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Sleep-disordered breathing on respiratory polygraphy in neonates with spina bifida

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Abstract

Introduction: Studies have shown a high prevalence of sleep-disordered breathing (SDB) in children with spina bifida. International standards for regular testing for SDB in this population are lacking. While there are studies investigating the prevalence of SDB in children with spina bifida, there are close to no studies in neonates.

Aim and Objective: To evaluate if routine respiratory polygraphy (RPG) testing is indicated for neonates with spina bifida and if yes, with what therapeutic consequence.

Methods: We conducted a retrospective cohort study of all neonates with spina bifida at the University (Children's) Hospital Zurich after fetal spina bifida repair born between 2017 and 2022, who had undergone at least 1 RPG evaluation during hospitalization on the neonatal ward. RPG were evaluated by a blinded group of experienced pediatric pulmonologists. Based on the neonatal RPG results and pediatric pulmonologist's recommendation for caffeine therapy the spina bifida cohort was divided into two groups. Neonatal baseline RPG and follow-up RPG at the age of the 3 months were evaluated.

Results: 48 neonates with RPG were included. Compared to the standard values in healthy neonates, the RPG results of this spina bifida cohort showed findings of SDB with central apnea and hypopnea. 22 (45.8%) neonatal RPG evaluations detected central SDB, prompting caffeine therapy. Follow-up RPG conducted after 3 months showed significant improvement of SDB with (almost) no need for continuation of caffeine.

Conclusion: We recommend the implementation of routine RPG testing in neonates with spina bifida to detect SDB and facilitate early targeted treatment.

Abbreviations: AASM, American Academy of Sleep Medicine; AHI, apnea hypopnea index; CAI, central apnea index; CM-II, chiari malformation II; ETST, estimated total sleep time; HI, hypopnea index; HR, heart rate; IQR, interquartile range; MMC, meningomyelocele; MRI, magnetic resonance imaging; OAHI, obstructive apnea hypopnea index; OAI, obstructive apnea index; ODI, oxygen desaturation index; PSG, polysomnography; RPG, respiratory polygraphy; SD, standard deviation; SDB, sleep-disordered breathing; VP, ventriculoperitoneal.

KEYWORDS
caffeine therapy, myelomeningocele, neonates, respiratory polygraphy, sleep-disordered breathing, spina bifida, sleep apnea

1 | INTRODUCTION

Over 300,000 neonates worldwide are yearly being diagnosed with a neural tube defect, the most common being spina bifida and anencephaly.[1] In Switzerland, spina bifida affects 1 of 6590 live births.[2] Spina bifida is the most complex form of neural tube defect. It is characterized by the incomplete closure of the bony vertebral arch, resulting in the protrusion of the meninges and the spinal cord. The level of the lesion determines the severity of the neurological complications such as lifelong paralysis, incontinence and cognitive disabilities.[3] Spina bifida is often accompanied by Chiari malformation type II (CM-II) and hindbrain herniation. This anomaly leads to an alteration of the anatomical relationship of the respiratory system within the brainstem as well as the lower cranial nerves controlling the upper airway, thereby facilitating the disturbance of respiratory pattern and reflexes, particularly during sleep.[4,5] More than a third of the children with spina bifida and CM-II are symptomatic. Among others, symptoms include dysphagia, neuro-ophthalmological disturbances and sleep-disordered breathing (SDB), such as central and obstructive apnea and sleep-related hypoventilation.[4,5]

The approximate global first-week mortality in neonates with spina bifida is 6.9%, varying strongly between countries.[6] SDB, respiratory failure and sudden unexplained death during sleep are the three most common causes for deaths in children with spina bifida.[7]

However, regular testing for SDB is not established as international standard of care for spina bifida. Patel et al. found that only 12% of all children diagnosed with spina bifida were examined with polysomnography between 1999 and 2013.[8] Similar findings were reported by Kirk et al. in 1999, when the testing rate for SDB in patients with spina bifida had only been 7.5%.[7]

While there are a few studies investigating the prevalence of SDB in children with spina bifida, there are close to no studies focusing on this topic in neonates.[8–12] Previously published papers, focusing on an older population with spina bifida, mostly reported obstructive apneas as the cause of SDB.[8,13] Appropriately, Rocque et al. reported a higher mean age of children with obstructive-only apnea than children with central apnea or both.[12] In contrast, studies focusing on neonates mainly showed central apnea as the cause of SDB.[10,14,15] This suggests a central etiology of SDB during the neonatal period and therefore needs a different therapeutic approach than SDB in older children.

In addition to a heterogeneous approach to diagnosis, there currently is no standardized therapy for SDB. Validated treatment options exist, such as methylxanthines, supplemental oxygen or noninvasive positive pressure ventilation.[8,13] If we identified SDB in neonates with spina bifida and treated them accordingly, this potentially modifiable risk factor for complications could be reduced and long-term outcomes could possibly be improved. As the Spina Bifida Center in Zurich is a referral center for fetal surgery for spina bifida, we conducted a retrospective cohort study to evaluate if routine respiratory polygraphy (RPG) testing is indicated for neonates with spina bifida and if yes, with what therapeutic consequence.

