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ORIGINAL ARTICLE

Micrognathia and cleft palate as a cause of obstructive sleep apnoea in infants

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Abstract

Aim: Obstructive sleep apnoea (OSA) is common in Robin sequence (RS). We investigated the significance of micrognathia, cleft palate and sleep positioning on OSA in infants.

Methods: We analysed our 13-year national reference centre polysomnography (PSG) dataset. PSG was performed as daytime recordings (97%) in the supine-, side- and prone sleeping position at the median age of 5 weeks (interquartile range 3–8 weeks).

Results: Our study included 113 infants with RS and cleft palate, 10 infants with RS but intact palate and 32 infants with cleft palate without micrognathia. The degree of OSA in infants with cleft palate without micrognathia was less severe than in infants with RS in terms of obstructive events (median OAHI 4 vs. 32 h^{-1}, respectively), SpO_2 desaturations ($ODI_{\geq 3}$OAH 0.4 vs. 3 h^{-1}), transcutaneous pCO_2 levels ($TcCO_2P_{95}$, 41 vs. 46 mmHg) ($p < 0.0001$) and work of breathing ($p = 0.01$). In the RS group, OSA was sleep-position dependent, with fewer obstructive events apparent in the side (18 vs. 24 h^{-1}, $p = 0.005$) and prone (39 vs. 27 h^{-1}, $p = 0.003$) sleeping positions than when supine.

Conclusions: The degree of OSA in RS infants is more dependent on micrognathia than on cleft palate.

KEYWORDS
Cleft palate, Infants, Polysomnography, Robin sequence, Sleep apnea

Abbreviations: AASM, American Academy of Sleep Medicine; C, cleft palate; CA, central apnoea; CAI, central apnoea index; CCMS, cerebro-consto-mandibular syndrome; Chi^2, Chi-square test; CPAP, continuous positive airway pressure; CSF, cerebrospinal fluid; DTD, diastrophic dysplasia; ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; $EtCO_2$ P_{95}, end-tidal carbon dioxide 95 percentile level; $EtCO_2$, end-tidal carbon dioxide; HFNC, high-flow nasal cannula; HNPP, hereditary brachial plexus neuropathy; IQR, interquartile range; LDS5, Loeys-Dietz Syndrome Type 5; M, micrognathia; MFDGA, Guion-Almeida Syndrome; MoveHF, movement sensor high-frequency band representing general movements; MoveLF, movement sensor low-frequency signal representing respiratory movements; NPA, nasopharyngeal airway tube; O_2, home oxygen therapy; OAHI, obstructive apnoea and hypopnoea index; $ODI_{\geq 3}$, oxygen desaturation index of ≥3%; $ODI_{\geq 3}$CA, oxygen desaturation index of ≥3% related to central apnoea episodes; $ODI_{\geq 3}$OAH, oxygen desaturation index of ≥3% related to obstructive and mixed apnoea and obstructive hypopnea episodes; OSA, obstructive sleep apnoea; pCO_2, partial pressure of carbon dioxide; PEBP, pre-epiglottal baton plate; Pleth, oximeter plethysmography; PSG, polysomnography; REM, rapid eye-movement sleep; Rib, respiratory inductance plethysmography; RS, Robin sequence; SEDC, spondyloepiphyseal dysplasia; $SpO_{2\ Min}$ OAH, minimum pulse oximeter saturation related to obstructive and mixed apnoea and obstructive hypopnoea episodes; SpO_2, pulse oximeter oxyhaemoglobin saturation; Surg, surgery; $TcCO_2$ P_{95}, transcutaneous carbon dioxide 95 percentile level; $TcCO_2$, transcutaneous carbon dioxide; TLA, tongue-lip adhesion; WOB, work of breathing.

