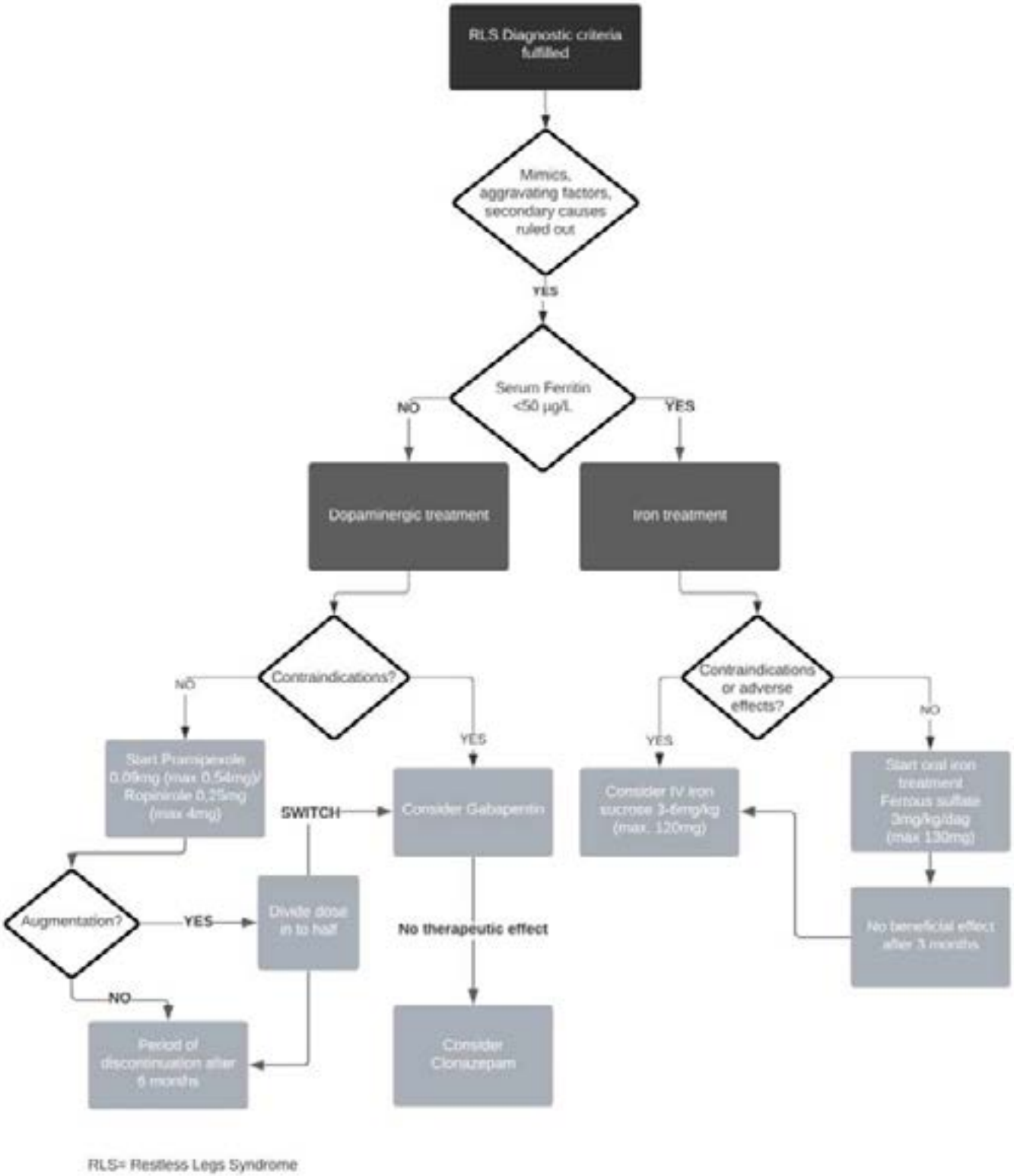
Conclusion

We aimed to provide adequate information for pediatricians to play a role in the detection and treatment of RLS in children. RLS is a sensory-motor disorder often not recognized or misdiagnosed in the pediatric population. Symptoms mostly appear as the inability to sit still, growing-pain-like sensations and/or disturbed and interrupted sleep. Apart from the diagnostic criteria published by the IRLSSG, diagnostic tools can be used to help identify RLS. Clinicians should be aware of common secondary causes, mimics and exacerbating factors. A PSG can be an additional objective diagnostic test. Due to different, yet partially unraveled pathophysiological mechanisms, the condition is likely heterogeneous. Before considering treatment options, a good assessment of sleep hygiene, sleep habits and possible exacerbating or co-occurring factors is recommended. Based on the proposed pathophysiological mechanisms, iron and dopamine agonists are the main therapeutic options. Therefore, a serum ferritin analysis, even though this cannot always be considered as the underlying cause, is worth to perform. Discontinuation of pharmacological treatment with a re-evaluation is important since the clinical features of RLS syndrome can vary during a lifetime.

Conflicts of interest

There are no conflicts of interest in this study

Figure 2 : *Flowchart treatment pediatric RLS (28, 30)*



RLS= Restless Legs Syndrome

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Indications for polysomnography in children – practical recommendations for the paediatrician

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Keywords

polysomnography, OSAS, narcolepsy, MSLT, hypnogram

Abstract

Sleep problems are frequent in children. The diagnosis of most sleep-related disorders starts with a detailed history and clinical examination.
Polysomnography (PSG) is the gold standard for objective measurement of neurologic and respiratory function during sleep, combining multiple data-collecting sensors.
Sleep-related breathing disorders are frequent, and PSG is needed for the diagnosis and quantification of obstructive sleep apnoea syndrome. Moreover, more rare disorders like central apnoea and hypoventilation can correctly be identified.
When narcolepsy is suspected, a multiple sleep latency test must be added to a PSG to objectify hypersomnolence.
This review describes the respiratory and neurologic indications for PSG in children and some practical and ethical considerations that must be taken into account when referring children for PSG.

Introduction

Sleep problems are frequent: 1/3-1/5 of the paediatric population experiences short or long term sleep problems. A real sleep disorder is present in 1-6% of healthy children, with an ever higher incidence in children with neurodevelopmental disorders.

The diagnosis of sleep disorders starts with a detailed history, both on sleep and daytime issues. The acronym BEARS describes the main issues to be discussed: bedtime behaviour, excessive daytime somnolence, awakenings during the night, the regularity and duration of sleep and the presence of snoring must be assessed. A general clinical history and physical examination are needed to detect underlying diseases, known risk factors or secondary effects of sleep disorders.

Polysomnography (PSG) is the gold standard diagnostic technique to evaluate sleep-related disorders, in combination with a full clinical evaluation. It is a complex test that evaluates all aspects of normal sleep (1,2).

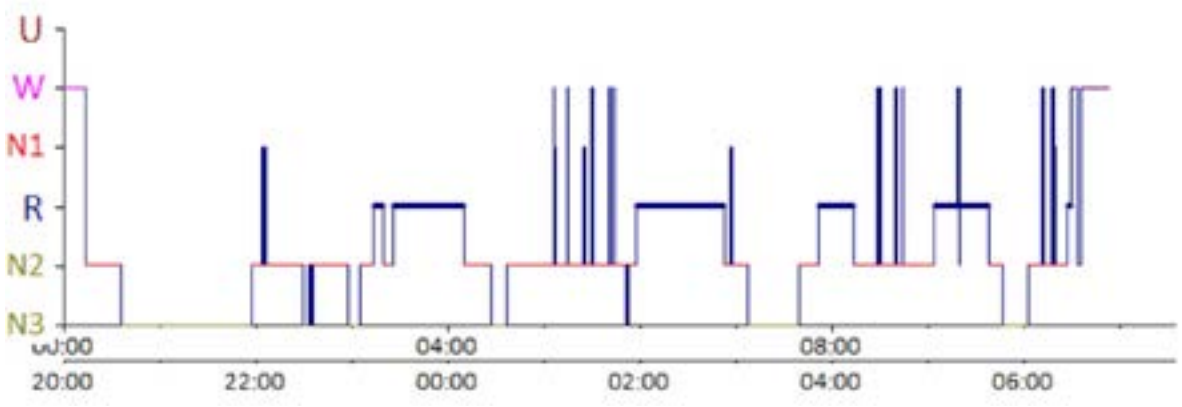
Because PSG is time-consuming, costly and quite invasive for young children, it is important to understand its strengths, limitations and clinical utility.

In this review, we will discuss the indications for childhood PSG apart from prematurity and infancy. We will not discuss the technical requirements and interpretation/scoring of paediatric PSG in detail.

What is measured?

The American Association of Sleep Medicine (AASM) has formulated strict guidelines on how to perform, evaluate and score polysomnography (3). First, a complete neurological evaluation is performed, with simplified electroencephalography (EEG) monitoring, mostly with 8-20 electrodes. Electrooculography (EOG) is performed with one electrode placed lateral from each eye, electromyography (EMG) mostly uses a submental and bilateral tibial electrode. Based on the EEG, EOG and EMG interpretation, sleep can be divided in sleep stages N1 (transition from wake to sleep, very short-lasting), N2, N3 (deep sleep) and REM (dream stage of sleep, characterized by rapid eye movements and minimal muscle tone). Arousals are short disturbances in sleep, due to varying causes. These different sleep stages appear in sleep cycles from 90-100 minutes. A hypnogram is the overview of all sleep cycles and sleep stages during the night and gives an overview of the sleep quality (Figure 1).

Figure 1: *Example of a hypnogram from a 7-year old child. The different sleep stages can visually be identified: wakefulness (W), stage N1, N2 and N3, and REM (R)-sleep. N3 is typically more abundant in the first part of the night, REM-sleep typically increases towards the morning. Short arousals are seen as very short periods of wakefulness.*



For the respiratory evaluation during sleep, respiratory muscle activity is evaluated by movement of thoracic and abdominal wall and by airflow measured at the nose and the mouth. In this way, interruptions of breathing (apnoea) can be detected by a drop of >90% in muscle activity or flow, hypopnea by a drop of 50-90% in muscle activity or flow. If the activity of all muscle groups decreases, the apnoea/hypopnea is of central origin, if thoracic and abdominal movement is preserved (can be paradoxical) with absent nasal and buccal flow, the apnoea/hypopnea is obstructive in origin. Age-appropriate scoring rules must be used. Additionally, oxymetry and electrocardiogram monitoring can detect subsequent desaturations and bradycardia, arousals can be identified on the EEG. Sound and video recordings (with infrared camera) are used to interpret noises (snoring, stridor,…) or abnormal movements (seizures, periodic limb movements,…). Registering body position can be helpful to identify position-related phenomena. The apnoea/hypopnea index (AHI) is defined as the number of detected apnoea/hypopneas per hour of sleep and is most frequently used as objective measure of sleep related breathing disorders. If night time hypoventilation is suspected, additional percutaneous or end-tidal CO_2 monitoring must be applied.

More abbreviated versions (simple overnight oximetry polygraphy which is a full respiratory evaluation without EEG monitoring) can be used to screen for sleep disorders and can even be applied in home settings, but are less sensitive and less specific for diagnostic purposes and evidence for their use is limited.

Respiratory indications for polysomnography in children

Physiology of respiration during sleep (Figure 2)

In healthy individuals, normal sleep is characterized by a generalized decrease of muscle tone. In combination with a reduced lung compliance, this leads to a reduction of the functional residual capacity, leading to micro-atelectasis and ventilation perfusion mismatch. Besides, decrease of the pharyngeal and tongue muscle tone causes an increase of the upper airway resistance. On top of the generalized decrease in muscle tone, the central ventilator drive decreases, resulting in a decrease of minute ventilation by around 10%. Overall, this results in a slight increase of Pa_{CO2} of 2-8 mmHg and a decrease of Pa_{02} of 3-11 mmHg compared to wakefulness. These effects are most pronounced during REM-sleep, as muscle tone is at its lowest level.

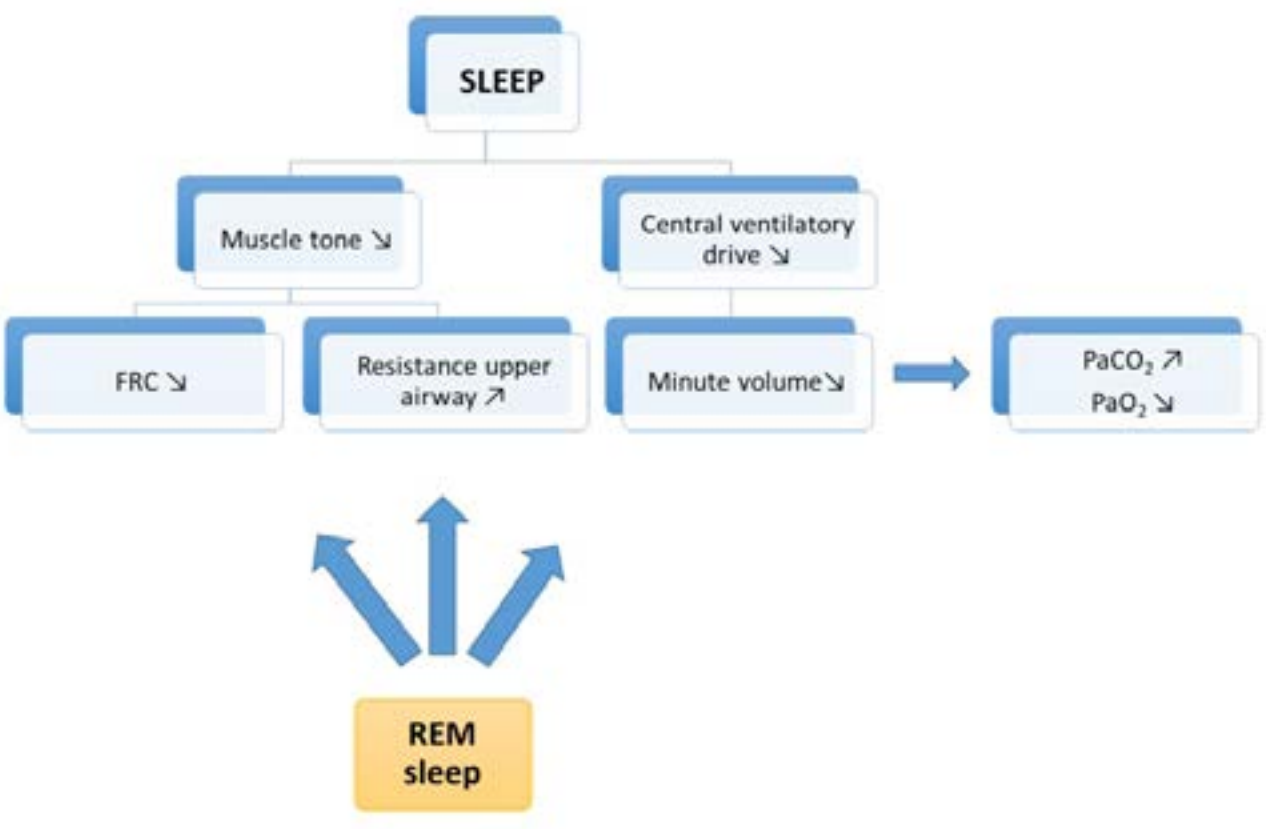
OSAS

Because of generalized decreased muscle tone during sleep compared to wakefulness, the resistance in the upper airway increases and this can lead to snoring (vibration of the weak tissues of the upper airway) or complete collapse of the upper airway (Figure 2). Sleep disordered breathing (SDB) is a spectrum of disorders caused by upper airway dysfunction during sleep, characterized by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility (4). When recurrent events of partial or complete upper airway obstruction occur, resulting in disruption of normal oxygenation, ventilation and sleep pattern, this is defined as obstructive sleep apnoea syndrome (OSAS) (4). OSAS is frequent in the paediatric population, with a reported prevalence between 1 and 4% (5).