2 | METHODS

2.1 | Study population

The University (Children's) Hospital Zurich is one of the European reference centers for fetal surgery for spina bifida. We conducted a retrospective cohort study of all neonates with spina bifida after fetal spina bifida repair, who were born at our hospital from 1 January, 2017 to 31 March, 2022. The spina bifida types included myelomeningocele (MMC), myeloschisis, limited dorsal myeloschisis and intermediate lesion. At our institution, modified MOMS trial criteria[16] are utilized for eligibility for fetal spina bifida repair. The fetal surgery at our institution was planned at a gestational age of 25 weeks followed by planned delivery via cesarean section at 37 weeks. We reviewed the medical records of 131 neonates with a diagnosis of spina bifida and selected the neonates who had undergone at least 1 RPG evaluation during hospitalization on our neonatal ward.

Neonates who had any significant fetal anomaly not related to spina bifida, any concurrent comorbidities or medications that predispose to SDB or an already established caffeine therapy or supplemental oxygen at the time of RPG were excluded.

2.2 | Data collection

At the beginning of the Spina Bifida program in Zurich, a data registry was created to record all pertinent data in a prospective and comprehensive way. Part of the data for the present study were retrieved from this REDCap®-based repository.

Each patient's medical record was reviewed to collect data concerning prenatal, perinatal and neonatal demographics and clinical information, including continuous oximetry and blood gas results if available, magnetic resonance imaging (MRI) findings and RPG results.

Fetal pre- and postoperative as well as neonatal brain MRIs were conducted for all neonates and evaluated for any correlates to SDB by an experienced pediatric neuroradiologist, blinded to the results of RPG.

2.3 | Respiratory polygraphy

To complete the RPG the Nox T3 Portable Sleep Monitor (Nox Medical, Iceland), Nonin WristOx2 BLE with Neo Flex Sensor (model 8001J), which was used on the foot (proximal Dig I), and Nox single use belts (size S) were used.

Nurses experienced with the use of the system set up the equipment. The following parameters were measured: (1) Airflow via a nasal pressure cannula connected to a pressure transducer, (2) Respiratory effort with respiratory inductance plethysmography using thoracic and abdominal belts, (3) Activity and position via an actigraph integrated in the Nox T3 system, (4) Oxygen saturation, and (5) Heart rate (HR) with pulse oximetry (Nonin 3150, Nonin Medical Inc). The recording was automatically set to stop after 10 h. Each RPG was interpreted by one of five experienced pediatric pulmonologists using the American Academy of Sleep Medicine (AASM) criteria.[17] The RPGs were analyzed for estimated total sleep time (ETST), apnea-hypopnea index (AHI), obstructive apnea hypopnea index (OAHI), oxygen desaturation index (ODI), obstructive apnea index (OAI), central apnea index (CAI), hypopnea index (HI), periodic breathing, levels of desaturation, maximal central apnea duration and number of bradycardias. According to AASM criteria,[17] central apneas occurring within a run of periodic breathing were scored as individual apneas. Hypopneas were not classified as obstructive or central.[17] Published data on polysomnography (PSG) reference values in healthy neonates were used for comparison.[18] Capillary blood gas results during admission to the neonatal ward were used to assess alveolar hypoventilation. A pCO_2 between 4.5 and 6.0 kPa was considered normal. If capillary blood gas was not available, venous blood gas measurements were used. Desaturations were defined by continuous saturation monitoring during hospitalization. Any desaturations <85% were noted as per unit protocol.

Routine RPG evaluations for neonates with spina bifida were established as standard of care at our hospital in 2020. Before 2020, the indication and timing of the RPG was based on clinical judgment of the attending neonatologist.

Caffeine therapy was started based on the RPG results combined with clinical judgment of the attending neonatologist. As per internal policy, the following RPG parameters were used to diagnose central SDB and indicated the need for caffeine therapy: minimal saturation <80%, ODI < 50/h, SpO_2 < 90% at >2%/ETST, >20 s of apnea, periodic breathing >10%/ETST or any bradycardic events.[15,18–21] Repeat-RPG was performed 3 months after initiation of caffeine therapy, with discontinuation of caffeine 3 days before the RPG assessment.

2.4 | Statistics and ethics

Demographic and clinical data were summarized with standard descriptive statistics. Categorical variables were expressed as counts and percentages. For continuous variables medians and interquartile ranges (IQR) or means and standard deviations (SD) were reported. The cohort was divided into two groups: one group with present SDB and one group with absent SDB based on the neonatal RPG results and pediatric pulmonologist's recommendation for caffeine therapy and afterwards compared using the chi-squared test for categorical variables, the t-test for continuous variables and the Wilcoxon test for non-parametric variables. The statistical significance level was set at $p < .05$. All statistical analyses were performed using RStudio version R4.3.2. This study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr. 2020-03048).