1 | INTRODUCTION

Robin sequence (RS) is defined as the triad of micrognathia, glossoptosis and a varying grade of airway obstruction.[1,2] Reported RS incidences vary from 12 600 to 1 122 400 live-births.[3–6] RS often occurs as one presentation of some other co-existing syndrome[2,7] and it has been related to over 50 syndromes such as Stickler syndrome and 22q11.2 deletion.[8–11] Although cleft palate is not a criterion for RS, most infants with RS have cleft palate (50%–90%).[12,13]

For infants with RS, obstructive sleep apnoea (OSA) is characteristic,[14–19] its incidence ranging from 60% to 90%. The nature of OSA in the RS-group infants typically differs from OSA in young infants without any clear anatomical OSA-predisposal factor.[18,20,21] The degree of OSA in RS is frequently far worse, being severe in more than half[14,22,23]; and obstructive events co-exists with significant partial upper airway obstruction with high work of breathing.[20,21] Cleft palate alone, even without micrognathia, is also associated with OSA in older infants and children,[15,24,25] whereas the data concerning young infants is scarce.[17,25]

First-line treatment to control breathing difficulty in RS has traditionally been sleep positioning,[1,9,26,27] with most RS infants seeming to benefit from either side- or prone positioning.[18] According to clinical estimates, the proportion of RS infants successfully managed through positional treatment alone is approximately 70%.[15–18,28] However, treatment approaches show great variability across nations and treating centres.[6]

Although a number of polygraphy and polysomnography (PSG)-based studies involve RS infants,[29] the effect of sleep positioning has been evaluated in only a few studies,[19] with only one study targeting young infants with cleft palate without micrognathia.[17]

In this PSG-based study, we evaluated the association of micrognathia and cleft palate with OSA in young infants. We also evaluated the effect on OSA of sleep position. Preliminary results involving some of these infants with RS have appeared.[18]

Key Notes

- Infants with Robin sequence (RS) show almost invariably moderate to severe degree of position dependent obstructive sleep apnoea (OSA).
- Obstructive sleep apnoea severity in infants with RS is more dependent on the presence of micrognathia than cleft palate.
- In infants with cleft palate without micrognathia, OSA appears less frequent and less severe than in infants with RS.

2 | METHODS

2.1 | Study design and patients

We studied obstructive sleep apnoea in infants with RS and in infants with isolated cleft palate without micrognathia.[2,30] We evaluated retrospectively national paediatric pulmonology reference centre and the Cleft and Craniofacial Centre HUSUKE 13-year data sets from October 2009 through January 2023. We defined RS as a combination of micrognathia, glossoptosis and breathing difficulties.[2,30] We divided the study group into three subgroups to study separately the influence of the two main structural features of RS, micrognathia and cleft palate, on OSA, (1) RS-group infants with micrognathia and cleft palate, (2) RS-group infants with micrognathia but intact maxilla and palate, (3) infants with isolated cleft palate without micrognathia but a normal-sized chin and mandible (Table 1 and Figure 1). We also studied the position dependence of OSA in this population.

In our clinical practice, we will perform PSG evaluation for all RS infants within 2–6 weeks of life, with the position dependence analysis as a part of our evaluation protocol. For this study purpose, we extended this systematic clinical practice to include all infants with cleft palate, thus also including the infants not having RS but isolated cleft palate, for a 3-year period from 2021 to 2023.

Polysomnographic recording were performed mostly as daytime recordings (Table 1) by two nurses of paediatric clinical neurophysiology and under supervision of a paediatric pulmonologist. We aimed to follow a stepwise approach in infant sleep positioning. Initially, the infant was placed in the supine position. If obstructive events occurred while supine, the sleep study continued after our shifting the infant into the side- or into the prone position. Sleep recording continued in each position until one proper non-REM and REM sleep period could be recorded. Some infants with RS, however, showed such a severe degree of breathing difficulty that supine positioning was not acceptable.

2.2 | Polysomnography

The PSG protocol (Figure 2) comprised monitoring of four electroencephalogram channels (Cz-Fz, Cz-O2, C4-M1 and O2-M1), two electro-oculography channels, chin and diaphragm electromyography (EMG), nasal airflow (pressure transducer), oral airflow with a thermistor when significant oral airflow was suspected or observed (six recordings, 4%), respiratory movements (thoracic and abdominal bands), electrocardiography, two pulse oximetries (SpO_2) with 2- to 4-s average intervals (Embla or SOMNO™ HD, and Masimo Radical Pulse CO-Oximeter), end-tidal carbon dioxide ($EtCO_2$) (CAP10 Capnograph, Medlab medizinische Diagnosegeräte GmbH), transcutaneous carbon dioxide ($TcCO_2$) (SenTec Inc.), a movement sensor mattress (Emfit Ltd.), position sensor and a synchronised video recording. For PSG, we used the Embla N700 system (Natus Medical

TABLE 1 Demographic and polysomnographic parameters.