Symptoms of OSAS are snoring, open mouth breathing, abnormal sleep position with extended neck or witnessed apnoeas, although the correlation between the presence of snoring and OSAS is bad. The aetiology of OSAS is multifactorial, but the most frequent causes in otherwise healthy children are adenotonsillar hypertrophy and obesity. Additional risk factors (congenital or acquired) are described in table 1 (4,6) growth delay, behavioural problems.

Screening for OSAS by means of PSG is indicated if suggestive symptoms are present: snoring, witnessed apnoea, unexplained fatigue, excessive daytime sleepiness or concentration problems, morning headaches and nausea, disturbed or restless sleep, persisting enuresis. In isolated cases, OSAS can be an aggravating factor in growth retardation and feeding difficulties, bad asthma control, systemic or pulmonary hypertension, metabolic syndrome, frequent otitis media and attention deficit and hyperactivity disorder (ADHD). For

Figure 2: *Physiology of normal respiration during sleep.*



certain populations (marked by * in Table 1), screening PSG is recommended, sometimes even irrespective of symptoms (7,8)no recent evidence-based practice parameters have been reported. These practice parameters are the first of 2 papers that assess indications for polysomnography in children. This paper addresses indications for polysomnography in children with suspected sleep related breathing disorders. These recommendations were reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine. Methods: A systematic review of the literature was performed, and the American Academy of Neurology grading system was used to assess the quality of evidence. Recommendations for PSG Use: 1. Polysomnography in children should be performed and interpreted in accordance with the recommendations of the AASM Manual for the Scoring of Sleep and Associated Events. (Standard.

It is important to quantify the severity of OSAS, as the risk of long-term morbidity (systemic and pulmonary hypertension, enuresis, cognitive and behavioural effects) are correlated to the severity of OSAS. An obstructive AHI ≥1 in the presence of suggestive symptoms is diagnostic of OSAS. Mild OSAS (obstructive AHI between 1 and 5) based on adenotonsillar hypertrophy can spontaneously improve, as was demonstrated in a large randomized controlled trial studying the effect of adenotonsillectomy in children with OSAS (9). If symptoms are invalidating and persisting, treatment can be considered. Moderate-to-severe OSAS (AHI>5) is unlikely to resolve spontaneously, predictive of long term morbidity (mainly cardiovascular) and needs intervention.

PSG can be performed to confirm the presence and severity of OSAS preoperatively before adenotonsillectomy is executed, as it is known that clinical symptoms badly correlate with the severity of OSAS (10). Contrary, there is a good correlation between the severity of OSAS and the perioperative risk for complications. PSG can be used for re-evaluation after adenotonsillectomy, for example in patients with moderate to severe OSAS, or to exclude incomplete resolution of OSAS in patients with additional risk factors (4). Those patients will need additional treatment, for example with continuous positive pressure (CPAP) or maxillofacial surgery.

In patients treated with CPAP therapy, PSG should be used for titration of the initial CPAP pressure, and for follow-up, as growth or changes in the airway morphology may impact the needed pressure for optimal control of OSAS. For patients needing extensive surgery like rapid maxillary expansion and more specialized craniofacial surgery, postoperative PSG is warranted to evaluate residual OSAS.

Central apnoea's

Congenital central hypoventilation (CCHS) is a very rare genetic condition, based on *PHOX2B* mutations, that is characterized by an abnormal central control of ventilation, resulting in central apnoeas, night time hypoventilation and other autonomic disorders (11). PSG with capnometry is indicated for diagnosis and follow-up of CCHS.

Patients with Chiari malformation or other intracranial causes of pressure on the brain stem (for example brain stem tumours, skeletal dysplasia, lysosomal storage diseases) are at specific risk for the development of central sleep apnoea, but also obstructive and mixed sleep apnoea. PSG can detect respiratory disturbances and can be used to evaluate the effect of neurosurgical intervention.

Night time hypoventilation

In children with neuromuscular disorders, further decrease of muscle tone during sleep can result in sleep-related hypoventilation (decrease of inspiratory respiratory muscle force) and/or OSAS (weakness of pharyngeal muscles resulting in upper airway collapse). A high prevalence of obesity due to immobility may further increase the risk of OSAS.

Symptoms of night time hypoventilation can be daytime fatigue or hypersomnolence, morning headaches, nausea or drowsiness, hyperactivity, cognitive problems, irritability, frequent arousals with poor sleep quality, recurrent respiratory infections, failure to thrive and cor pulmonale. However, symptoms are nonspecific and underreported.

Table 1: *Risk factors for OSAS in children can be divided in 3 categories: general risk factors, structural risk factors and factors influencing the upper airway tone. Factors marked in bold or the most frequent risk factors in otherwise healthy children.*

General risk factors	Structural risk factors	Upper airway tone
Allergic rhinitis	**Adenotonsillar hypertrophy**	**Obesity**
Prematurity	Nasal septum deviation	Neuromuscular disease*
Familial OSAS	Hypertrophic conchae	Cerebral palsy - epilepsy
♂ > ♀	Laryngotracheamalacia	Arnold-Chiari malformation*
African-American ethnicity	Subtle craniofacial abnormalities in non-syndromic children: – Dolichocephaly – teeth malocclusion – retrusive chin – steep mandibular plane – vertical direction of craniofacial growth	Prader Willi syndrome*
Passive smoking	Complex craniofacial abnormalities: – mandibular hypoplasia (f.e. Pierre Robin sequence*) – midfacial hypoplasia – Treacher-Collins, Crouzon, Apert, Pfeiffer* – Palatal cleft – Achondroplasia* – Mucopolysaccharidosis* – Choanal atresia – Beckwidth-Wiedemann syndrome – Marfan Syndrome – Ehlers-Danlos	Down syndrome*

In children with progressive neuromuscular diseases, it is suggested that the risk for sleep disordered breathing dramatically increases when forced vital capacity (FVC) drops below 60% (12–14). Therefore, guidelines suggest to perform systematic screening PSGs in this group irrespective of the presence of symptoms, always in combination with CO_2 monitoring (15). Moreover, loss of (or inability to attain) ambulation, severe diaphragmatic weakness and rigid spine syndrome are regarded as additional risk factors for the development of night time hypoventilation (15).

The respiratory status in patients with neuromuscular disorders can further be compromised by progressive scoliosis, chronic aspiration, recurrent and chronic infections, etc. When invasive surgery with general anaesthesia is needed (e.g. scoliosis surgery), PSG is advised in the pre-operative evaluation in patients with severe restrictive lung disease.

Other patient groups with severe generalized hypotonia and risk of development of night time hypoventilation are: cerebral palsy, Prader Willi syndrome, Down syndrome, acquired hypotonia due to steroid myopathy, diaphragmatic paralysis, metabolic decompensation, excessive sedative drug use, high cervical lesion,....

Severe restrictive lung disease from respiratory (end-stage cystic fibrosis, bronchopulmonary dysplasia, interstitial lung disease, …) or non-respiratory origin (congenital diaphragmatic hernia, skeletal dysplasia, (kypho)scoliosis) can lead to night time hypoventilation and children with these disorders should be screened by PSG.

Once ventilation is started, PSG can be used for optimal titration of the ventilator settings (ventilatory pressure, frequency, synchronisation, to identify leaks, etc) and to adapt the settings in function of growth and improvement or worsening of the ventilatory capacity in function of the underlying disease.

Non-Respiratory indications for polysomnography in children

Narcolepsy

Narcolepsy is a neurologic disorder that is characterized by daytime hypersomnolence (recurrent attacks of irresistible daytime sleepiness) and cataplexy (sudden loss of muscle control in the legs, trunk, face or neck in response to emotional stimuli). Night time sleep is typically fragmented, and REM-sleep can occur abnormally early. The diagnosis of narcolepsy can be made based on a typical clinical history, in combination with a PSG with a multiple sleep latency test (MSLT) (16–18)and assessment requires a thorough history and in many cases, objective assessment in the sleep laboratory. These practice parameters were developed to guide the sleep clinician on appropriate clinical use of the Multiple Sleep Latency Test (MSLT. MSLT is feasible and can be interpreted reliably from the age of 5 years. After a normal night with PSG recording, the patient is given the opportunity to do 4-5 daytime naps of 20 minutes every 2 hours. The time needed to fall asleep (sleep latency) is measured and the time to REM onset is also evaluated. A mean sleep latency below 8 minutes in combination with at least one SOREMP (sleep onset REM periods) is diagnostic for narcolepsy, although normative data for children and adolescents are scarce. The PSG is needed to exclude other causes of hypersomnolence like severe OSAS and can illustrate the abnormal sleep architecture in these patients. PSG alone is not sufficiently sensitive for the diagnosis of narcolepsy.

An MSLT cannot be interpreted correctly in patients with sleep deprivation or in patients that are treated with neurostimulatory drugs.

Parasomnia

Parasomnia is a phenomenon of abnormal movements and behaviour during sleep, as a consequence of transition between different sleep stages or between sleep and wakefulness. It is relatively frequent in the paediatric population, but is mostly harmless and disappears with age.

A suspicion of parasomnia is not a primary indication to perform PSG. Mostly, a detailed history can sufficiently adequately diagnose typical parasomnia in children (e.g. sleep terrors, sleep walking, rhythmic movement disorders,…) (17). A video recording made by the parents can be very helpful to have a good view on the specific type of the parasomnia. Only when the parasomnia is atypical, dangerous, or suggestive of nocturnal epilepsy, or when there is a suspicion of concomitant OSAS, a PSG can be indicated.

Restless legs syndrome

Restless legs syndrome (RLS) is a clinical diagnosis that includes sensorimotor discomfort of the legs, worsening in the evening hours, particularly when the child is at rest. PSG can identify abnormally frequent (>5/h) periodic limb movements (PLMs) in most patients with RLS, and can support the diagnosis in this way, as parental reporting of movements is unreliable (17).

Delayed sleep phase syndrome

The diagnosis of circadian rhythm disorders such as delayed sleep-wake phase disorder is based on a detailed history in combination with a sleep diary of at least one week (weekend included). Actigraphy, a measurement of movement during the night, can be used to support the diagnosis. PSG does not show typical abnormalities and doesn't contribute to the diagnosis.

Insomnia

Insomnia is not an indication for PSG, only in exceptional cases, for example when there is a suspicion of a discordance between objective and perceived sleep duration. Sleep history with a detailed sleep diary is mostly sufficient for a correct diagnosis and adequate treatment.

Practical considerations and limitations

Performing a PSG of good quality is not easy in young children and it is regarded as quite invasive. Especially children with limited mental capacities are not able to understand the need for all applied electrodes. Therefore, the examination should be performed in optimal circumstances; good information should be provided in advance by a brochure or a visit to the sleep lab; presence of a parent at the moment of application of all electrodes and during the night; presence of a lab technician or nurse with experience and patience in dealing with children and a child-friendly environment are important factors to be considered.

PSG is typically a one-night examination, with the possibility of a reduced sleep quality because of external factors (noise, unfamiliar environment, fear) and the risk of missing non-frequent night time events. However, studies have shown that the variability in respiratory evaluation between different nights is limited and not clinically relevant in most cases.

In children, there is insufficient evidence for the use of home PSG for diagnostic purposes (19). Similarly, nap or abbreviated polysomnography has been proven insufficiently sensitive. In children needing oxygen treatment, full PSG is generally not indicated, unless there is an additional suspicion of sleep related breathing disorders or hypoventilation (7)no recent evidence-based practice parameters have been reported. These practice parameters are the first of 2 papers that assess indications for polysomnography in children. This paper addresses indications for polysomnography in children with suspected sleep related breathing disorders. These recommendations were reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine. Methods: A systematic review of the literature was performed, and the American Academy of Neurology grading system was used to assess the quality of evidence. Recommendations for PSG Use: 1. Polysomnography in children should be performed and interpreted in accordance with the recommendations of the AASM Manual for the Scoring of Sleep and Associated Events. (Standard).

It must be realized that PSG is different from EEG: the electrodes used are different, another reading frame is used (10 sec for EEG versus 30 sec for PSG), and the reader is different. Clear seizures can be recognized on PSG, but subtle epileptic activity can be missed. If there is a suspicion of epilepsy, an extended EEG monitoring could be applied.

PSG provides a lot of information, but cannot give answers to questions such as 'Why does a child wake up?', 'Why is a child tired?', 'Why is sleep quality bad?', 'What is a child dreaming?', 'Are there night mares?'. Isolated fatigue, nightmares, fibromyalgia, parasomnia or a disturbed sleep without indication of OSAS, epilepsy or underlying disease are therefore no good indication for a PSG in children. Whenever a child is referred for PSG, a clear explanation of the indication will allow the reader to provide a correct and complete protocol.

Ethical considerations

When a PSG is planned, the impact on therapeutic decisions should be questioned in advance. For otherwise healthy children, it is obvious that an abnormal result will be followed by an adequate treatment.

For severely disabled children (for example cerebral palsy with severe mental disability), caregivers should evaluate whether the treatment plan would be changed in function of the result of the PSG. In patients with a limited life expectancy, would quality of life or prognosis change? Treatment options for OSAS in this population are often limited: a considerable number of patients need orthopaedic appliances for abduction of the hips and therefore choices have to be made between optimal sleep position for respiratory (lateral decubitus for optimal respiration and reduction of upper airway obstruction) or orthopaedic reasons (dorsal decubitus). Similarly, CPAP therapy is not always efficacious because of open mouth breathing, or may not be tolerated because of drooling, risk of aspiration, uncontrolled movements and epilepsy. A multidisciplinary approach is absolutely needed, and parents should be counselled in advance. The risk of treatment and abstinence of treatment should openly be discussed.

Conclusions

Paediatric PSG is a very useful technique that provides extensive information on the neurologic and respiratory activity during sleep. It is indicated for the diagnosis of OSAS and narcolepsy, and can be helpful for detecting other sleep-related disorders. Correct interpretation requires expertise in paediatric sleep medicine. Caregivers should be aware of the utility and limitations of PSG, especially in children with underlying disorders.

Conflict of interest

The authors have no conflict of interest to declare.

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Hereditary spherocytosis: How to optimize its diagnosis

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Keywords

Hereditary spherocytosis; diagnosis; red blood cells; hemolysis; membrane protein defect

Abstract

Objectives: Hereditary spherocytosis is the most frequent inherited hemolytic anemia. Through an observational retrospective study of 8 years, this review aims at optimizing hereditary spherocytosis diagnostic approach. Our objectives were to characterize our population, adjust local cut-offs for confirmatory tests and revise our diagnostic algorithm on basis of international guidelines.

Method: Clinical and laboratory data of a Belgian cohort of 33 patients with hereditary spherocytosis were analyzed and compared to 44 non-spherocytosis patients.

Results: Hereditary spherocytosis patients were mostly children (median age of 6 years), jaundice and splenomegaly were rather common. The most discriminating routine tests between hereditary spherocytosis and patients with other hemolytic conditions were red blood cell distribution width and most of the reticulocyte parameters measured ($p \leq 0.01$). While confirmatory tests for hereditary spherocytosis, e.g., cryohemolysis, eosin-5'-maleimide binding test, ektacytometry O min and ektacytometry area under the curve were also discriminating between those two populations ($p \leq 0.0001$) with cut-off values for an AUC on ROC curve ≥ 0.8 of 15%, 14%, 17% and -24.5%, respectively. Compared to an international algorithm, no false positive or false negative cases were found with our simplified algorithm and the application of the new cut-off values for confirmatory tests.