3 | RESULTS

Between January 2017 and March 2022, 131 neonates with spina bifida were born after fetal spina bifida repair at our hospital. Out of the 53 neonates who received a RPG evaluation, another 5 were excluded due to the reasons listed in Figure 1, resulting in a total of 48 eligible neonates. 22/48 (45.8%) neonatal RPG evaluations corresponded with central SDB and led to a caffeine therapy recommendation. Except for one case, in which the symptoms subsided after the RPG, all recommendations to start caffeine were followed, therefore indicating a follow-up RPG. Out of the 21 recommended follow-up RPGs, 11 (52.4%) were performed (Figure 1). All but one infant were able to stop the caffeine therapy after approximately 3 months.

Basic clinical and demographic characteristics are depicted and compared between the two groups (SDB absent (caffeine therapy not indicated, $n = 26$) vs. SDB present (caffeine therapy indicated, $n = 22$)) in Table 1. Overall median gestational age at delivery was 37.00 weeks [35.00, 37.00], ranging from 27 0/7 (1/48, 2.1%) to 37 6/7 (1/48, 2.1%) weeks gestation. Median birthweight did not differ between the groups (2755 g vs. 2660 g, $p = .641$). Out of the 48 included neonates, 30 (62.5%) had a MMC, 13 (27.1%) a myeloschisis, 2 (4.2%) a limited dorsal myeloschisis and 3 (6.3%) an intermediate lesion. While the anatomic level of the spina bifida lesion ranged from S2 to Th12 with an absolute majority between L4-5 (36/48, 75.0%), the functional level ranged from S1 to L2 with an absolute majority between L4-5 (42/48, 87.5%). Review of the fetal and neonatal MRIs did not reveal any comorbidities relevant to the development of SDB ((Supporting Information S1: Table 1).

Out of the 40 (40/48, 83.3%) neonates with desaturations during routine continuous saturation monitoring in our cohort, 19 (19/40, 47.5%) had no signs of SDB in the RPG (Table 1). The groups of neonates with and without desaturations during routine continuous saturation monitoring are compared in Supporting Information S2: Table 2. A median pCO_2 of 5.56 kPa [5.19, 5.89] (SDB absent) versus 5.80 kPa [5.43, 6.20] (SDB present) ruled out any chronic hypercapnia at the time of neonatal RPG. Basic demographic and clinical characteristics of neonates with spina bifida born before 2020 (before the implementation of routine RPG) without RPG versus with RPG did not differ significantly (Supporting Information S3: Table 3).

Compared to the standard values of PSG in healthy neonates[18] our RPG results of neonates with spina bifida showed findings of