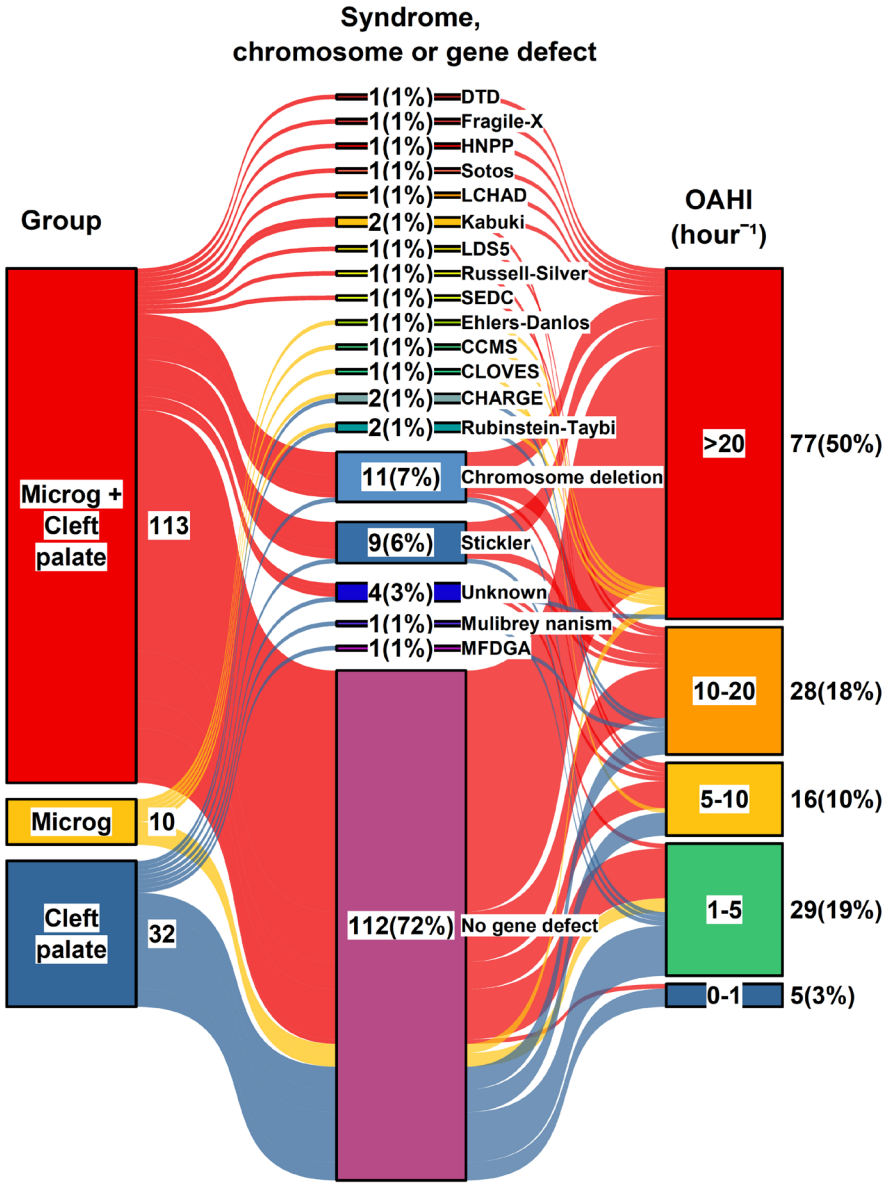
	Micrognathia + Cleft palate	Micrognathia	Cleft palate	Mann–Whitney *p*-value		
				M + C vs M	M + C vs C	M vs C
Infants (*n*)	113	10	32			
Corrected age (weeks)	4.2 (2.9–7.3)	2.8 (1.9–6.1)	7.1 (5.3–8.7)	0.17	0.002	0.01
Female (*n*)	60 (53%)	5 (50%)	14 (44%)	0.86	0.35	0.74
Male (*n*)	53 (47%)	5 (50%)	18 (56%)			
Gestational age (weeks)	39.7 (38.7–40.6)	40.1 (38.6–40.9)	39.6 (39.1–40.3)	0.80	0.95	0.79
Premature (*n*)	10 (9%)	0 (0%)	2 (6%)	0.33	0.64	0.45
Term (*n*)	103 (91%)	10 (100%)	30 (94%)			
Polysomnography						
Day/Night recording (*n*)	110/3	10/0	31/1	0.61	0.89	0.61
Positions studied (*n*)	2.3 (2–3)	2.0 (1–3)	1.9 (1–3)	0.12	0.004	0.75
Sleep characteristics						
Total recording time (min)	258 (229–294)	253 (230–287)	208 (170–257)	0.98	0.002	0.09
Total sleep time (min)	152 (127–170)	134 (124–199)	130 (114–159)	0.77	0.02	0.43
Sleep efficiency (%)	59 (50–68)	54 (50–69)	64 (55–76)	0.94	0.14	0.36
REM (min)	51 (37–68)	49 (42–60)	43 (34–58)	0.55	0.08	0.43
Non-REM (min)	97 (84–110)	93 (77–134)	89 (73–103)	0.88	0.10	0.58