Conclusion: The use of reticulocyte parameters is a simple tool as a first step in screening for hereditary spherocytosis in a large number of laboratories. It allows to select patients who need further or not more complex analysis in a context where optimal healthcare costs repartition seems more important than ever.

Introduction

Hereditary spherocytosis (HS) is a worldwide reported pathology. It is an inherited disease due to red blood cell (RBC) membrane protein defect. The highest prevalence is estimated at 1:2000 among Caucasians (1). It is the most common non-immune hemolytic anemia (2) . However, the heterogeneous character of this disease makes its diagnosis complex. Typical presentation comprise anemia, jaundice, splenomegaly and reticulocytosis (3) . The severity of the disease can be defined on basis of the degree of anemia in minor, moderate, moderate to severe or severe HS. (1) Most patients present with minor to moderate form, and up to one third have an isolated compensated hemolysis (3). Diagnosis is then often delayed, especially in the absence of family history. However, in cases of decompensation, anemia may be severe (1). Rarely, HS can be associated with more complex syndromes due to large genomic deletions (2). The challenge is to optimize identification of suspect cases and common hematological parameters could be an effective screening tool.

Current guidelines states that HS diagnosis can be made without any further tests in case of spherocytes on blood smear, compatible red cells indices, negative direct antiglobulin test (DAT) and positive family history (3) . If not clear, at least one screening test for HS should be performed (3). As none of those screening tests has a sensitivity of 100%, a combination of tests is recommended (4). There are various screening tests available for HS, i.e. the osmotic fragility test (OFT), the acid glycerol lysis time test (AGLT), the cryohemolysis (CH) test and the eosin-5'-maleimide binding test flow cytometry based (EMA).

The classic OFT is based on evaluating the degree of hemolysis induced by a hypotonic solution of NaCl. The drawback of this first test is its lack of sensitivity and specificity, often leading to undetermined results. The AGLT is based on measuring the time needed to obtain 50% of hemolysis of a blood sample in a buffered solution of hypotonic saline/glycerol (3).

The CH test is based on the increased susceptibility of spherocytic RBC to hemolysis in cold and hypertonic conditions (5). It has a better sensitivity and specificity than the first two tests cited, varying from 48.5% to 100 % and 77% to 96% respectively according to the cut-off value applied (6). Finally, the EMA test is the most frequently recommended test for HS screening. Dye binding is usually decreased in erythrocyte membrane in HS. It has a higher specificity (93% to 99.1%) than osmotic fragility tests but a lower sensitivity (89% to 99%) (7–10). It can fail to identify some HS cases associated with ankyrin defects and dye binding is also decreased in other conditions like elliptocytosis, pyropoïkylocytosis, and Southeast Asian ovalocytosis (SAO) (7–10). In this context, it might be useful to confirm HS diagnosis with more specific tests but always associated with careful examination of blood films. Osmotic ektacytometry is the analysis of the RBC deformability in changing osmotic conditions with constant shear stress applied. It provides distinct profiles with precise points that enable a good discrimination between different inherited RBC membrane disorders such as HS, hereditary stomatocytosis or elliptocytosis (11). Another test used for HS confirmation is sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). It aims to separate RBC membrane proteins on a gel according to their molecular weight and identify quantitative or qualitative alterations of those proteins (11). However it lacks sensitivity in mild HS cases and is usually used in specific situations, as before a splenectomy or if previous tests are equivocal (12). Finally, a molecular analysis is reserved for enigmatic cases.

Through an observational retrospective study of 8 years in our reference center, the present study aimed to optimize HS diagnostic approach. We based our work on a cohort of patients with a confirmed diagnosis of HS and a complete medical record. Our objectives were (a) to characterize HS disease in terms of clinical and biological features, (b) to adjust our previously established cut-offs for screening and diagnostic tests and (c) to compare our diagnostic approach with the International Council for Standardization in Haematology (ICSH) algorithm of 2015 and to elaborate our local diagnostic algorithm (3).

Materials and methods

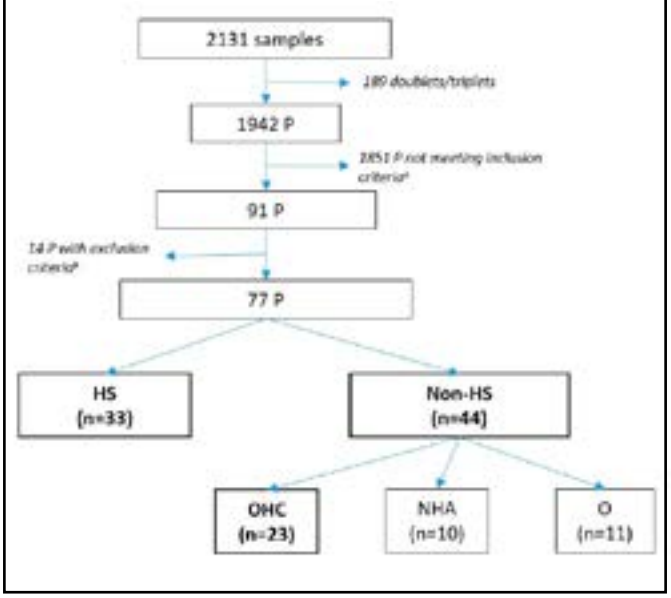
Patients

This study considered patients from 10 different Belgian hospitals located in Brussels and Liege areas: Institut Jules Bordet, CHU Brugmann, CHU de

Liège, CHU Saint-Pierre, HUDERF, CHR Citadelle, CHR Verviers, CUB hôpital Erasme, Esperance and Saint-Joseph (CHC, Liège). Cohort selection process is presented in Figure 1. Patients samples were tested for HS in our laboratory between April 2009 and December 2016. Selection criteria included a complete medical record with follow-up, availability of hematological parameters (at least hemoglobin level and reticulocyte count), and 2 negative screening tests or at least one confirmatory test result in case of a positive screening test. Patients were excluded when splenectomized before sampling (9 patients, 6 with HS) or transfused with RBC within 3 months before sampling (5 patients, none with HS). HS diagnosis was based on family history, clinical and laboratory features of chronic hemolysis, the presence of spherocytes at the peripheral blood smear, and at least one screening test positive, i.e. cryohemolysis or EMA and one confirmation test compatible with HS, i.e. SDS-PAGE or ektacytometry. Other causes of hemolysis were excluded (negative DAT, RBC enzymopathies and hemoglobinopathies).

The final cohort included 77 patients: 33 with a diagnosis of HS and 44 representing non-HS population (Fig. 1). Given the heterogeneous character of the non HS population, subjects were divided into 3 subgroups according to biological parameters 1) other hemolytic conditions (OHC; n=23; decreased haptoglobin and/or an increased lactate dehydrogenase or unconjugated bilirubin; 1 picnocytosis, 1 elliptocytosis, 1 idiopathic thrombocytopenic purpura (ITP), 1 atypical hemolytic uremic syndrome, 2 sickle cell diseases, 1 pernicious anemia, 2 myelodysplastic syndrome, 1 Kaposi sarcoma, 2 autoimmune hemolytic anemia, 1 iso-immunization, 2 cirrhosis, 7 undetermined diagnosis), 2) non-hemolytic anemia (NHA; n=10; 1 infection, 1 myelodysplastic syndrome, 1 acute myeloid leukemia, 3 prematurity, 1 thalassemia and 3 iron deficiency), 3) other subjects (O; n=11; neither anemia nor hemolysis in non-related HS; 7 healthy, 1 transitory idiopathic splenomegaly event, 1 infection and 2 splenomegaly due to onco-hematologic disorders).

Figure 1 : *Cohort selection and repartition.*
a complete medical record and follow-up, hemoglobin level and reticulocyte count, 2 negative screening test or at least one confirmatory test result in case of a positive screening test; b red blood cell transfusion within 3 months before sampling or splenectomy before sampling
P, patients; HS, hereditary spherocytosis; OHC, other hemolytic conditions; NHA, non hemolytic anemia; O others



Samples

Peripheral blood samples were collected into tubes containing dipotassium ethylenediaminetetraacetic acid (K2-EDTA). A heparinized tube was added if an SDS-PAGE analysis was requested. All blood samples were processed within 24 hours of sampling and where then stored between 4-7°C within 8 hours after receipt. For samples sent from other laboratories, blood smear and mean corpuscular volume (MCV) were not considered.

Routine biochemical and hematological tests

Serum lactate dehydrogenase activity, haptoglobin, total bilirubin and unconjugated bilirubin concentrations were performed with the Modular P800 (Roche Diagnostics, Vilvoorde, Belgium), hemoglobin level, MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC distribution width (RDW-CV), reticulocyte count, immature reticulocyte fraction (IRF), mean reticulocyte volume (MRV), mean sphered cell volume (MSCV) where obtained through UniCel DxH 800 (Beckman Coulter, Namur, Belgium). The analytical variability was less than 1% for all considered parameters. The operation mode was described previously (13). Given a large heterogeneity of age in our cohort and therefore different reference ranges, parameters were expressed as a percentage of the mean reference value of a test (hemoglobin level, MCV, MCH, MCHC, absolute reticulocyte count) or percentage of the upper reference value of a test (total bilirubin and LDH).

Hereditary spherocytosis specific screening and confirmatory tests

Cryohemolysis and EMA are the two specific screening tests used in our laboratory. Both methods were described previously (11). In order to minimize intra-assay variations in cryohemolysis, patient's sample is compared with a control sample and results are expressed in percentage of hemolysis. Our established performances are a sensitivity of 95% and a specificity of 90% for a cut-off value of 10% (personal data, unpublished). For EMA, results are expressed as the percentage reduction of mean fluorescence intensity (MFI) compared to the mean MFI of 6 healthy donors. Our established performances for a cut-off value of 19% are a sensitivity of 100% and a specificity of 82% (personal data, unpublished).

Ektacytometry and SDS-PAGE tests were described previously (11,12). As there are no standard available for these tests, patient's sample is always processed and compared with a control sample. Our evaluation of ektacytometry sensitivities and specificities were respectively of 42% and 97% for a cut-off value of 21.5% for the osmolality point at the minimal elongation index (0 min), and 70% and 95% for a cut-off value of -18.5% for area under the curve (AUC) (12).

Statistical analysis

Data were analyzed using GraphPad Prism 8 software (SanDiego, USA). Descriptive statistics were computed for each parameter. Gaussian distribution was assessed using Shapiro-Wilk normality test.

Concerning HS and non-HS groups comparison, mean and standard deviation (SD) was determined using unpaired Student's t-test for data with Gaussian distribution, while median and interquartile range (IQR) were determined using a Mann-Whitney test for data with non-Gaussian distribution. Multiple comparison tests, i.e. ANOVA and Dunnett for data with Gaussian distribution, Kruskal-Wallis test and Dunn for non-Gaussian distribution data were used to compare HS with non-HS subgroups, with a special attention to OHC, in order to establish which parameter remained discriminant for HS in a context of hemolysis. Data were considered statistically significant if p value ≤ 0.05 (*: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$; ****: $p \leq 0.0001$).

In order to adjust our cut-off values for relevant identified parameters, the area under the receiver-operating characteristic (ROC) curve was calculated and diagnostic values were compared.

Results

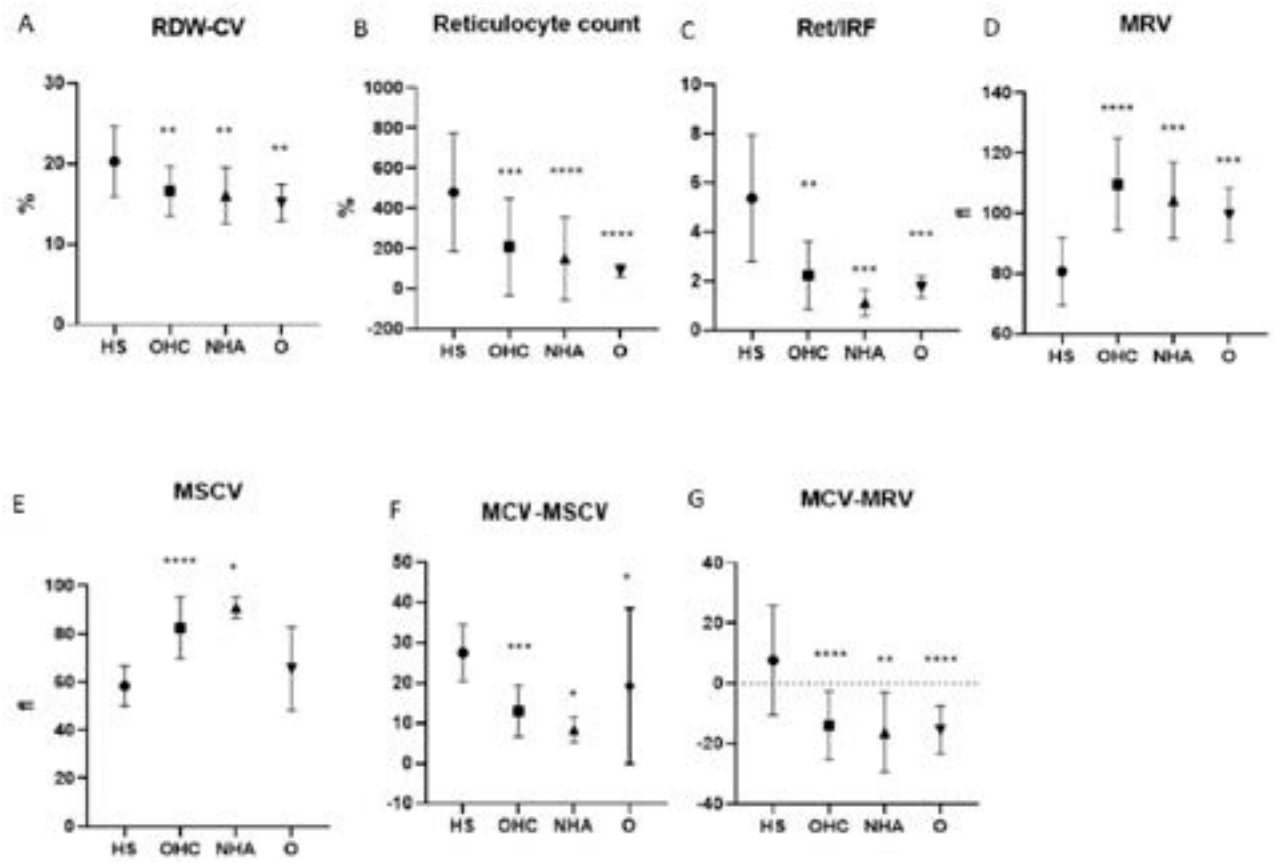
Cohort characterization

Clinical and laboratory characteristics are depicted in Table 1. HS patients were significantly younger than non-HS patients with no significant difference of gender repartitions between the two groups. Jaundice and splenomegaly, a positive family history of HS and transfusion requirement were significantly more frequent in HS patients ($p \leq 0.01$). Decrease in haptoglobin and increase in total bilirubin, MCHC and RDW-CV were significantly more often observed in HS patients ($p < 0.05$).

Fig. 2 shows RDW-CV and parameters provided by the reticulocyte channel that are statistically significantly different between HS and non-HS different subgroups.