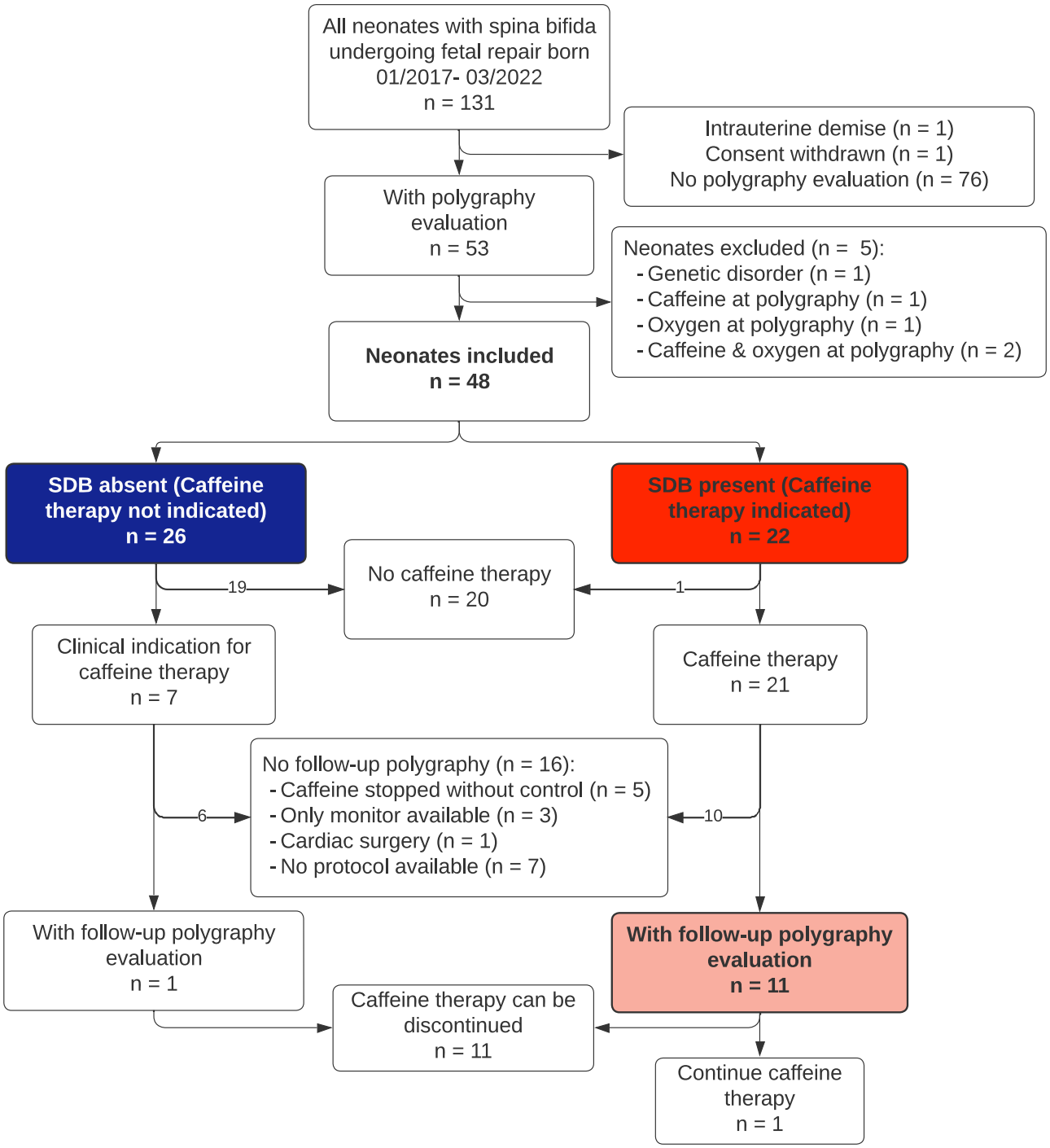

FIGURE 1 Flowchart of study population by presence of sleep-disordered breathing (SDB). [Color figure can be viewed at wileyonlinelibrary.com]

central SDB with central apnea and hypopnea (Table 2). Obstructive apnea in neonates with spina bifida were similar to standard reference values for healthy neonates.[18]

The neonatal RPG results of the 48 neonates compared between the two groups (SDB absent vs. SDB present) are shown in Table 3. The median corrected gestational age at the time of RPG was 38.29 weeks [37.75, 38.71] versus 38.36 weeks [37.89, 38.71] ($p = .934$). RPG results revealed 45.8% (22/48) of the neonates with present SDB, while the remaining 54.2% (26/48) did not display any signs of SDB. When comparing the RPGs before and after routine testing was implemented in 2020, significantly more SDB (13/19 (68.4%) vs. 9/29 (31.0%), $p = .025$) was found in the clinically indicated RPGs done before 2020. The other 6 out of the 19 (31.6%) showed no signs of SDB (Supporting Information S4: Table 4). Eventhough the median AHI in the routinely performed RPGs was significantly lower than in the clinically indicated RPGs (27.10 [17.90, 41.40] vs.

TABLE 1 Demographics of study population, overall and by pulmonologist's recommendation for caffeine therapy.

	Overall	SDB absent (caffeine therapy not indicated)	SDB present (caffeine therapy indicated)	p value
n	48	26	22	
Sex (%)				.942
Male	21 (43.8)	12 (46.2)	9 (40.9)	
Gestational age at delivery, days (median [IQR])	259.00 [251.00, 259.00]	259.00 [258.25, 259.75]	256.50 [250.25, 259.00]	.089
Maternal age at delivery, years (mean (SD))	31.40 (4.07)	31.54 (3.97)	31.23 (4.26)	.795
Head circumference, cm (median [IQR])	34.45 [32.48, 35.62]	34.45 [33.00, 35.38]	34.25 [32.10, 35.88]	.901
Apgar 5 min (median [IQR])	9.00 [8.00, 9.00]	9.00 [9.00, 9.00]	9.00 [8.00, 9.00]	.379
Arterial cord pH at delivery (median [IQR])	7.34 [7.31, 7.37]	7.35 [7.31, 7.38]	7.34 [7.32, 7.37]	.819
Ventilatory support needed (%)				.718
No	28 (58.3)	15 (57.7)	13 (59.1)	
Noninvasive Ventilation	17 (35.4)	10 (38.5)	7 (31.8)	
Invasive ventilation	1 (2.1)	0 (0.0)	1 (4.5)	
Both	2 (4.2)	1 (3.8)	1 (4.5)	
Desaturations during hospitalization (%)[a]				.092
No	8 (16.7)	7 (26.9)	1 (4.5)	
Yes	40 (83.3)	19 (73.1)	21 (95.5)	
VP shunt insertion before discharge (%)				1
No	45 (93.8)	24 (92.3)	21 (95.5)	
Yes	3 (6.2)	2 (7.7)	1 (4.5)	
Chronological age at RPG, days (median [IQR])	11.50 [8.00, 18.00]	10.00 [7.00, 13.00]	14.50 [10.00, 19.50]	.062
Indication neonatal RPG (%)				.025
Routine (as of 2020)	29 (60.4)	20 (76.9)	9 (40.9)	
Symptomatic (2017–2019)	19 (39.6)	6 (23.1)	13 (59.1)	

Abbreviations: IQR, interquartile range; RPG, respiratory polygraphy; SD, standard deviation; SDB, sleep-disordered breathing; VP, ventriculoperitoneal shunt.