Breathing						
OAHI (h^{-1})	32.0 (12.2–58.3)	35.4 (4.8–74.4)	4.1 (2.8–10.4)	0.97	<0.0001	0.005
Obstructive apnoea index (h^{-1})	16.9 (7.5–32.8)	14.0 (3.2–43.5)	2.2 (0.6–5.1)	0.91	<0.0001	0.55
Central apnoea index (h^{-1})	2.9 (1.2–5.8)	6.1 (3.4–14.9)	6.4 (2.9–13.1)	0.06	0.002	0.09
Mixed apnoea index (h^{-1})	1.9 (0.9–3.7)	2.7 (0.6–5.3)	0.5 (0–1.2)	0.69	<0.0001	0.02
Diaphragm EMG activity (WOB) (0–2)	0.9 (0–2)	0.9 (0–2)	0.6 (0–2)	1	0.02	0.13
Respiratory rate (min^{-1})	34 (29–40)	33 (27–52)	34 (30–39)	0.71	0.60	0.68
$ODI_{\geq 3}$ (h^{-1})	10.1 (5.3–18.4)	14.3 (11.4–35.2)	7.8 (1.6–13.9)	0.08	0.05	0.009
$ODI_{\geq 3}$OAH (h^{-1})	3.0 (1.2–7.1)	5.2 (0.5–18.9)	0.4 (0–0.8)	0.48	<0.0001	0.01
$ODI_{\geq 3}$CA (h^{-1})	0.4 (0–1.4)	2.3 (1.1–6.0)	1.5 (0.5–5.2)	0.006	0.001	0.49
$SpO_{2\ Min}$ OAH (%)	89 (85–91)	87 (84–91)	94 (91–96)	0.67	0.0002	0.02
$EtCO_2$ P_{95} (mmHg)	42.8 (40.5–45.8)	42.4 (41.3–45.0)	41.3 (38.3–43.1)	0.62	0.01	0.37
$TcCO_2$ P_{95} (mmHg)	46.1 (42.8–51.0)	46.1 (38.3–48.0)	40.5 (39.0–43.5)	0.26	<0.0001	0.07