Cryohemolysis and EMA were strongly discriminating between HS and the

Figure 1 : *Discriminant hematological parameters between HS and non-HS subgroups.*
*(A) RDW-CV was significantly higher in HS compared to all non-HS subgroups. (B) Reticulocyte count was significantly higher in HS compared to all non-HS subgroups. (C) Ret to IRF ratio was significantly higher in HS compared to all non-HS subgroups. (D) MRV was significantly lower in HS compared to all non-HS subgroups. (E) MSCV was significantly lower in HS patients compared to OHC and NHA subgroups. No statistically significant difference was observed between HS and O subgroup. (F) Delta MCV-MSCV was significantly higher in HS compared to all non-HS subgroups. (G) Delta MCV-MRV was significantly higher in HS compared to all non-HS subgroups. HS, hereditary spherocytosis; MCV, mean cell volume; MRV, mean reticulocyte volume; MSCV, mean sphered cell volume; NHA, non-hemolytic anemia; O, others; OHC, other hemolytic conditions; RDW-CV, red blood cell distribution width; Ret/IRF, ratio between reticulocyte count and immature reticulocyte fraction; *, p≤0.05; **, p≤0.01; ***, p≤0.001; ****, p≤0.0001.*



different subgroups, as shown in Fig. 3 (p<0.0001). Regarding ektacytometry, O min appeared particularly useful for HS differential diagnosis with other hemolytic conditions (p<0.0001). AUC and EI max were only discriminating between HS and "others" group (p<0.01). There was no osmoscan data for patients from the NHA group.

Table 1 - Characteristics of HS and non-HS patients.

Characteristic	HS (n=33)	Non-HS (n=44)	*P* value
Age (years; median (IQR))	6 (1-31)	28 (4-45)	0.0274
Gender (% males)	67	52	ns
Typical clinical and laboratory features (n; median (IQR))[a]	3 (2-4)	2 (1-3)	0.0004
Positive family history (%)	79	5	<0.0001
Transfusion requirement (%)	42	14	0.0044

[a]neonatal jaundice, anemia, gallbladder stone, hemolysis, splenomegaly, jaundice.
n, number of typical features that are present within an individual patient; IQR, interquartile range; HS, hereditary spherocytosis; ns, non-significant

Cut-off values

Cut-off values were established on basis of ROC curve analysis results. Parameters with an AUC ≥ 0.8 were considered. Chosen cut-off values as well as those previously published are depicted in Table 2.

Working algorithm evaluation

In order to evaluate our diagnostic approach, the algorithm proposed by the ICSH in 2015 was applied to the entire cohort. Based on these patients' diagnoses of HS, neither false negative nor false positive cases of HS were found with the old nor the new cut-off values. However, it appeared that several tests could have been avoided. In fact, ektacytometry and SDS-PAGE analysis were both performed in 6 patients despite the absence of family history and negative results for cryohemolysis and EMA. All these cases were finally negative for HS. Also, cryohemolysis, EMA and at least one confirmation test were performed in 15 patients who had a positive family history and spherocytes seen on blood smear. They were eventually all positive for HS.

Based on this experience, we elaborated a local diagnostic algorithm inspired by the one published by ICSH in 2015 (Fig. 4). Step 1: in case of HS suspicion facing typical HS features and/or positive family history, in order to confirm hemolysis, RDW-CV and parameters from the reticulocyte channel are required and a blood smear is performed for the detection of spherocytes or other abnormalities in red blood cells morphology. If relevant, frequent other hemolytic conditions have to be excluded. Step 2: if a diagnosis of HS is still retained, cryohemolysis and EMA tests are performed. If both of them are negative, there is no need for further exploration. In contrast, if results are positive or doubtful, or if spherocytes are seen on the blood smear without any other explanation, we go to step 3. Step 3: an ektacytometry is conducted. If the profile is typical for HS, the diagnosis can be retained. If the profile is doubtful or if a splenectomy is planned, SDS-PAGE is performed in order to exclude CDA II, to confirm the diagnosis of HS and to determine the type of protein defect. Molecular analysis is only performed in specific cases of chronic transfusion or discrepancies between clinical picture and analytical results.

Table 2 – Cut-off values based on ROC curve analysis of the entire cohort.

	AUC	95% CI	New cut-off value			Old cut-off value		
			Value	Ss (%)	Sp (%)	Value	Ss (%)	Sp (%)
Delta (MCV-MSCV)	0,9	0,8-1,02	**>18**	100	80	>18[c]	92	94
MRV (fl)	0,9	0,9-1	**<96**	88	70	<92[c]	92	94
Ret /IRF	0,9	0,8-1	**>2.2**	92	81	>2.6[c]	92	89
MSCV (fl)	0,9	0,8-1	**<71**	87	70	<70.2[c]	92	90
CH[a]	0,9	0,9-1	**>15**	94	70	>10	95	90
EMA[a]	1	0,9-1	**>14**	88	100	>19	100	82
Ektacytometry O min[b]	0,9	0,8-1	**>17**	67	100	>21.5[d]	42	97
Ektacytometry AUC[b]	0,8	0,6-1	**<-24.5**	71	80	<-18.5[d]	70	95

a patient/control (%), b patient/control ratio, c proposed cut-off for clinical use by Lazarova et al in 2014 (13), d proposed cut-off for clinical use by Lazarova et al in 2017 (12) ROC, receiver operating characteristics; AUC, area under the curve; CI, confidence interval; Ss, sensitivity; Sp, sensitivity; MCV, mean cell volume; MSCV, mean sphered cell volume; MRV, mean reticulocyte volume; Ret/IRF, ratio between reticulocytes count and immature reticulocyte fraction; CH, cryohemolysis; EMA, eosin-5'-maleimide flow cytometric test; ektacytometry O min, ektacytomatry osmolality point at the minimal elongation index; ektacytometry AUC, ektacytometry area under the curve

Figure 3 : *Results distribution of the most efficient tests for HS diagnosis. (A) Cryohemolysis was significantly increased in HS patients (p<0.0001); (B) MFI reduction of Band 3 protein was significantly more important in HS patients (p<0.0001); (C) On the osmoscan curve, O min point was the only discriminant point between HS and OHC, moving to the right (p=0.0303). Ektacytometry was not performed in NHA group. HS, hereditary spherocytosis; OHC, other hemolytic conditions; NHA, non-hemolytic anemia; O, others; EMA, decrease eosin-5'-maleimide binding test; *, p≤0.05; **, p≤0.01; ***, p≤0.001; ****, p≤0.0001.t*

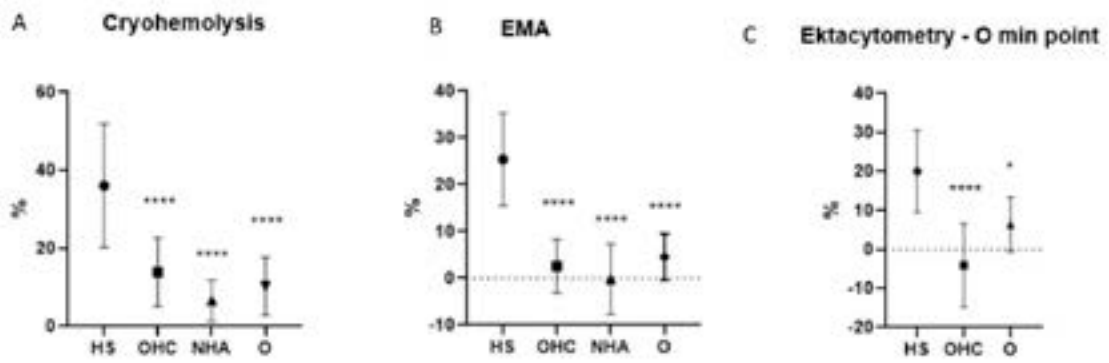
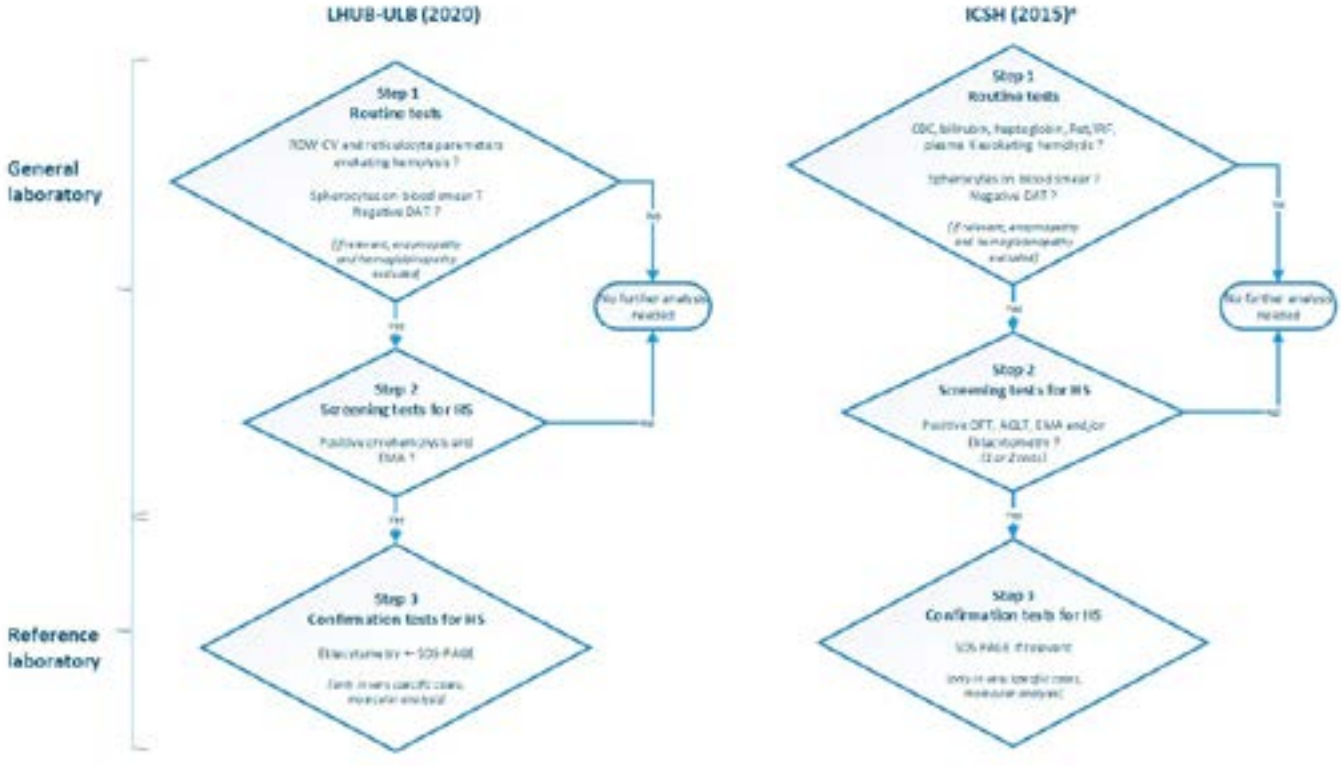


Figure 4 : *Diagnostic approach facing biological and clinical features and family history evoking HS: A summary of our "step-by-step" approach in comparison with the 2015 ICSH guidelines (3).*
a Adapted from 2015 ICSH guidelines (3). RDW-CV, red blood cell distribution width; DAT, direct antiglobulin test; HS, hereditary spherocytosis; EMA, eosin-5'-maleimide flow cytometry; SDS-PAGE, sodium dodecyl sulphate polyacrylamide gel electrophoresis; CBC, complete blood count; Ret/IRF, ratio between reticulocyte count and immature reticulocyte fraction; K: potassium; OFT, osmotic fragility test; AGLT, acidified glycerol lysis test



Discussion

In order to optimize HS diagnosis in our reference center, the first objective of this work was to characterize a confirmed cohort of HS patients in terms of clinical and biological data. HS patients were mostly children at time of exploration, as it is an inherited condition. The higher rate of positive family history in this population and the most discriminant characteristics were consistent with those reported in the literature (1,14). The reticulocyte count was significantly higher in HS and remained a discriminating parameter while compared only to other hemolytic conditions. One explanation is a real increase of the reticulocyte count in HS, due to a stimulation of erythropoiesis by decreased oxygenation conditions (15)a hypoxia-inducible cytokine, is required for survival, proliferation, and differentiation of erythroid progenitor cells. EPO can also stimulate proliferation and angiogenesis of endothelial cells that express EPO receptors (EPORs. Another hypothesis is related to a prolonged retention of the endoplasmic reticulum (ER) in HS. It is well known that altered vertical membrane interactions in HS lead to migration disorders (16). As reticulocytes are distinguished from mature erythrocytes by the presence of their ER, this phenomenon could lead to an increase of the total amount measured. Immature reticulocyte fraction (IRF) appeared only discriminating between HS patients and those without anemia and hemolysis. The reticulocyte count showed a higher proportional increase than IRF in HS and this explain that the ratio reticulocyte count/IRF is a sensitive screening test for HS, as described previously (17–19)leading to the release of microparticles. All the reference tests suffer from specific limitations. The aim of this study was to develop easy to use diagnostic tool for screening of hereditary spherocytosis based on routinely acquired haematological parameters like percentage of microcytes, percentage of hypochromic cells, reticulocyte counts, and percentage of immature reticulocytes. The levels of haemoglobin, mean cell volume, mean corpuscular haemoglobin concentration, reticulocytes (Ret. Indeed, potential retention of the ER could lead to a bigger proportion of « old » reticulocytes (16). Since IRF represents the proportion of highly fluorescent reticulocytes, this would result in an under estimation of this parameter. MRV and MSCV were significantly lower in HS compared to non-HS subgroups, and especially compared to other hemolytic conditions. This is due to the increased fragility of spherocytes, as these volumes are measured after spherization of RBC. Moreover, as membrane loss mainly occurs during erythroblast maturation in HS, it is not surprising to get a lower MRV than in other hemolytic conditions (16). Finally, delta MCV-MSCV and MCV-MRV were significantly higher in HS and were still discriminating in a context of hemolysis, as attested in the literature (20–22)conductivity and scatter technology. It has been observed that the difference between mean corpuscular volume (MCV. For cryohemolysis, there was a slight recovery between HS and other hemolytic conditions, as this test is often positive in AIHA. However, EMA is most of the time negative in the latter, which enables the distinction in case of positive DAT (23,24). This emphasizes the interest to combine cryohemolysis and EMA when HS is suspected, as none of the specialized tests available is able to identify all cases, in particular mild and moderate forms of this condition (12). Using our updated cut-offs, cryohemolysis provides a sensitive test for detecting slight membrane protein deficiency while EMA is more specific but might lead to false negative (3). Ektacytometry, O min and AUC parameters were significantly different between HS and non-HS patients, as described previously (12). However, sole the O min appeared helpful to make a differential diagnosis when presence of hemolysis.

The second objective of our work was to revise our cut-off values. As RBC parameters constitute a first line screening tool in the overall population, cut-off values were chosen in order to ensure a sensitivity > 85%, leading to a specificity from 70 to 81%. A cut-off value of 15% was determined for cryohemolysis, ensuring high sensitivity (94%) but rather low specificity (70%). The resulting performance values were similar to those found in the literature, and seem appropriate for a screening test (6). EMA (cut-off value >14%) revealed a lower sensitivity (88%) but a maximal specificity (100%), in accordance with other centers as well (7–10). Finally, regarding ektacytomatry (osmoscan) profiles, cut-off values were selected for O min (>17) and AUC (<-24.5) with rather low sensitivity (67 and 71%, respectively), but a good specificity (100 and 80%, respectively), given that this last test is mainly used as a confirmatory test, to distinguish HS from other hereditary membrane disorders (12).