[a]Clinical manifestation or detected on continuous saturation monitoring.

65.30 [32.60, 106.35]), it was still significantly higher than in healthy neonates (14.50 [1.0, 37.7]; Table 2). Apart from the minimal SpO_2 in the neonatal RPG (83.50 vs. 79.50, $p = .03$), no statistically significant differences were found when analyzing the RPG outcomes of neonates born at term (≥37 weeks gestation, 28/48, 58.3%) in contrast to those born preterm (<37 weeks gestation, 20/48, 41.7%) (Supporting Information S5: Table 5).

Data of the neonatal and follow-up RPGs of neonates with present SDB is compared in Table 4 and Figure 2. The neonatal RPG of those neonates receiving caffeine therapy was conducted at a median corrected gestational age of 38.43 weeks [37.86, 38.71]. The median corrected gestational age at the time of the follow-up RPG was 54.57 weeks [52.29, 59.00]. Out of the 11 follow-up RPGs, 7 (63.6%) were performed at our hospital, the other 4 (36.4%) at hospitals closer to home. Comparison of the externally performed RPGs to our RPGs revealed no significant differences (Supporting Information S6: Table 6). Comparing the two time-points of the RPGs (neonatal RPG vs. follow-up RPG), most parameters of SDB improved significantly in the follow-up RPGs (Table 4 and Figure 2).

4 | DISCUSSION

The purpose of this retrospective cohort study was to evaluate if routine RPG testing is indicated for neonates with spina bifida and to assess the therapeutic consequences of such testing. The key results of our study are a high prevalence of central SDB of 45.8% in neonates with spina bifida. Follow-up RPG at 3 months of age after caffeine therapy showed significantly improved SDB. The high prevalence of SDB in neonates with spina bifida was consistent with

TABLE 2 Neonatal respiratory polygraphy results of study population compared to polysomnography reference values in healthy neonates.

	Healthy neonates[a]	Study cohort
n	30	48
Gestational age at delivery, weeks (median [IQR])	39.00 [38.0, 41.0]	37.00 [35.00, 37.00]
Chronological age at RPG, days (median [IQR])	19.5 [7.0, 30.0]	11.50 [8.00, 18.00]
Estimated total sleep time, min (median [IQR])	258.30 [160.0, 362.0]	312.50 [259.25, 378.25]
Apnea Hypopnea Index (median [IQR])	14.50 [1.0, 37.7]	40.15 [20.62, 71.58]
Oxygen Desaturation Index (median [IQR])	16.60 [0.5, 41.0]	51.30 [32.00, 86.30]
Obstructive Apnea/hour (median [IQR])	1.80 [0.2, 12.5]	0.45 [0.18, 1.40]
Central Apnea/hour (median [IQR])	3.30 [0.0, 27.2]	13.10 [7.80, 25.05]
Hypopnea/hour (median [IQR])	5.90 [0.7, 12.9]	14.40 [8.73, 30.73]
Baseline SpO_2 (median [IQR])	98.20 [95.5, 99.7]	96.00 [95.00, 98.00]
Minimal SpO_2 (median [IQR])	85.00 [69.0, 93.0]	81.50 [78.00, 85.00]
Time SpO_2 < 90%/ETST, % (median [IQR])	0.30 [0.0, 2.0]	1.35 [0.38, 4.78]

Abbreviations: ETST, estimated total sleep time; IQR, interquartile range; RPG, respiratory polygraphy.

[a]Daftary, Ameet S./Hasnaa E. Jalou/Lori Shively/James E. Slaven/Stephanie D. Davis: Polysomnography Reference Values in Healthy Newborns, in: Journal of Clinical Sleep Medicine, Bd. 15, Nr. 03, 2019, doi:10.5664/jcsm.7670.

previously published findings in children with spina bifida. Considering potential sequelae of SDB, these results suggest a benefit of screening for SDB through RPG starting at a neonatal age.