Note: Results presented as median (*IQR* interquartile range), except for work of breathing and position studied which are presented as mean (range).
Abbreviations: C, cleft palate; CA, central apnoea; $EtCO_2$ P_{95}, end-tidal carbon dioxide 95 percentile level; M, micrognathia; OAHI, obstructive apnoea and hypopnoea index; $ODI_{\geq 3}$, oxyhaemoglobin desaturation index of ≥3%; $ODI_{\geq 3}$CA, oxygen desaturation index of ≥3% related to central apnoea episodes; $ODI_{\geq 3}$OAH, oxyhaemoglobin desaturation index of ≥3% related to obstructive and mixed apnoea episodes and obstructive hypopnoea episodes; REM, rapid eye movement sleep; $SpO_{2\ Min}$ OAH, minimum pulse oximeter saturation related to obstructive and mixed apnoea episodes and obstructive hypopnoea episodes; $TcCO_2$ P_{95}, transcutaneous carbon dioxide 95 percentile level; WOB, work of breathing.

Inc.) prior to August 2018 and SOMNO™ HD (Somnomedics GmbH) systems from September 2018 onwards.

All PSG recordings were reanalysed and scored by T.K., by use of Embla® RemLogic™ (Natus) or SOMNOmedics DOMINO software (SOMNOmedics), together with our extensive additional special-purpose software for detailed analysis of SpO_2, $EtCO_2$, $TcCO_2$ and respiratory rate.

The sleep-stage and respiratory-event analyses we performed visually by applying American Academy of Sleep Medicine (AASM) guidelines.[31,32] We recognised central, obstructive, mixed apnoea



		Group	Syndrome	OAHI
Group	Pearson Correlation	1	-0.03	**0.52**
	p-value	--	0.74	**<0.0001**
Syndrome	Pearson Correlation	-0.03	1	-0.14
	p-value	0.74	--	0.08

FIGURE 1 Alluvial presentation of patient characteristics concerning the relation of patient group, co-existing syndromes and the number of obstructive apnoea and hypopnea episodes (OAHI) in our sleep study. OAHI is divided into five categories, 0–1, 1–5, 5–10, 10–20 and >20 h^{-1}. The frequency of co-existing syndromes in the micrognathia group (60%) was higher than in infants with a combination of cleft palate and micrognathia (28%, $p = 0.04$) or isolated cleft palate alone (22%, $p = 0.03$). The presence of a co-existing syndrome did not correlate with OAHI ($p = 0.08$). CCMS, cerebro-consto-mandibular syndrome; DTD, diastrophic dysplasia; HNPP, hereditary brachial plexus neuropathy; LDS5, Loeys-Dietz syndrome type 5; MFDGA, Guion-Almeida syndrome; SEDC, spondyloepiphyseal dysplasia.

episodes and obstructive hypopnoea episodes based on airflow, diaphragm EMG activity and respiratory movements. Work of breathing (WOB) we estimated from diaphragm EMG activity, and graded from 0 to 2, where 0 represented low (normal), 1 slightly increased and 2 clearly increased activity.[20] Oxyhaemoglobin desaturations over 3% ($ODI_{\geq 3}$) we analysed both separately and in relation to the preceding apnoea or hypopnoea episodes ($ODI_{\geq 3}CA$, $ODI_{\geq 3}OAH$).

2.3 | Statistical methods and analysis

We performed statistical analysis using IBM® SPSS® Statistics software version 29 and OriginPro 2023b. The PSG parameters were not normally distributed, and we used non-parametric tests for the analysis. Group analyses were done using Mann–Whitney test (Table 1 and Figure 3) and repeated measure comparisons using the Paired Sample Wilcoxon Signed Ranks Test (Figure 4 and Table S1).