The last objective of this study was to evaluate our diagnostic algorithm. Our approach appears similar to what was proposed in the latest published guidelines (3). All patients with typical clinical picture, positive family history and spherocytes on blood smear were positive for HS. This supports the assessment of British guidelines suggesting to avoid any further analysis when the diagnosis is evident (14). Also, should we give more importance to RDW-CV and reticulocyte parameters, which provide a quick and inexpensive first screening step. According to our experience, specific diagnostic tests are performed too frequently. Such practice incurs a significant cost, generates false positive results, and complicates the differential diagnosis with other RBC disorders. Caution is therefore required when a positive result does not fit with clinical presentation, biological parameters and blood smear. If results interpretation is equivocal, a family study should be performed.

According to 2011 British guidelines, SDS-PAGE is the method of choice when a confirmation test is needed. In particular, it enables to exclude CDA II (14). In 2015, ICSH recommendations were updated and improved the awareness for the differential diagnosis between HS and hereditary stomatocytosis. Indeed, the latter is associated with an increased risk of thromboembolic events after splenectomy. This is why ektacytometry, which is currently the only simple and reliable diagnostic test for hereditary stomatocytosis in addition to the blood smear, takes part of these new guidelines. In our laboratory, ektacytometry is currently our confirmation method of choice, and SDS-PAGE is eventually performed if relevant. Molecular analysis should be restricted to specific cases, after a multidisciplinary discussion.

An important limitation of our study is the restricted character of our cohort. As a reference center, we receive a lot of external samples and it was decided to use very strict inclusion and exclusion criteria in order to insure a reliable cohort, with known final diagnoses. In a future and ideally prospective study, it would be interesting to confirm our results on a larger cohort of patients. A second limitation of our study is the heterogeneity of the control group. Given the retrospective nature of our study, healthy control subjects were rare since HS exploration is mainly performed in case of hemolysis and/or anemia. However, comparison of HS patients with a control group including a large panel of differential diagnoses of these two features enabled to evaluate our diagnostic approach in real life conditions, and to highlight the most discriminant biological parameters and specific diagnostic tests in this context.

Conclusion

This work supports previously published results regarding the major clinical features and the most discriminant biological factors for HS exploration. It highlights the importance of blood smear, RDW-CV and reticulocyte channel parameters in all anemia or hemolysis exploration. Some parameters are specific to the DxH800, others being available on most modern devices. Cut-off values for the most relevant variables were defined on basis of an extended study period and on a restricted cohort of patients with a confirmed diagnosis of HS and a complete medical record. Application of these cut-offs could provide a simple tool for HS screening in a large number of laboratories. Moreover, in a reference laboratory, they could be integrated in the first steps of HS diagnosis.

Research funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interests: There is no conflict of interest to disclose.

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Choosing the optimal ventilatory support at birth for very preterm infants to prevent evolution to bronchopulmonary dysplasia

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Keywords

Bronchopulmonary dysplasia; Nasal continuous positive airway pressure; Sustained lung inflations; Delivery room; Very preterm infant

Abstract

Bronchopulmonary dysplasia remains a severe complication of prematurity and invasive ventilation is a major risk factor for developing bronchopulmonary dysplasia. Our aim is to compare different ventilation methods in the delivery room and the subsequent risk of bronchopulmonary dysplasia. Medline database was searched from 2005 to 2019. Articles in English including infants born at ≤ 32 weeks who received non-invasive respiratory support in the delivery room were considered. Sixteen articles were included. A systematic review and meta-analysis found a reduction of bronchopulmonary dysplasia in very preterm infants treated with nasal continuous positive airway pressure. Pooled analysis found a significant reduction in the combined outcome of bronchopulmonary dysplasia or death or both at 36 weeks in infants randomized to the nasal continuous positive airway pressure group, number needed to treat of 25. Another meta-analysis found a significant lower risk on death or bronchopulmonary dysplasia using strategies avoiding mechanical ventilation (P=0.008), number needed to treat of 32. Only one study, a cohort study with a historical control group, found a statistically significant lower occurrence of bronchopulmonary dysplasia in very preterm infants who received sustained lung inflations.

Conclusion: prevention of bronchopulmonary dysplasia in very and extremely preterm infants should start in the delivery room. The use of early nasal continuous positive airway pressure could be recommended. Sustained inflations and nasal intermittent positive pressure ventilation in the delivery room do not reduce the incidence of bronchopulmonary dysplasia and are not recommended.

Introduction

The number of very preterm infants (infants born at 28 - 32 weeks) and extremely preterm infants (infants born < 28 weeks) is increasing every year (1). Many of these infants have functional and structural immaturity of the lung needing respiratory support at birth. Despite the use of surfactant replacement therapy, antenatal and postnatal corticosteroids and non-invasive ventilation bronchopulmonary dysplasia (BPD) remains a major cause of morbidity and mortality in very and extremely preterm infants. The overall incidence of BPD in infants born ≤ 32 weeks is around 45% (2). Non-invasive ventilatory support started in the delivery room instead of intubation and mechanical ventilation is thought to reduce the rate of BPD and death (2).

BPD or neonatal chronic lung disease (CLD) is a major complication of prematurity. BPD is most often defined as the need for supplemental oxygen at 36 weeks postmenstrual age (2). BPD can be mild, moderate or severe and is categorized by the respiratory support method used at 36 weeks postmenstrual age: grade 1 BPD, infants receiving nasal cannula ≤ 2 L/min, grade 2 BPD, infants receiving nasal cannula > 2 L/min or non-invasive positive airway pressure, grade 3 BPD, infants receiving mechanical ventilation (3). The pathogenesis of BPD is multifactorial (2). The structural complexity of the lung is lost, causing reduced alveolar development with loss of surface area for gas exchange. Genetic susceptibility and hereditary influences on the expression of genes important for the synthesis of surfactant, regulation of inflammation and development of blood vessels play a role in the development of BPD. Various prenatal exposures (intrauterine growth restriction, chorioamnionitis,…) can make the lungs more susceptible for injury (4). The more premature the infant and the lower the birth weight, the higher the risk of BPD. Since invasive ventilation is also an important risk factor for developing BPD in preterm infants, the use of non-invasive ventilation is an important way of preventing BPD (1).

There are various non-invasive ventilatory support strategies that can be started in the delivery room. Continuous positive airway pressure (CPAP) ensures stabilization of the upper airways and chest wall, improves functional residual capacity, tidal volume and oxygenation and ensures less work of breathing, apneas and lung resistance (1). Nasal intermittent positive pressure ventilation (NIPPV) is another form of non-invasive respiratory support. NIPPV can reduce work of breathing and the risk of BPD (1). Sustained lung inflation (SLI) is a positive pressure inflation that is used to establish an increase in functional residual capacity. The inflation times range between 5 and 15 seconds. SLI provides early functional residual capacity, augments lung aeration and facilitates transition at birth. Many different interfaces for delivery of non-invasive ventilatory support can be used. It is unknown what the best delivery method is (5,6).

By far there has been little clinical comparison on the risk of BPD in infants ≤ 32 weeks between the different ventilatory support modes used immediately after birth, in the delivery room. This review compares different modes of ventilatory support used in infants ≤ 32 weeks who need support in the delivery room and their risk of BPD and may thus guide clinical practice.

Methods

Search strategy

We searched and analyzed the Medline database to identify all relevant published articles starting from 2005 up to and including 2019. This period was chosen arbitrarily. We used the Pubmed advanced search builder. We used the following search terms 'Respiratory support at birth' AND 'Preterm infants', 'Ventilatory support at birth' AND 'Preterm infants', 'Nasal CPAP at birth' AND 'Preterm infants', (((intubation) OR resuscitation) OR nasal CPAP) OR positive pressure ventilation AND preterm infants AND ((bronchopulmonary dysplasia) OR chronic lung disease) OR mechanical ventilation AND (("2005"[Date - Publication] : "2019"[Date - Publication])), (respiratory support at birth) OR ventilatory support at birth AND preterm infants AND ((bronchopulmonary dysplasia) OR chronic lung disease) OR mechanical ventilation AND ("2005"[Date - Publication] : "2019"[Date - Publication])

Inclusion criteria

All relevant articles from 2005 up to and including 2019 published in English were included in this review. Older articles and articles in other languages were excluded. We selected articles based on title and abstract containing BPD or CLD as primary or secondary outcome. In the second search the references of the articles included in the first search were read. Articles from before 2005 were also included in the second search. Various types of studies were considered for this review.

Type of participants

Studies whose study population consists of infants born at ≤ 32 weeks of gestational age, were included in this review.

Type of interventions

Different types of interventions were eligible for inclusion. Nasal continuous positive airway pressure (nCPAP), positive pressure ventilation (PPV), NIPPV, administered through an interface for delivery of non-invasive ventilatory support. For inclusion, the intervention had to start in the delivery room, immediately after birth.

Outcomes

All articles with BPD or CLD as primary or secondary outcome were included. BPD is defined as the need for supplemental oxygen at 36 weeks postmenstrual age or 28 days after birth.

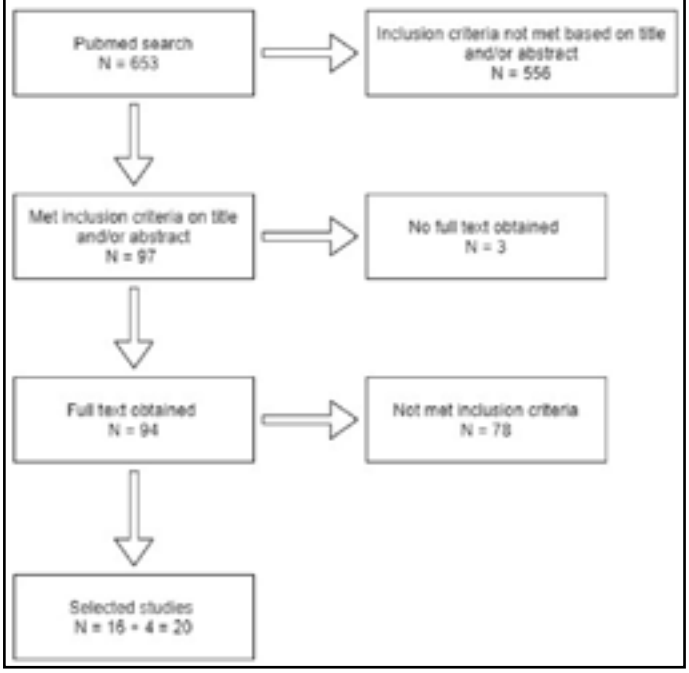
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was not used because this review is not a systematic review or meta-analysis and no statistical analysis was performed.

Results

Results of the literature search

The Pubmed search led to 653 articles. Of these articles, 556 did not meet the inclusion criteria based on title and/or abstract. Of 3 articles no full text could be obtained. Ninety-four articles were completely read. Of these 94 articles, 78 did not meet the inclusion criteria. These articles were excluded based on study population (preterm infants > 33 weeks of gestational age), type of intervention, BPD not as primary or secondary outcome and intervention not started in the delivery room, immediately after birth. Twenty articles were included in this review. Four articles were added after the initial search based on the references of the initial 16 articles. Of these twenty articles, seven are randomized controlled trials (RCT), two systematic reviews and meta-analysis, one meta-analysis, four retrospective studies, two cohort study and one policy statement (Figure 1).

Figure 1 : *Flowchart of the literature search. N, number*



Nasal CPAP

The characteristics of the studies on nCPAP are summarized in table 1.

Morley et al. conducted a RCT to investigate whether nCPAP at a pressure of 8 cm H2O compared to intubation would reduce the rate of death or BPD in very preterm infants (7). A total of 610 infants between 25 and 28 weeks of gestational age were randomized. There was a lower risk of the combined outcome of death or the need for oxygen therapy at 28 days after birth in the CPAP group (odds ratio 0.63; 95% confidence interval (CI) 0.46-0.88; P=0.006). There was no statistically significant difference in the rate of death or BPD at 36 weeks gestational age, 33.9% in the CPAP group and 38.9% in the intubation group (odds ratio 0.80; 95% CI 0.58-1.12; P=0.19).

In the RCT of Badiee et al. 72 preterm infants were randomized to either very early CPAP initiated at 5 minutes after birth or late CPAP initiated 30 minutes after birth (8). Infants in the very early CPAP group received continuous distending pressure of 6 cm H2O through a nasopharyngeal tube. The infants allocated to the late CPAP group received initial oxygen through an oxygen hood until 30 minutes after birth. Then they received CPAP at a pressure of 6 cm H2O through a nasopharyngeal tube. No statistically significant differences in BPD between the two groups was found (P=0.5). In the very early CPAP group BPD occurred in 2.8% and in the late CPAP group in 5.6%.

A retrospective study carried out by Mehler et al. evaluated 164 extremely low gestational age newborn infants under 26 weeks (9). These infants were treated with CPAP via face mask, fraction of inspired oxygen (FiO2) 0.6 and positive end-expiratory pressure (PEEP) of 8 cm H2O. Surfactant through an endotracheal catheter was administered if necessary. The outcomes of these infants were compared to 44 extremely low gestational age infants in the control group. Infants in the control group who were not breathing at birth received PPV with FiO2 0.6. The infants who were breathing were stabilized with CPAP. The incidence of BPD in the study group was significantly lower (18% vs. 37%, P<0.05).

Schmölzer et al. conducted a systematic review and meta-analysis (10). Four RCTs were included. In total 2782 infants < 32 weeks were randomized to either nCPAP or intubation at birth. There was a reduction of BPD with borderline statistical significance in favor of the nCPAP group (risk ratio 0.91; 95% CI 0.82-1.01). A pooled analysis was conducted. This demonstrates a significant reduction in the combined outcome of BPD or death or both at 36 weeks corrected gestational age for infants randomized to the nCPAP group (risk ratio 0.91; 95% CI 0.84-0.99). Twenty-five infants need to be treated in the delivery room with nCPAP to prevent one additional infant from having BPD at 36 weeks of gestational age.

Fischer et al. conducted a meta-analysis that compared non-invasive respiratory strategies with mechanical ventilation (11). Different methods of nCPAP with or without surfactant administration were compared with endotracheal mechanical ventilation or intubation, surfactant and extubation (INSURE). Nine RCTs of 3486 infants were included in this meta-analysis. The risk of death or BPD significantly decreased by using strategies to avoid mechanical ventilation (risk ratio 0.90; 95% CI 0.84-0.97; P=0.008), number needed to treat of 32. There was no significant effect of avoiding mechanical ventilation on death (risk ratio 0.88; 95% CI 0.73-1.06; P=0.18) or BPD alone (risk ratio 0.92; 95% CI 0.83-1.01; P=0.09).

The retrospective study of Miksch et al. compared the effect of early nCPAP use to a historical control group (12). They found a statistically significant difference between both groups: 24% of the infants in the control group and 8% of the infants in the intervention group had BPD at 36 weeks of postmenstrual age (P=0.003). Gittermann et al. however found no statistically significant difference in the prevalence of BPD after the introduction of early nCPAP (P=0.94) (13). In the study of De Klerk et al. the introduction of early nCPAP did not change the number of infants needing respiratory support at 36 weeks of gestational age, compared to a historical cohort (14).

Since 2014, the American Academy of Pediatrics recommends the use of CPAP immediately after birth followed by selective surfactant administration as an alternative to intubation with prophylactic or early surfactant administration (15).