The prevalence of SDB in children with spina bifida varies strongly between research centers and studies. It ranges from 42% to 81%,[8–12] increasing with the percentage of patients being tested for SDB.[7] In a recently published paper, Rocque et al. found a prevalence of 42% of SDB in children aged between 1 month and 21 years.[12] In comparison, the general pediatric population has a prevalence of estimated 4% of SDB.[22] Moreover, Shellhaas et al. were able to show a doubling of the mean AHI - serving as a marker for the severity of SDB-in neonates with spina bifida compared to age-matched controls, who also required intensive care.[23] At our institution routine testing was only implemented in 2020. When comparing the neonates born before 2020 not referred to RPG to the neonates with symptoms and therefore referred to RPG we could not find any significant differences in basic demographics. The respiratory markers for SDB, especially the AHI, ODI and desaturation indices were significantly more abnormal in the RPG before 2020, which can be well explained by the clinical indication for these RPG. Nevertheless, desaturations during hospitalization, measured as clinical manifestation or on continuous saturation monitoring, did not reliably correlate with our RPG findings. Shellhaas et al. found that bedside monitoring for apnea events >20 s could also underestimate the degree of SDB since only very few apnea events last more than 20 s.[23]

Studies show that SDB in children can have long- term effects, such as pulmonary hypertension, failure to thrive, permanent neurologic damage, behavioral disturbances, development delays and sudden death. This is the case even if SDB only occurred in the first year of life[24–31] and thus SDB warrants early diagnosis and treatment.

In this study, we did not find any significant differences in the demographics between the two groups, revealing no demographic characteristic as an independent risk factor for SDB. Sub-analysis of term versus preterm neonates with spina bifida as well as neonatal MRIs did not reveal an association of prematurity or MRI findings with SDB.

Our cohort had a much higher AHI compared to PSG reference values in healthy neonates, which is in line with the findings of Shellhaas et al., who found a median AHI of 34.2 in neonates with spina bifida.[23] While only relying on the AHI to diagnose SDB is not sufficient, it can give a sense of degree of SDB. This supports our thesis, that SDB is more common in neonates affected by spina bifida and underscores the need for early detection and treatment of SDB in this population.

While the number of central apneas was elevated, the number of obstructive events was similar to that of healthy newborns. Our cohort showed elevated OAHI, which can be explained by the included central hypopneas, which possibly lead to an overestimation. The OAHI as well as the CAI showed significant improvement after 3 months, indicating that the majority of hypopneas were central. This is in accordance with previously published reports showing that obstructive apnea is mostly found in children and young adults with spina bifida but not in neonates with spina bifida.[8,12] This indicates different etiologies of SDB and therefore a need of different therapeutic approaches depending on age. After 3 months we detected only one case of persistent SDB, raising the question if later detected central apnea in older children were missed during the neonatal age and therefore could be prevented with routine neonatal

TABLE 3 Neonatal respiratory polygraphy results of study population by pulmonologist's recommendation for caffeine therapy.

	SDB absent (caffeine therapy not indicated)	SDB present (caffeine therapy indicated)	*p* value
n	26	22	
Chronological age at RPG, days (median [IQR])	10.00 [7.00, 13.00]	14.50 [10.00, 19.50]	.062
Estimated total sleep time, min (median [IQR])	342.50 [280.00, 379.75]	295.50 [255.00, 344.75]	.084
Apnea Hypopnea Index (median [IQR])	24.15 [17.90, 39.35]	71.65 [40.50, 104.22]	<.001
Obstructive Apnea Hypopnea Index (median [IQR])	10.70 [4.95, 18.17]	30.40 [5.82, 58.97]	.019
Oxygen Desaturation Index (median [IQR])[a]	35.70 [24.65, 51.22]	82.70 [63.90, 106.90]	<.001
Obstructive apnea/hour (median [IQR])	0.40 [0.20, 0.88]	0.50 [0.12, 1.98]	.596
Central apnea/hour (median [IQR])	11.10 [6.03, 18.32]	21.10 [8.62, 45.23]	.029
Hypopnea/hour (median [IQR])	12.40 [8.85, 16.90]	28.70 [9.60, 53.33]	.019
Periodic breathing/ETST, % (median [IQR])[a]	0.00 [0.00, 4.78]	6.80 [0.70, 33.10]	.004
Baseline SpO_2 (median [IQR])	97.00 [95.25, 98.00]	95.00 [94.25, 96.00]	.017
Minimal SpO_2 (median [IQR])	85.00 [80.50, 85.75]	79.50 [75.25, 81.00]	<.001
Time SpO_2 < 90%/ETST, % (median [IQR])	0.55 [0.12, 1.65]	3.65 [1.63, 8.47]	<.001
Mean central apnea duration, sec (median [IQR])[b]	5.70 [5.30, 6.40]	6.00 [5.53, 6.38]	.593
Maximal central apnea duration, sec (median [IQR])[c]	11.30 [10.45, 13.65]	13.10 [10.30, 14.60]	.378
Number bradycardias (median [IQR])[d]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0

Abbreviations: ETST, estimated total sleep time; IQR, interquartile range; RPG, respiratory polygraphy; SDB, sleep-disordered breathing.