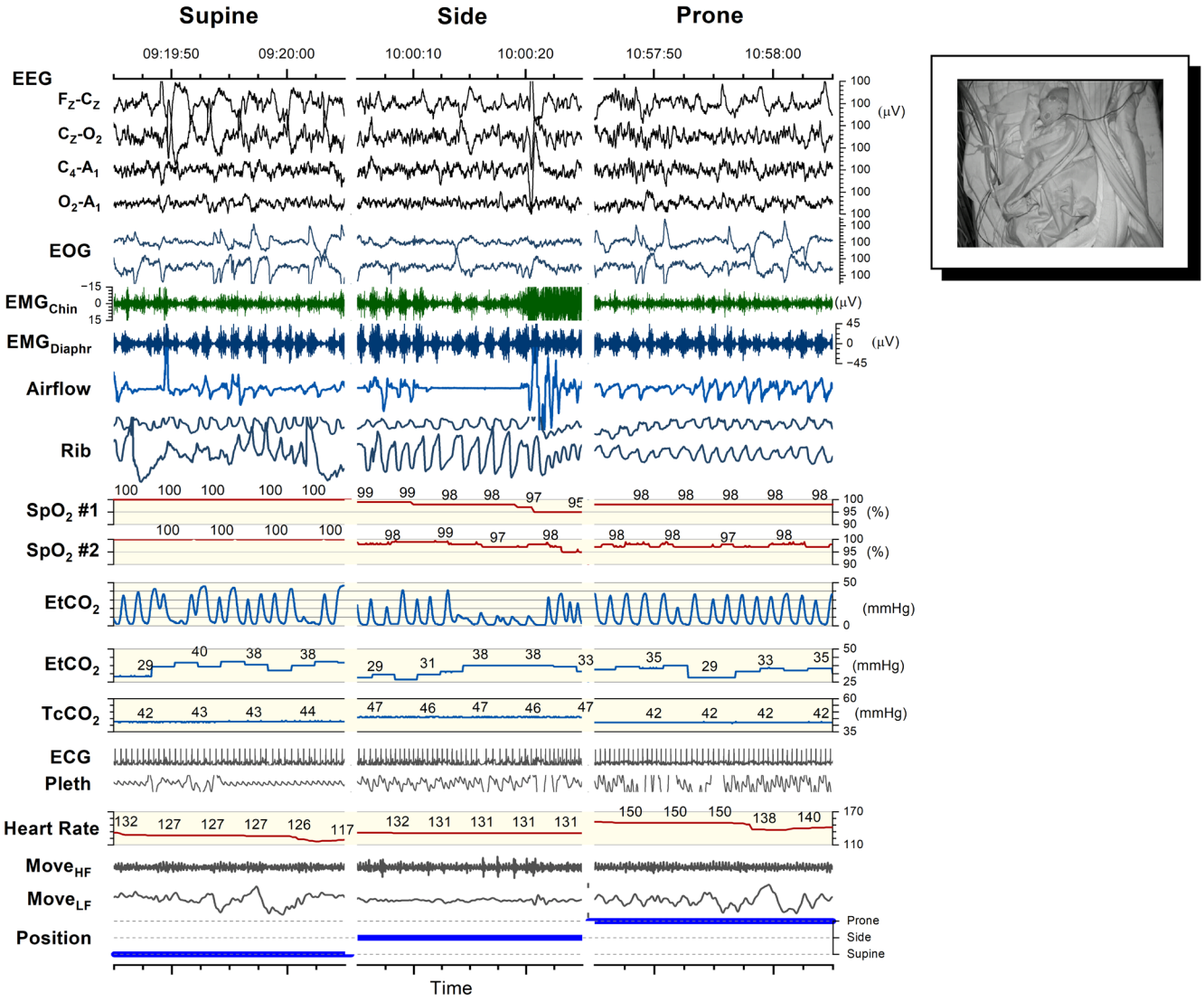


FIGURE 2 Three 30-s polysomnographic (PSG) recordings examples in the supine-, side- and prone sleeping positions in a 3-month-old infant with cleft palate and small chin. PSG included a continuous video monitoring. ECG, electrocardiogram; EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; $EtCO_2$, end-tidal carbon dioxide; $Move_{HF}$, movement sensor high-frequency band representing general movements; $Move_{LF}$, movement sensor low-frequency signal representing respiratory movements; Pleth, oximeter plethysmography; Rib, respiratory inductance plethysmography; SpO_2, pulse oximeter oxyhaemoglobin saturation; $TcCO_2$, transcutaneous carbon dioxide.

In addition, we also used the Pearson Correlation test for correlations between categorial parameters (Figure 1 and Figure S2). SPSS automatic linear modelling allowed us investigation of correlations between treatment invasiveness grouping (no treatment < sleep positioning or caffeine < high-flow nasal cannula (HFNC) or continuous positive airway pressure (CPAP) or supplemental oxygen < nasopharyngeal airway tube (NPA), supraglottoplasty (SGP), or tongue-lip adhesion (TLA) < tracheostomy), obstructive apnoea and hypopnoea index (OAHI), OAHI in the best position with lowest OAHI, over 3% SpO_2 desaturations in relation to obstructive breathing events ($ODI_{\geq 3}OAH$), $ODI_{\geq 3}OAH$ in the best position with lowest OAHI and the date of recording performed. We set statistical significance at $p < 0.05$.

3 | RESULTS

During the study period, a total of nine infants with RS received treatment without PSG analysis, among whom, eight exhibited severe breathing difficulties with intermittent hypoxia and laborious breathing.[18] These we excluded from study analyses.