Table 1 Characteristics of the studies on nCPAP

Study	Study population	Intervention	Outcome (BPD)	BPD definition
Morley et al., 2008 (7) RCT	n = 610 GA 25+0–28+6	CPAP vs. intubation	Death or BPD at 36 weeks: 33.9% CPAP group 38.9% intubation group Odds ratio 0.80; 95% CI 0.58-1.12; P=0.19 Death or oxygen therapy at 28 days: odds ratio 0.63; 95% CI 0.45-0.88; P=0.006	Need for oxygen at 36 weeks corrected gestational age Need for oxygen at 28 days
Badiee et al., 2012 (8) RCT	n = 72 GA 25–30	Very early CPAP vs. late CPAP	2.8% very early CPAP 5.6% late CPAP P=0.5	Need for oxygen at 28 days
Mehler et al., 2012 (9) Retrospective study	n = 164 (study group) GA < 26 n = 44 (control group) GA < 26	CPAP vs. PPV	18% CPAP group 37% PPV group P<0.05	Need for oxygen at 36 weeks corrected gestational age
Schmölzer et al., 2013 (10) Systematic review + meta-analysis	n = 2782 GA < 32	nCPAP vs. intubation	BPD: risk ratio 0.91; 95% CI 0.82-1.01 BPD or death, or both (pooled analysis): risk ratio 0.91; 95% CI 0.84-0.99; NNT = 25	Need for oxygen at 36 weeks corrected gestational age
Fischer et al., 2018 (11) Meta-analysis	n = 3486 GA 23+0–29+6	nCPAP vs. mechanical ventilation	Death or BPD: risk ratio 0.90; 95% CI 0.84-0.97; P=0.008; NNT = 32	Need for oxygen at 36 weeks corrected gestational age
Miksch et al., 2008 (12) Retrospective study	n = 93 (study group) n = 63 (control group) GA < 32	nCPAP vs. IPPV or intubation	8% study group 24% control group P=0.003	Need for oxygen at 36 weeks corrected gestational age
Gittermann et al., 1997 (13) Retrospective study	n = 70 (study group) n = 57 (control group) GA 28+0-32+0	Early nCPAP vs. other ventilatory support methods	30% study group 32% control group P=0.94	Need for oxygen at 28 days
De Klerk et al., 2001 (14) Retrospective study	n = 59 (study group) n = 57 (control group) GA < 35	Early nCPAP vs. nCPAP or oxygen without positive pressure or intubation and IMV	BPD: 0% study group, 6% control group; P=0.22 Death or BPD: 3% study group, 11% control group; P=0.25	Need for oxygen at 36 weeks corrected gestational age

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; IMV, intermittent mandatory ventilation; vs., versus; GA, gestational age; RCT, randomized controlled trial; NNT, number needed to treat; CI, confidence interval

Table 2 Characteristics of the studies on SLI

Study	Study population	Intervention	Outcome (BPD)	BPD definition
Te Pas et al., 2007 (16) RCT	n = 207 GA 25–32	SI + nCPAP (EFURCI group) vs. manual inflations + nCPAP (conventional group)	BPD moderate – severe: 9% EFURCI group vs. 19% conventional group P=0.04	Need for oxygen at 36 weeks corrected gestational age
Lista et al., 2015 (17) RCT	n = 291 GA 25+0–28+6	SLI + nCPAP vs. nCPAP alone	38.5% SLI group 35% nCPAP group unadjusted odds ratio 1.17; 95% CI 0.80-1.71; P=0.42	Need for oxygen at 36 weeks corrected gestational age
Jiravisitkul et al., 2016 (18) RCT	n = 81 GA 25–32	SLI vs. PPV	10% SLI group 22% non-SLI group P=0.15	Moderate BPD: need for <30% oxygen at 36 weeks Severe BPD: need for ≥30% oxygen at 36 weeks
Ngan et al., 2017 (19) RCT	n = 162 GA 23+0–32+6	SI-guided exhaled carbon dioxide vs. PPV	23% SI group 33% PPV group P=0.09	Need for oxygen at 36 weeks corrected gestational age
Kirpalani et al., 2019 (20) RCT	n = 426 GA 23+0–26+6	SI vs. IPPV	42.8% SI group 43.6% IPPV group risk ratio 1.0; 95% CI 0.8-1.2; P=0.92	Need for oxygen at 36 weeks corrected gestational age
Lindner et al., 1999 (21) Retrospective cohort study	n = 123 GA < 29	MV (1994) vs. SLI (1996)	32% MV group 12% SLI group P<0.05	Need for oxygen at 36 weeks corrected gestational age
Lista et al., 2010 (22) Cohort study	n = 208 GA < 32	SLI vs. PEEP	7% SLI group 25% control group P=0.004	Need for oxygen at 36 weeks corrected gestational age
Schmölzer et al., 2015 (23) Systematic review + meta-analysis	n = 611 GA < 33	SLI vs. IPPV	BPD: risk ratio 0.84	Need for oxygen at 36 weeks corrected gestational age
Fischer et al., 2018 (11) Meta-analysis	n = 854 GA 23+0–32+6	SI vs. IPPV	BPD: risk ratio 0.78; 95% CI 0.57-1.05; P=0.10 BPD or death: risk ratio 0.85; 95% CI 0.65-1.12; P=0.25	Need for oxygen at 36 weeks corrected gestational age

BPD, bronchopulmonary dysplasia; nCPAP, nasal continuous positive airway pressure; PPV, positive pressure ventilation; IPPV, intermittent positive pressure ventilation; SI, sustained inflation; SLI, sustained lung inflation; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; EFURCI, early functional residual capacity intervention; vs., versus; GA, gestational age; RCT, randomized controlled trial; CI, confidence interval

Sustained lung inflation

The characteristics of the studies on SLI are summarized in table 2.

Te Pas et al. compared a sustained inflation (SI) through a nasopharyngeal tube followed by early CPAP or repeated manual inflations through a self-inflating bag and mask if necessary followed by nCPAP (16). A total of 207 very preterm infants, 25-32 weeks of gestational age, were randomized. Very preterm infants in the early functional residual capacity intervention (EFURCI) group received a SI of 20 cm H2O for 10 seconds through a nasopharyngeal tube and T-piece ventilator. This could be repeated with a pressure of 25 cm H2O if breathing remained insufficient. After this early nCPAP at 5-6 cm H2O was initiated. Infants randomized to the conventional intervention group received initial inflation pressures of 30-40 cm H2O during 30 seconds. They only received nCPAP in the neonatal intensive care unit if necessary. Very preterm infants in the EFURCI group developed less moderate-severe BPD compared with very preterm infants in the conventional group (9% vs. 19%, P=0.04). There was also a lower rate of BPD (22% vs. 34%, P=0.05) in infants receiving SI followed by nCPAP.

Lista et al. conducted a RCT to compare prophylactic SLI (25 cm H2O for 15 seconds) followed by nCPAP at 5 cm H2O with CPAP alone at birth (17). Infants born at 25 weeks to 286/7 weeks were randomly assigned to one of these two groups. The secondary outcome was BPD. The overall incidence of BPD in the SLI group was 38.5% and in the nCPAP group 35% (unadjusted odds ratio 1.17; 95% CI 0.80-1.71; P=0.42). In infants surviving at 36 weeks the rate of BPD was 54.8% in the SLI group and 53.2% in the nCPAP group.

Jiravisitkul et al. conducted a RCT which compared SLI with standard resuscitation in very preterm infants (25-32 weeks GA) (18). Eighty-one infants were included. Very preterm infants allocated to the SLI group received a pressure-controlled inflation of 25 cm H2O for 15 seconds using a mask via a T-piece resuscitator. This was followed by CPAP at 6 cm H2O via face mask for 5-10 seconds. Very preterm infants in the non-SLI group received PPV with peak inspiratory pressure (PIP) of 15-20 cm H2O and PEEP of 5 cm H2O for 30 seconds via a T-piece resuscitator. In this RCT no difference in the incidence of BPD between the groups was observed (10% SLI group, 22% non-SLI group, P=0.15).

In the RCT of Ngan et al. infants ≤ 32 weeks were randomized to a SI guided by exhaled carbon dioxide (ECO2) or to mask PPV with a PIP of 24 cm H2O (19). Infants randomized to the SI group received an initial SI with a PIP of 24 cm H2O over 20 seconds. The second SI depended on the amount of ECO2. When the ECO2 was ≤ 20 mm Hg the second SI was 20s. When the ECO2 was > 20 mm Hg the second SI lasted 10s. Both groups had similar rates of BPD (SI group 23%, PPV group 33%, P=0.09).

The SAIL randomized clinical trial by Kirpalani et al. randomly assigned extremely preterm infants from 23 to 26 weeks to either intermittent positive pressure ventilation (IPPV) or SI (20). A total of 426 infants completed the trial. Infants randomized to the SI group received an initial SI at a pressure of 20 cm H2O for 15 seconds. A second SI at a peak pressure of 25 cm H2O for 15 seconds was given if necessary. Infants in the standard resuscitation group received IPPV with PEEP. The rate of BPD in the SI group was 42.8% vs 43.6% in the resuscitation group (risk ratio 1.0; 95% CI 0.8-1.2; P=0.92). SI compared with IPPV did not reduce the risk of BPD. The study was closed early because of an excess mortality rate with SI in the first 48 hours and may therefore be underpowered.

Lindner et al. performed a retrospective cohort study. Between 1994 and 1996 there was a change of delivery room management. In 1994 the infants received an inflation using a flow-inflating bag followed by mechanical ventilation or endotracheal intubation. In 1996, 67 infants < 29 weeks in the delivery room received a SI of 20 cm H2O for 15 seconds using a nasopharyngeal tube. The SI could be repeated a second time with a pressure of 25 cm H2O if required. This was followed by CPAP. If necessary these infants received mechanical ventilation. In 1994, 13 infants (32%) developed BPD compared with 6 infants (12%) in 1996 (P<0.05) (21).

Lista et al. conducted a cohort study with a historical control group (22). A total of 208 infants < 32 weeks of gestational age were included. The infants enrolled in the intervention group (SLI group) were studied prospectively and the infants in the control group were studied retrospectively. Eighty-nine infants in the SLI group received an initial SLI of 25 cm H2O using a mask and T-piece ventilator for 15 seconds. This was followed by delivery of 5 cm H2O PEEP. If breathing remained insufficient this could be repeated a second time. Hundred and nineteen infants were enrolled in the control group. They received 5 cm H2O PEEP after birth. After the initial ventilation both groups received nCPAP of 5 cm H2O or IPPV with a PIP < 25 cm H2O. A significant lower occurrence of BPD was found in the SLI group (7% vs. 25%, P=0.004).

A systematic review and meta-analysis was conducted by Schmölzer et al. (23). SI during resuscitation at birth was compared with IPPV. Four trials with a total of 611 infants < 33 weeks of gestational age were included in the analysis. No significant difference in BPD, death or the combined outcome of BPD and death could be found.

Another meta-analysis was conducted by Fischer et al. where SI was compared with IPPV (11). In this meta-analysis six RCTs were included. A total of 854 infants < 33 weeks of gestational were studied. The infants in the SI group received 1-3 sustained inflations for 5-20 seconds with a pressure of 20-30 cm H2O. No effect could be found of SI on death, BPD or the combined outcome of death or BPD (BPD: risk ratio 0.78; 95% CI 0.57-1.05; P=0.10; death: risk ratio 1.31; 95% CI 0.80-2.14; P=0.29; combined outcome: risk ratio 0.85; 95% CI 0.65-1.12; P=0.25).

NIPPV

A retrospective study was performed by Biniwale et al. The impact of non-invasive ventilation using NIPPV for resuscitation in very low birth weight infants was evaluated. A total of 221 very low birth weight infants < 32 weeks were included. One hundred nineteen infants received NIPPV and were compared to a historical control group of 102 infants who received PPV through a face mask. The infants had a mean gestational age of 27 weeks in the NIPPV group and 27.1 weeks in the face mask group. The intubation rates in the NIPPV group in the delivery room were significantly lower than in the face mask group (31% vs. 85%; P<0.001). No significant differences in the rates of BPD between both groups could be found (37% (face mask group) vs. 39% (NIPPV group); P=0.88) (24).

Discussion

Effect of nCPAP on BPD

Two meta-analyses and a RCT compared nCPAP with intubation immediately after birth (7,10,11). CPAP aims to avoid immediate intubation and thus additional lung damage after birth. While there are clear advantages in the short term, the effect on BPD is not as clear. The RCT only found a trend towards less death or BPD at 36 weeks postmenstrual age, the first meta-analysis a borderline statistically significant effect and the second meta-analysis only a statistically significant effect on the combined outcome of death or BPD, not on BPD alone (7,10,11).

There are several limitations to these studies. None of the four RCTs in the meta-analysis of Schmölzer et al. were blinded (thereby increasing the chance of bias) and the studies were performed when there was no consensus on the oxygen concentration initially used during neonatal resuscitation (10). In the RCTs that applied less invasive surfactant administration or minimally invasive surfactant therapy, intervention could take place within 2 hours after birth, possibly outside the delivery room (11).

Only one study found a statistically significant difference on BPD at 36 weeks postmenstrual age by introducing the use of early nCPAP (12). While nCPAP still seems to be the best way to prevent BPD in the delivery room, the exact settings for an optimal effect are not clear yet. Badiee et al. found no statistically significant difference between infants receiving CPAP at 5 minutes vs. 30 minutes after birth (8). Early use of nCPAP could reduce the incidence of atelectasis by increasing functional residual capacity during expiration and improves oxygenation and lung compliance. The role of the devices that are used to provide nCPAP is also not clear, neither is the optimal amount of FiO2. Finally, a lot of other delivery room protocol interventions like delayed cord clamping, the application of surfactant etc. can influence the results.

Effect of SLI on BPD

Based on the reviewed studies (Table 2) there is no evidence that the use of SI in the delivery room could reduce the incidence of BPD and it is therefore not recommended. These studies also have their limitations however, the most important of which we will discuss here.

The systematic review of Schmölzer et al. found no significant difference in BPD, death or the combined outcome of BPD and death in infants receiving SI after birth (23). The four RCTs included in this analysis used different oxygen concentrations (from 21% to 100%). Only one study included infants < 25 weeks of gestational age. These infants have the highest risk of needing intubation immediately after birth. Different ventilation devices were used to deliver SI or IPPV. The SAIL randomized clinical trial and the RCT of Ngan et al. were both underpowered (19,20). Different aspects of delivery room care changed over time (use of a nasopharyngeal tube and a mechanical ventilator, positive pressure ventilation and sustained inflations). In the meta-analysis of Fischer et al. different definitions of BPD were used in the included RCTs (11). They remark that the lack of effect may possibly be due to too high pressure and too long duration of SI or due to inefficient SI in infants with apnea at birth.

Only three studies found a statistically significant reduction of BPD by SI, but also here important limitations play a role.

The RCT conducted by Te Pas et al. found a significant reduction in the rate of moderate-severe BPD in infants in the EFURCI group, but this intervention not only included a SI, but also PEEP through a T-piece ventilator (whereas the control group received repeated manual inflations through a self-inflating bag and mask with only minimal PEEP) (16). They also found less BPD in infants receiving a SI followed by nCPAP. In this study there are more delivery room changes than just a SI. Prolonged inflations, use of a nasopharyngeal tube as interface, the delivery of PEEP and nCPAP in the delivery room could have contributed to the lower rate of BPD. Because various aspects of delivery room care have changed over time, it is difficult to determine how much difference (if any) can be attributed to SI.

The cohort study of Lista et al. found a statistically significant lower incidence of BPD in the SLI group (22). A historical control group constitutes a bias because over time various changes took place in the care for preterm infants. Another limitation could be the use of a neonatal mask instead of a nasopharyngeal tube which could be more efficient in preventing PEEP leakage.

In the retrospective cohort study (with small sample size) of Lindner et al. there was a statistically significant difference of BPD in the early low birth weight infants born in 1996 (21). This can be attributed to various factors such as the use of higher doses of prenatal betamethasone, more infants with intrauterine growth retardation and the use of CPAP after SI in the delivery room.