[a]1 (2.1%) missing.

[b]3 (6.2%) missing.

[c]4 (8.3%) missing.

[d]2 (4.2%) missing.

RPG and caffeine treatment or if with age new SDB occurs. In any case, with different etiologies of SDB and with onset at different age, longitudinal studies with regularly repeated RPG might be necessary in context of spina bifida. Due to the missing standardized diagnosis criteria of SDB, clinical judgment played a role in the decision whether caffeine therapy was recommended or not. Standardized diagnosis is needed to enable the best possible use of caffeine, as it is an affordable and well-tolerated therapy option. Although caffeine is routinely and safely administered for apnea of prematurity,[32,33] there is limited evidence regarding the use of caffeine in term neonates with central apnea. While RPG to control the efficacy of caffeine was not part of this study, this should be subject of future studies in addition to clinical response to caffeine. Furthermore, we found significant improvement in SDB after 3 months. The remarked improvement of central apnea suggests a sufficient maturation of the brain's respiratory control centers and the drive to breathe after 3 months.[34] However, further research is needed to establish optimal caffeine dosage and to assess treatment duration as well as its potential to shorten initial hospital stay of neonates with spina bifida.

A risk stratification for SDB based on clinical, demographic, or radiological findings does not seem to be possible, which is why we think the implementation of routine RPG for spina bifida during the neonatal period may be beneficial. Moreover, we recommend additional continuous saturation monitoring until SDB can be ruled out with RPG. RPG is a noninvasive and cost-effective diagnostic bedside monitoring tool. In limited resource settings, however, continuous saturation monitoring combined with clinical findings, when used with caution, could serve as screening tool to decide which neonates should get a RPG.

Further data on the evolution of SDB during infancy and childhood is needed. Future research should investigate the hypothesis that consistent screening and treatment of SDB in neonates with spina bifida will lead to improved neurocognitive performance and behavior.

4.1 | Strengths and limitations

We recognize that there are limitations to our study, including its retrospective nature, single center design and the lack of long-term follow-up data. However, the Spina Bifida Center in Zurich is one of the European reference centers for fetal surgery for spina bifida with many years of expertise, a prospective data registry and a standardized pre- and postnatal follow-up care. Pediatric neuroradiologists assessing the MRIs were blinded to results of RPGs. The change of policy after 2020 for the indication of RPG might have led

TABLE 4 Respiratory polygraphy results of neonates with present SDB and carried-out caffeine therapy.

	Neonatal respiratory polygraphy results	Follow-up respiratory polygraphy results	*p* value
n	21	11	
Chronological age at RPG, days (median [IQR])	15.00 [10.00, 20.00]	125.00 [109.50, 162.50]	<.001
Estimated total sleep time, min (median [IQR])	285.00 [255.00, 349.00]	456.00 [371.75, 471.00]	<.001
Apnea Hypopnea Index (median [IQR])	71.80 [40.50, 105.00]	9.30 [6.40, 15.30]	<.001
Obstructive Apnea Hypopnea Index (median [IQR])[a]	32.10 [5.30, 60.40]	5.45 [1.75, 7.70]	.011
Oxygen Desaturation Index (median [IQR])[b]	86.30 [65.80, 107.23]	11.20 [5.53, 14.63]	<.001
Obstructive apnea/hour (median [IQR])	0.50 [0.10, 2.00]	0.30 [0.00, 1.00]	.495
Central apnea/hour (median [IQR])	22.10 [8.40, 46.70]	3.90 [0.75, 6.15]	<.001
Hypopnea/hour (median [IQR])	30.00 [8.50, 54.60]	1.20 [0.60, 3.50]	<.001
Periodic breathing/ETST, % (median [IQR])[c]	8.60 [0.85, 34.80]	0.00 [0.00, 0.80]	.012
Baseline SpO_2 (median [IQR])	95.00 [94.00, 96.00]	98.00 [96.75, 98.00]	.001
Minimal SpO_2 (median [IQR])[a]	79.00 [75.00, 81.00]	87.50 [81.25, 88.00]	.002
Time SpO_2 < 90%/ETST, % (median [IQR])[a]	3.60 [1.60, 8.70]	0.05 [0.00, 0.33]	<.001
Mean central apnea duration, sec (median [IQR])[a]	6.00 [5.60, 6.40]	6.20 [5.80, 6.40]	.687
Maximal central apnea duration, sec (median [IQR])[d]	13.10 [9.98, 14.75]	10.30 [8.27, 11.42]	.153
Number Bradycardias (median [IQR])[e]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	.105

Abbreviations: ETST, estimated total sleep time; IQR, interquartile range; RPG, respiratory polygraphy; SDB, sleep-disordered breathing.

[a]1 (3.1%).

[b]4 (12.5%).

[c]5 (15.6%).

[d]2 (6.2%).

[e]3 (9.4%).