Effect of NIPPV on BPD

The retrospective study of Biniwale et al. showed a decrease in intubation and invasive ventilation rates, but no significant difference in the incidence of BPD between both groups could be found. The use of a nasal interface lowers the intubation rates in the delivery room, but has no effect on the incidence of BPD. Further studies are needed to compare NIPPV with nCPAP in the delivery room (24).

Ventilation devices and interfaces used in the delivery room

Different ventilation devices can be used in the delivery room such as self-inflating bags, flow-inflating bags and T-piece devices. Currently there is not enough evidence to guide clinicians' choice of ventilation device used during delivery room respiratory support. A self-inflating bag cannot provide PEEP or CPAP. A flow-inflating bag provides PEEP that is operator-depended and variable. T-piece devices deliver a predetermined level of PEEP and PIP. These three can all be used for mask ventilation. A T-piece device is most accurate to deliver a SI. Face masks and nasal prongs are interfaces used in the delivery room. A single nasal prong can reduce airway obstruction by the tongue, but air leak through the mouth and contralateral nostril can occur. Double nasal prongs can effectively be used to deliver PEEP and CPAP after birth. There are several factors that can affect mask ventilation and reduce its effectiveness: improper seal of the mask to the neonate's face which may cause leakage or airway obstruction, movements of the neonate and procedures such as repositioning the neonate (25,26). There are also several reflexes that can be induced by applying non-invasive ventilation during delivery room stabilization of preterm infants. Some of these reflexes, such as the trigeminocardiac reflex and the laryngeal chemoreflex, can compromise breathing. Consideration must be given to which device and interface can best be used during delivery room stabilization of preterm infants (27).

Conclusion

Lung-protective strategies should start immediately at birth, in the delivery room. The lungs of very preterm infants are susceptible to injury because of functional and structural immaturity of the lungs, no support by a stiff chest wall and surfactant deficiency. Most very and extremely preterm infants need respiratory support in the delivery room. Starting nCPAP in the delivery room in very preterm infants seems to result in a lower incidence of death and BPD at 36 weeks of gestational age. There is no evidence that the use of SI in the delivery room could reduce the incidence of BPD and SI is therefore not recommended as initial non-invasive respiratory support method. Before NIPPV can be implemented in the delivery room, more studies are needed.

Further studies are also needed to answer the following questions. How early should nCPAP be initiated after birth? Which type of interface, face mask, nasal mask or nasal prongs, could best be used to deliver nCPAP? Should different ventilation methods or interfaces be used in the delivery room depending on gestational age?

Conflict of interest: The authors declare that they have no conflict of interest.

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Parafalcine subdural empyema as an uncommon complication of acute odontogenic sinusitis: a case report and literature review

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Keywords

Subdural empyema, proflavine, sinusitis, odontogenic

Abstract

Parafalcine subdural empyema is a relatively uncommon but important suppurative infection of the central nervous system. We present a case of a 15-year old boy who developed headache with an altered level of consciousness, confusion, a right hemiparesis and fever three weeks after tooth extraction. Magnetic resonance imaging confirmed the diagnosis of a parafalcine subdural empyema on the left side. Intravenous ceftriaxone, metronidazole and acyclovir were administered, and emergency trepanation and functional endoscopic sinus surgery were performed. Dexamethasone sodium phosphate was given in the context of cerebral edema and an anticonvulsant was started preemptively. Culture from the empyema showed the presence of multisensitive Streptococcus anginosus. The hemiparesis improved gradually and 28 days after admission the boy was discharged. Neurological examination at discharge was normal. Parafalcine subdural empyema is an uncommon complication after tooth extraction and diagnosis can be challenging. An early multidisciplinary approach is important to prevent complications. Neurologic sequelae are common. Morbidity rate is 33% after six months and mortality rate is 5-10%.

Introduction

Intracranial subdural empyema (SE) is a suppurative infection localized between the dura and arachnoid matter (1). Most of the SE's are localized within the frontal lobe or convexity (2). They largely arise from direct extension of adjacent infection, hematogenous seeding, or trauma (3). Suppurative otitis media is regarded as the commonest cause of intracranial suppuration, with an incidence of approximately 39% (4). Bacterial paranasal sinusitis is the underlying cause in 3.7% to 11% (2, 5, 6). A parafalcine localization is only described in less than 20% of SE's and has a worse prognosis. Most patients present with non-specific symptoms such as (severe) headache, fever and vomiting (7). However, symptoms can be more subtle in case of a preexisting sinusitis, which makes the diagnosis of a SE challenging (8, 9). Neurological symptoms often consists of alteration of consciousness, focal deficit, hemiparesis, nuchal rigidity and seizures (1). It is important to diagnose and treat SE's promptly because life threatening complications, such as cerebral thrombophlebitis, cerebral edema and cerebral infarction, can cause increased intracranial pressure leading to coma and death within one to two days (8, 10). Parafalcine SE's, particularly, are associated with a worse prognosis (10). We present the case of a 15-year old boy with parafalcine empyema as result of an acute odontogenic sinusitis caused by tooth extraction.

Case presentation

A fifteen-year old Caucasian boy presented with recurrent episodes of fever in the last three weeks. The fever started five days after extraction of his dental elements 18, 28, 38 and 48. He started vomiting since a few days and had anorexia. One day before admission, he had headache, an altered level of consciousness with confusion and a right hemiparesis. Clinical examination revealed a pale apathic boy with a high fever and cognitive impairment. Cardiorespiratory parameters were normal. He had nuchal rigidity, photophobia and a right hemiparesis most pronounced at his right foot. Blood examination showed a leukocytosis of 24 800/µl (normal range 4000/µl-13000/µl) with neutrophilia and a C-reactive protein (CRP) of 86.5 mg/l (normal < 10 mg/l). A computed tomography (CT) of the cerebrum without contrast revealed a hypodense parafalcine structure, suspicious for empyema. Cerebrospinal fluid contained 49 leukocytes/field, mainly polymorphonuclear cells, an increased protein level of 73 mg/dl (normal < 45 mg/dl) and a normal glucose level of 78 mg/dl (with a serum glucose of 142 mg/dl). Intravenous ceftriaxone (100 mg/kg/day, max: 4 g/day), metronidazole (30 mg/kg/day) and acyclovir (1g/m2/day) were administered. A magnetic resonance imaging scan (MRI) confirmed the diagnosis of a parafalcine SE on the left side. (figure 1). There were signs of underlying cerebritis and cortical edema. The parafalcine SE was presumably caused by a breakthrough sinusitis of odontogenic nature.

Emergency trepanation and functional endoscopic sinus surgery (FESS) were performed to evacuate the SE. Post-operative neurologic controls were stable and anticonvulsive therapy with levetiracetam (20 mg/kg/day) was started preemptively. Dexamethasone sodium phosphate (0.25 mg/kg/day) was given in the context of the cerebral edema. Cultures from the empyema were positive for multisensitive *Streptococcus anginosus.* As blood cultures and culture from the cerebrospinal fluid remained sterile with negative PCR for the herpes simplex virus, acyclovir and metronidazole were ceased. Post-surgery MRI showed residual empyema, parafalcine, posterior, parietal to occipital with signs of frontal, parietal and occipital meningitis on the left side. The MRI also showed a small zone suspicious for hemorrhagic cerebritis and two small left frontal infarcts. Nevertheless, there was a favorable biochemical and clinical evolution with slow improvement of the right hemiparesis. On postoperative day eleven continuous headache reappeared. Blood examination showed a leukocytosis of 18 800/µl with neutrophilia and a CRP of 13,8 mg/L. MRI showed an overall decrease of the volume of the empyema but an increased lateral diameter of the dorsal component of the collection (Figure 2). The SE was rinsed through a left occipital trepanation on day fourteen. Sinus endoscopy showed clear sinuses. Peroperative cultures remained sterile. At day 21, the MRI showed no residual collection (figure 2).

Further immunological work-up was performed because of this impressive clinical picture. There were no severe infections in the boy's history. Familial history was negative. A previous immunological work-up showed a low T CD3+/HLA-DR+,

Figure 1 : *3T-MRI of the brain on admission. Axial T1-weighted images after Gadolinium administration show focal leptomeningeal contrast enhancement in the left frontal lobe (red circle in A), a finding compatible with meningitis. A left paramedian subdural fluid collection is seen along the falx cerebri (blue arrows in B) with increased signal on b1000-diffusion weighted imaging (C) and low signal on the ADC-map (images not shown), compatible with a subdural empyema.*

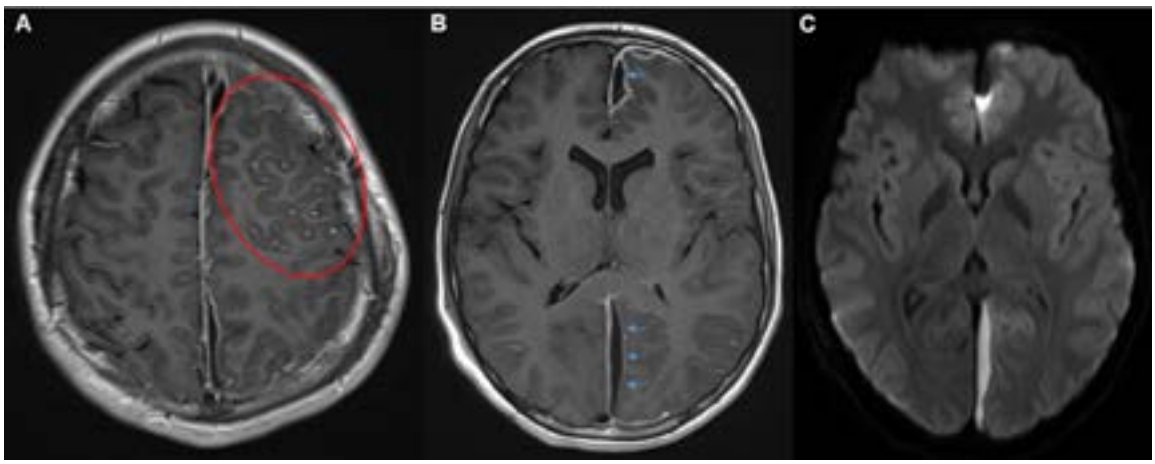
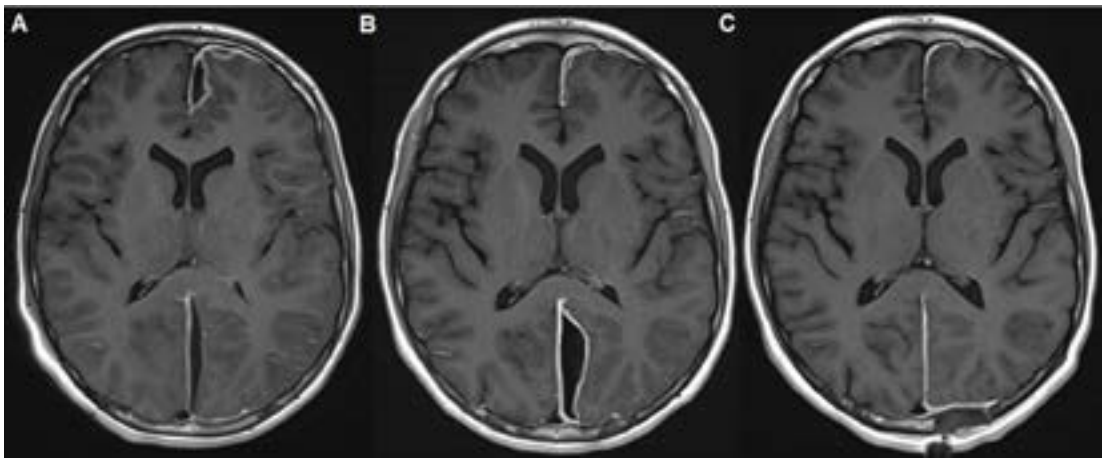


Figure 2 : *Evolution of the subdural empyema. Axial T1-weighted images after Gadolinium administration on admission (A), day 13 (B) and day 21 (C). Between the scan on admission (A) and day 13 (B) a clear volume-increase of the dorsal component of the subdural empyema can be seen. Control MRI on day 21 shows complete regression of the subdural empyema with some residual most likely reactive left parafalcine dural enhancement (C).*



T CD3+/CD8, B CD19 and lowered IgG and IgM at the age of two years. These values normalized by the age of three. Immunological testing after resolution of the disease showed a lower IgG of 5.4 g/l (normal > 7.12 g/l) with normal IgG2 and IgG3, normal IgA, IgM, total hemolytic complement (CH50) and complement fractions (C3 and C4). A mannose-binding lectin deficiency was detected. Pneumococcal antibody response after vaccination was normal.

The hemiparesis regressed progressively and 28 days after admission the boy was discharged. The neurological examination at discharge was normal. Levetiracetam and intravenous ceftriaxone therapy were continued during twelve weeks. MRI, six weeks after discharge, showed no residual collection and ceftriaxone was ceased. Electroencephalogram (EEG) was normal. Levetiracetam was continued for six months.

Discussion

We found only five articles concerning 82 children with parafalcine SE (10-14). In our case the parafalcine empyema was a complication of an acute odontogenic sinusitis caused by tooth extraction. In 3.7 % to 11% the cause of a SE is a sinusitis. Other known causes of SE include neurosurgical infection, head trauma, otitis media, osteomyelitis of the skull and meningitis (2). An important origin of sinusitis, especially unilateral maxillary sinus infection, is odontogenic. This is because the roots of the premolars and molars are situated just below the floor of the maxillary sinus (5). Evolution towards pansinusitis is possible through the osteomeatal complex. An oro-antral communication between the maxillary sinus and the oral cavity can be created during tooth extraction. This allows the passage of anaerobic bacteria into the sinus (15, 16). There are two major mechanism for the formation of SE from sinusitis. The most common mechanism is retrograde thrombophlebitis through the valveless diploe veins which causes translocation of bacterial seeds to the subdural space. Between the age of 7 and 20 years there is a peak in the vascularity of this diploe system and the development of the sinuses, especially the frontal sinus. This explains the peak prevalence of SE in the second decade of life (5, 17). The second mechanism is a direct breakthrough trough the facial bones with osteomyelitis and subsequent erosion into the epidural space (2, 8).

Patients with a SE mostly present with non-specific symptoms such as headache, recurrence of fever or vomiting (7). Neurological symptoms often consist of altered sensorium, focal deficit, hemiparesis, nuchal rigidity, photophobia and seizures (1). Seizures arise in 25-80% and are more common in SE than in any other intracranial complication of paranasal sinusitis (1, 2, 7, 8, 13, 17). However, when a sinusitis precedes the SE, it usually presents as an insidious process with purulent nasal discharge, headache and fever, as seen in our patient (8, 9). Once the infection reaches the intracranial space, neurologic deterioration follows rapidly because of the lack of anatomical constraints. Acute or progressive headache is the most important indicator of intracranial involvement (18). In patients with a parafalcine SE a typical presentation is the 'Falx syndrome' where the contralateral lower extremity is most affected.

The gold standard for the diagnosis of SE is MRI with gadolinium enhancement (9). However, CT scans are often the first choice of imaging modality because they are more available in the emergency setting (19). Additionally, CT is the best modality to visualize the paranasal sinuses and associated bony abnormalities. However, CT may fail to visualize intracranial complications (9). MRI with gadolinium and contrast enhanced CT are complementary examinations when evaluating complications of sinusitis (9, 19, 20).

Microbiological cultures of sinogenic empyema reveal in 67% bacteria belonging to the *Streptococcus milleri* group. *Streptococcus anginosus*, as in our patient, belongs to this group and accounts for 11% of intracranial abscesses (13, 17, 19). Anaerobic streptococci are known to cause invasive suppurative infections in different tissues. *Streptococcus anginosus* is the most frequently involved bacterium in intracranial complications of sinusitis and is related to a higher probability of neurosurgical intervention and long-term neurologic deficits (8, 19). Laboratory data are non-specific: white blood cell count, CRP and erythrocyte sedimentation rate may be elevated. Lumbar puncture is not indicated because of its poor diagnostic yield, technical difficulty and the risk of transtentorial herniation, neurologic deterioration and death. However, when a lumbar puncture is performed, the cerebrospinal fluid shows pleocytosis with polymorphonuclear predominance, elevated protein and normal glucose level. Cerebrospinal fluid cultures remain negative in more than 85% of the cases (2, 9, 17). Research indicates a possible association between mannose-binding lectin deficiency and increased susceptibility to recurrent and/or severe infections (21, 22).

The management and treatment of intracranial SE necessitates a multidisciplinary approach (23). Broad-spectrum intravenous antibiotic therapy consisting of a third-generation cephalosporine in combination with metronidazole should be initiated a soon as possible. The incidence of intracranial sinogenic complications has decreased dramatically since the advent of broad-spectrum antibiotics and improvement in diagnostic imaging. Antibiotic treatment however does not absolutely prevent intracranial suppurations and can sometimes delay diagnosis and treatment (2, 8, 17). Once the results of microbiological cultures are known, the antibiotic therapy can be adjusted. Intravenous antibiotic therapy should be continued for at least two weeks followed by up to six weeks of oral antibiotics. If osteomyelitis is present the therapy should be prolonged to eight weeks (8). However, the duration of the intravenous antibiotic therapy should be adjusted to the clinical circumstances and evaluated on a case-by-case basis. Adjuvant therapy should consist of preemptive anticonvulsants and corticosteroids to reduce the cerebral edema (2). Preemptive antiepileptic drugs are often administered due to the high incidence of seizures both before and after treatment. In Cowie et al, a case series of 89 patients, of those who had no early seizures, 42% had late seizures, the majority appearing within 16 months (24). The use and dosage of corticosteroids in brain abscess is still being debated. Dexamethasone is the corticosteroid of choice when treating brain abscess patients for associated vasogenic edema (25). Despite the anti- inflammatory and possible immunosuppressive properties of dexamethasone, the results of Simjian *et al.* suggested that there was no mortality benefit obtained from withholding dexamethasone (26). Because of the rapid progression, SE nearly always requires surgical drainage with a combined neurosurgical and rhinological approach (8, 9, 27). The most effective procedure is a direct and large drainage through craniotomy. An alternative approach through burr holes and saline irrigation is less effective and will often require additional surgery or conversion to craniotomy (19). Surgical intervention is the most important factor in the prognosis and subsequently a low threshold should be maintained (23). The goal is to evacuate the intracranial pus collection which improves the clinical condition, provides microbiological samples and allows managing of the source of infection. Drainage of the infected sinuses trough endoscopic sinus surgery should be done at the same time. Other approaches include maxillary irrigation, external fronto-ethmoidectomy, sphenoid sinusotomy, antral washout and frontal trephine (2). Because of the tricky localization of the pus in a narrow space, parafalcine empyema's represent a challenge to neurosurgeons. It is often necessary to redo the surgical procedure (8,15). Patel et al. reported that about 22% of children needed early revision surgery (17). Follow up MRI scans are therefore indicated four to seven days post-surgery (10, 13).

Neurologic sequelae after resolution are quite common, morbidity rate is estimated at 33% after six months and mortality rates are between 5-10% (28). Headache and limb weakness are frequently seen as short-term morbidities. On the long-term cognitive deficits, expressive aphasia and epilepsy have been reported (2, 8, 17, 23). Factors defining outcome include the level of consciousness and neurologic status at admission, time to diagnosis and treatment, a parafalcine localization, extent of the collection and underlying immunodeficiency (9).

Conclusion

Parafalcine SE secondary to tooth extraction is uncommon in children and diagnosis can be challenging as symptoms can be non-specific. MRI with gadolinium enhancement is the gold standard for the diagnosis. Early multidisciplinary approach is important to prevent complications. Management consists of neurosurgical interventions, intravenous broad-spectrum antibiotics and supportive care. Morbidity and mortality are high in SE with important neurodevelopmental consequences on the long-term. Early diagnosis and prompt treatment are key factors determining the outcome. Therefore, a good education of pediatricians and family physicians in combination with a high index of suspicion are of preeminent importance.

Declarations

Consent for publication: Informed consent was obtained from all individual participants included in the study.

Competing interests: The authors declare that they have no competing interests.

Funding: This study received no funding.

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Offspring born after maternal bariatric surgery

PhD thesis presented online on the 16th of December 2020 in a joint PhD project VUB-KUL

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Keywords

Maternal obesity, maternal bariatric surgery, childhood obesity

The main topic of this thesis revolves around a better understanding of the long-term effects on the offspring of women who underwent bariatric surgery before their pregnancy. Pregnant women with obesity (BMI ≥ 30 kg/m² at start of the pregnancy) have been a growing population of interest because their offspring is at risk for development of childhood obesity, an adverse metabolic and inflammatory profile and possible premature cardiovascular morbidity. Since bariatric procedures have been relatively "new", there is still a lack of scientific data on the long-term outcomes in the offspring. However, the management of obesity and its associated comorbidities (such as diabetes and cardiovascular diseases) and a better understanding of the intergenerational programming circle remain a huge challenge for current health care systems around the world.

To gain insight in the topic, the first aim was to review the existing literature and knowledge. Since the offspring of women with obesity during their pregnancy have been exposed to an altered intra-uterine environment, a subsequent influence on the cardiovascular development during fetal life is assumed (1). Based on animal studies, different contributing mechanisms have been hypothesized. Insulin resistance, increased levels of leptin, chronic inflammatory state, perturbation of sympathetic tone and epigenetic modifications contribute to a suboptimal nutrient environment and changed hemodynamics. The ensuing aberrant cardiomyocyte development, impaired endothelial cell relaxation and atherogenic lipid profile put the children of mothers with obesity during pregnancy at risk for the development of endothelial cell dysfunction. Increasing possibilities for the early detection of this preliminary stage of atherosclerotic disease and the proven reversibility of this condition make it an excellent prevention and treatment target.

Since many questions remain unanswered about the actual endothelial cell function in the offspring of mothers with obesity, we designed the EFFECTOR-study as a cross-sectional cohort study (children aged 4 -12 years old) (2). We compared the offspring born after maternal bariatric surgery to the offspring of a group of women with overweight or obesity during pregnancy and the offspring of a group of women with normal weight during pregnancy. A prospective data collection was performed to gain insight in the body composition, metabolic and inflammatory state as well as the vascular function (measured by peripheral arterial tonometry) of the children. In the following paragraphs, we elaborate on the outcomes of the EFFECTOR-study per topic.

Non-therapeutic research and especially long-term follow-up studies are characterized by challenging inclusion processes. Therefore, the second aim of this PhD research was to develop a study framework to maximize the participation of the children. All study documents and measurements were assembled into a superhero framework, to make the study attractive and as child-friendly as possible. Children received age-appropriate information before the study visit by a visually attractive assent and a short superhero video. During the study visit, the investigator used a sticker diploma and provided a superhero-cape for the toddlers. The children were actively involved during the study visit. 294 eligible subjects were contacted by mail and subsequently by phone. One hundred and seven children were lost- to-follow-up because of changed postal address or phone number (5 to 11 years gap between original and follow-up study). From the 187 remaining subjects another 44 parents refused to participate. Resulting in an overall participation rate of 143 out of 294 eligible study subjects (48%) or 143 out of 187 subjects reached by phone (76.5%) (3).

As a first topic, we studied the body composition and psychomotor development of the children born after maternal bariatric surgery. In order to have comparable subgroups, the children of the bariatric surgery group (BS) were matched based on pre-pregnancy body mass index (BMI) to children from mothers that had overweight or obesity during pregnancy (OW/OB). A third control group consisted of children whose mothers had a normal weight during pregnancy (NW). The children born after bariatric surgery (n = 36) presented with the highest body weight SD (standard deviation) score, BMI SD scores, excess in body fat percentage and waist circumference SD score in comparison to the matched OW/OB offspring (n = 36) or NW offspring (n = 35) (figure). Despite a comparable school career, the parents of the BS group reported more behavior problems. The Strength and Difficulties Questionnaire revealed a higher amount of overall problems in the BS offspring as well as higher Externalizing score at the Child Behavior Checklist (4).

The mean interval between surgery and pregnancy was almost 4 years; 22% of the women got pregnant within the first year after the weight-loss procedure. The majority of the women underwent a Gastric Bypass Surgery (n=24; 66.7%), the others underwent a laparoscopic adjustable gastric banding (LABG) (n=10; 27.8%) or a Scopinaro Procedure (n=2; 5.6%). The difference in maternal BMI (pre-surgery to pre-pregnancy) was comparable in all studied BS women. However, since a Gastric Sleeve is currently the most performed intervention in women of a childbearing age; future research should aim to include these women as well and compare the different weight-loss interventions.

A second studied topic was the eating habits and meal pattern of the BS children. Since we know that women after bariatric surgery can have worrisome eating habits, we were interested in the eating habits of their

children. For these outcomes we did not perform a matching since we did not focus on neonatal outcomes (total n = 142; BS n = 36; OW/OB n = 71; NW n = 35). Meal-skipping behavior was comparable between the groups. We did not find any difference in fruit and vegetable consumption. We did found that the BS group consumed more low-calorie sweetened beverages compared to the NW group but less fruit juice compared to the NW and OW/OB groups. We hypothesized that these results may indicate a sugar-avoiding behavior in children of the BS group, fitting dietary maternal habits in a strategy to prevent dumping syndrome (5).

A third topic revolved around the vascular function of the BS children, measured by a non-invasive manner by peripheral arterial tonometry (PAT). Since the feasibility and discomfort related to this technique has mainly been studied in adults and adolescents, we collected Faces Pain Scale (FPS-R) data in 109 children. We compared the reported discomfort and pain after PAT measurement to calliper and ultrasound examination of peripheral skinfolds. We found that the proportion of higher FPS-R after PAT was significantly higher than the pain experienced after calliper measurements of peripheral skinfolds. 59 of the 109 children (54.1%) did not experience any pain. The reactive hyperemia index (RHI) could be calculated in 111 out of 142 performed PAT measurements (success rate of 78.2% in a group of children with a median age of 10.5 years old). The most frequently reported error messages by the software was a signal that was "too noisy" and/or "poor quality". The success rate was higher in children aged older than 6 years (83.1% versus 44.4%; p<0.001).

Since we hypothesized that bariatric surgery before pregnancy might influence the endothelial function in the offspring, we wanted to study this with the PAT measurements. Children of the BS group had a higher diastolic blood pressure SDS and a lower RHI compared to the children of the OW/OB and NW group. After log transforming the data and correcting it for the child's age, the weight SDS, the BMI SDS, body fat percentage and diastolic blood pressure SDS, RHI was comparable between the groups. Therefore, we were not able to demonstrate a disturbed endothelial function in pre-pubertal BS children, when their increased diastolic blood pressure and degree of adiposity was taken into account (6).

All of these above-mentioned findings stress the vulnerability of the offspring born after maternal bariatric surgery. The different findings presented in this thesis underline the susceptibility of certain families for an intergenerational, vicious circle of obesity and oblige us to view this disease as a multifactorial entity. The presented data support the idea that bariatric surgery can not be perceived as "a holy grail" solving everything for these women and all their future generations. Therefore, we urge health care workers across different specialties to bundle forces in order to prevent obesity in women of childbearing age and provide a stable and accessible environment for health care without stigmatizing. Emphasis should be made on performing pre-conceptual counseling before surgery, improving the lifestyle of women after bariatric surgery and giving advice to postpone a pregnancy until two years after surgery. In addition, future research and clinical practice should aim to provide a regular, prospective follow-up for the children born after maternal pre-pregnancy bariatric surgery.

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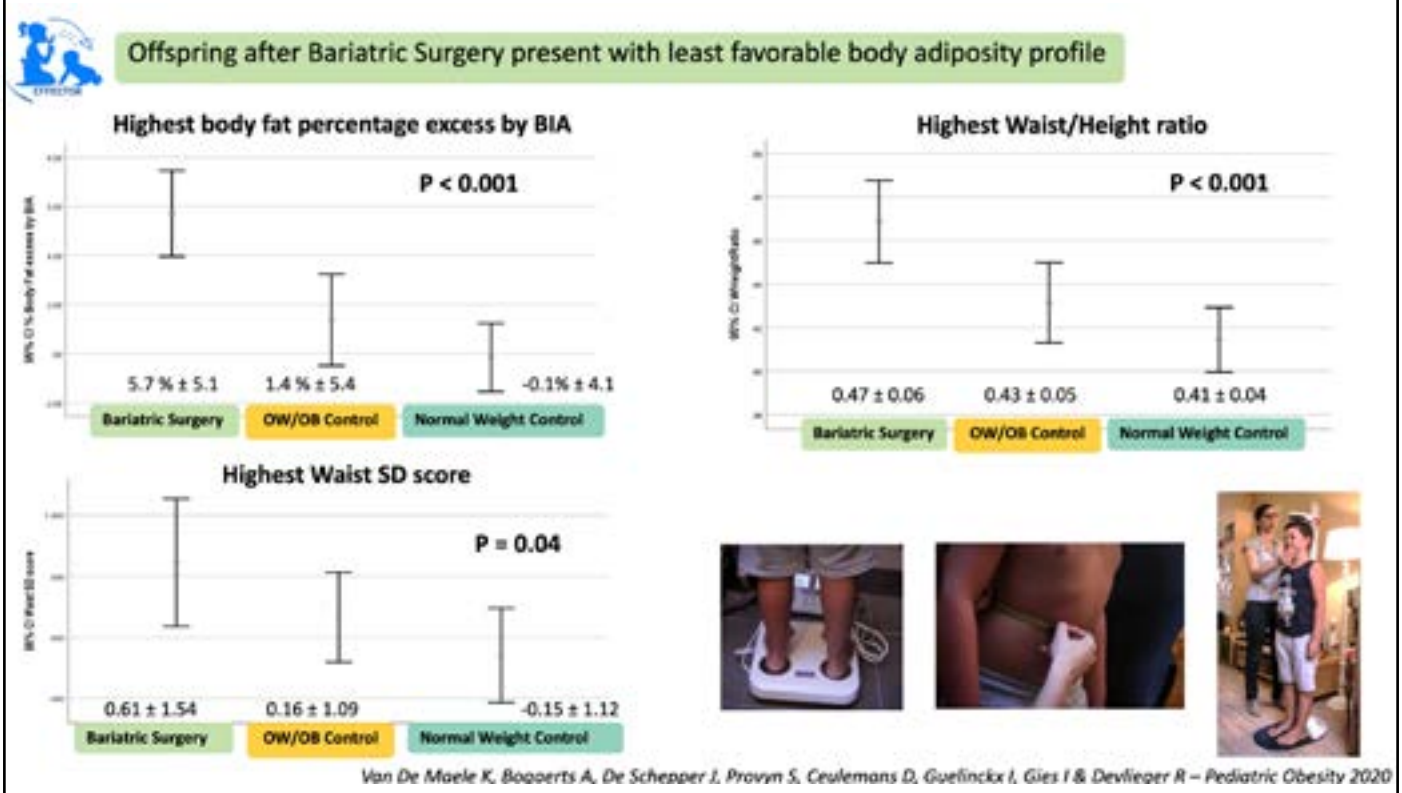
Figure : *Comparison of adiposity profile of children born after maternal bariatric surgery to ofspring of obese/overweight women and normal weight women*



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