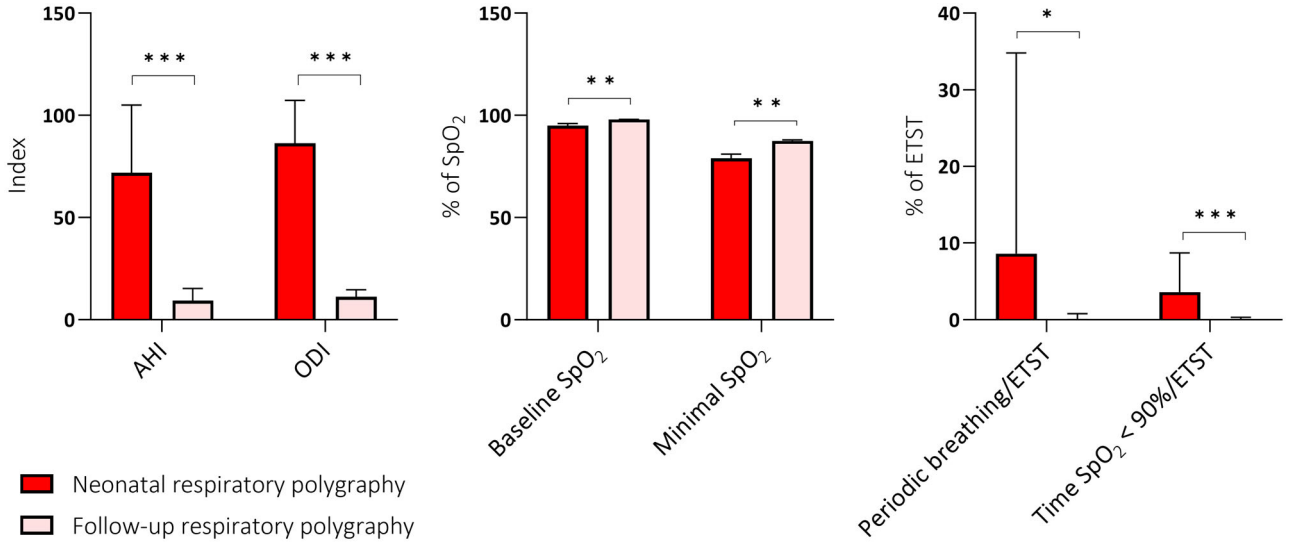

FIGURE 2 Comparison of neonatal and follow-up respiratory polygraphy results of neonates with present SDB and carried-out caffeine therapy. AHI apnea-hypopnea index; ODI oxygen desaturation index; ETST estimated total sleep time. *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$. [Color figure can be viewed at wileyonlinelibrary.com]

to bias. By not measuring arousals (as in polysomnographies) we might have underestimated the respiratory events. However, respiratory arousals are rare compared to all respiratory events.[18] Since hypopneas were not classified into central and obstructive, the OAHI also contained central hypopneas and was thus overestimated. Systematic standardized CO_2 measurements as an additional index for SDB should be considered in future studies. Furthermore, only neonates who underwent fetal closure of spina bifida were included in this study. As a result, no conclusions can be made regarding the impact of fetal closure on SDB. While not all follow-up RPGs were performed at our center, we did not find any significant differences between the RPGs, so we believe that the location bias is minimal. About half of the recommended follow-up RPGs were not performed or were not available for evaluation, possibly leading to attrition bias. Finally, parents were advised to discontinue caffeine 3 days before follow-up RPG. However, no medication levels were measured for caffeine before follow-up RPGs since blood sampling seemed disproportionate, expensive with no clinical benefit and thus was not standard of care. Nevertheless, our data represents the first to look at SDB in neonates with spina bifida over a longer period and therefore raises important questions regarding early diagnosis and treatment of SDB.

5 | CONCLUSION

In conclusion, we recommend the implementation of routine RPG testing in neonates with spina bifida. This will aid in the early detection and treatment of central SDB. Further research is needed to optimize treatment strategies and investigate the long-term effects of SDB and its management on neurocognitive performance and behavior in neonates with spina bifida.

AUTHOR CONTRIBUTIONS

Lorine Wachsmuth: Conceptualization; data curation; formal analysis; writing—original draft; methodology; visualization. **Christian Bieli**: Methodology; data curation; writing—review and editing. **Patrice Grehten**: Writing—review and editing; data curation. **Theres Moehrlen**: Data curation; Writing—review and editing. **Ueli Moehrlen**: Writing—review and editing. **Vera Bernet**: Writing—review and editing. **Cornelia Hagmann**: Writing—review and editing; conceptualization. **Beate Grass**: Supervision; writing—review and editing; conceptualization; formal analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no potential, perceived or actual competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATMENT

Data collection, evaluation and publication for this study was approved by the Ethics Committee of the Canton of Zurich (KEK-ZH-Nr. 2020-03048).

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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