The PSG study population comprised 123 infants with RS and 32 infants with isolated cleft palate without micrognathia. RS infants were divided into two subgroups, 114 with micrognathia and cleft palate, and 10 with micrognathia but intact maxilla and plate. For infant characteristics see Table 1 and Figure 1. The frequency of co-existing syndromes in the micrognathia group (60%) was higher than in infants with a combination of micrognathia and

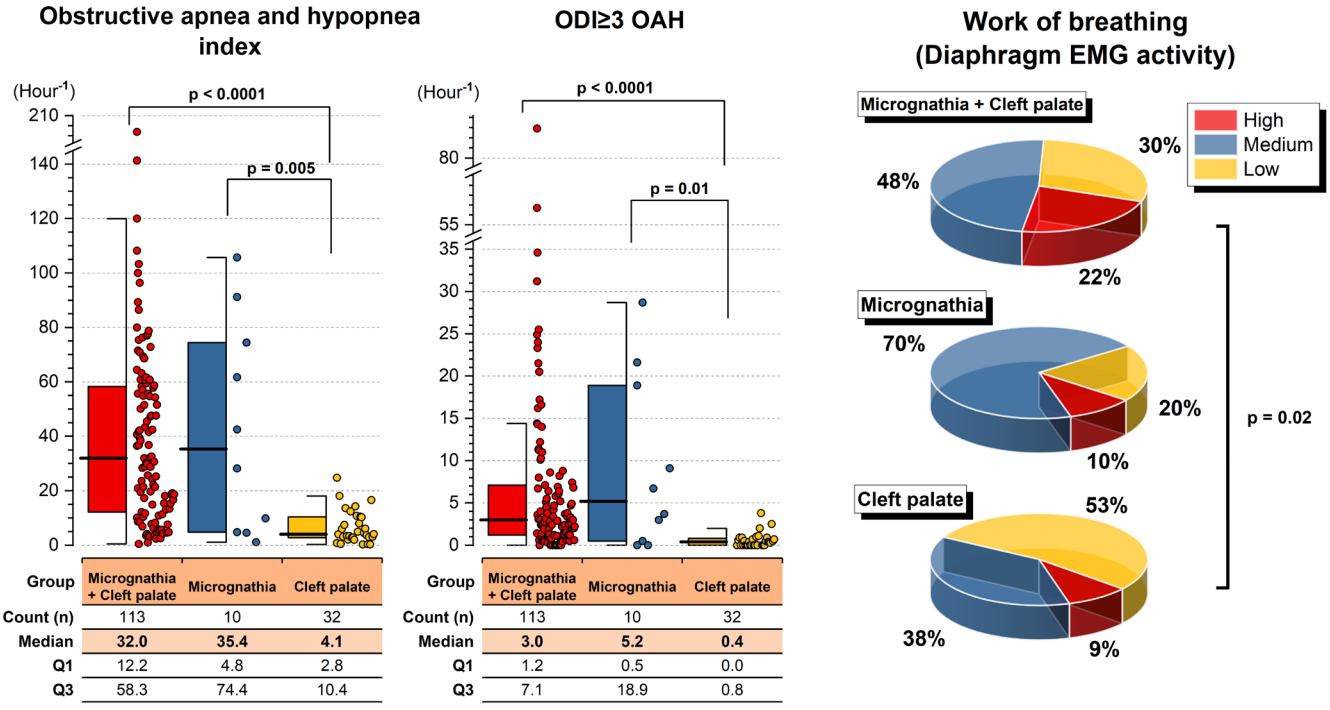


FIGURE 3 Boxplot (two left panels) and pie (right panel) presentation showing obstructive apnoea and hypopnoea index (OAHI), frequency of SpO_2 desaturation and estimated work of breathing in different patient groups. On average, OAHI, frequency of oxygen desaturations, and work of breathing was higher in infants with micrognathia than in those infants with isolated cleft palate without micrognathia. $ODI_{\geq 3}$ OAH, oxygen desaturation index of ≥3% related to obstructive and mixed apnoea and obstructive hypopnoea episodes; SpO_2, pulse oximeter oxyhaemoglobin saturation.

cleft palate (28%, $p = 0.04$) or cleft palate without micrognathia (22%, $p = 0.03$).

3.1 | Obstructive breathing in PSG

Severe OSA was common in RS-group infants both with and without cleft palate (Table 1): only one infant with RS (0.8%) had OAHI of less than $1\,h^{-1}$, but 76 (62%) of infants had OAHI over $20\,h^{-1}$ and 44 (36%) had $ODI_{\geq 3}$OAH over $5\,h^{-1}$. We found no clear differences is OSA between RS-group infants with or without cleft palate (Figure 3).

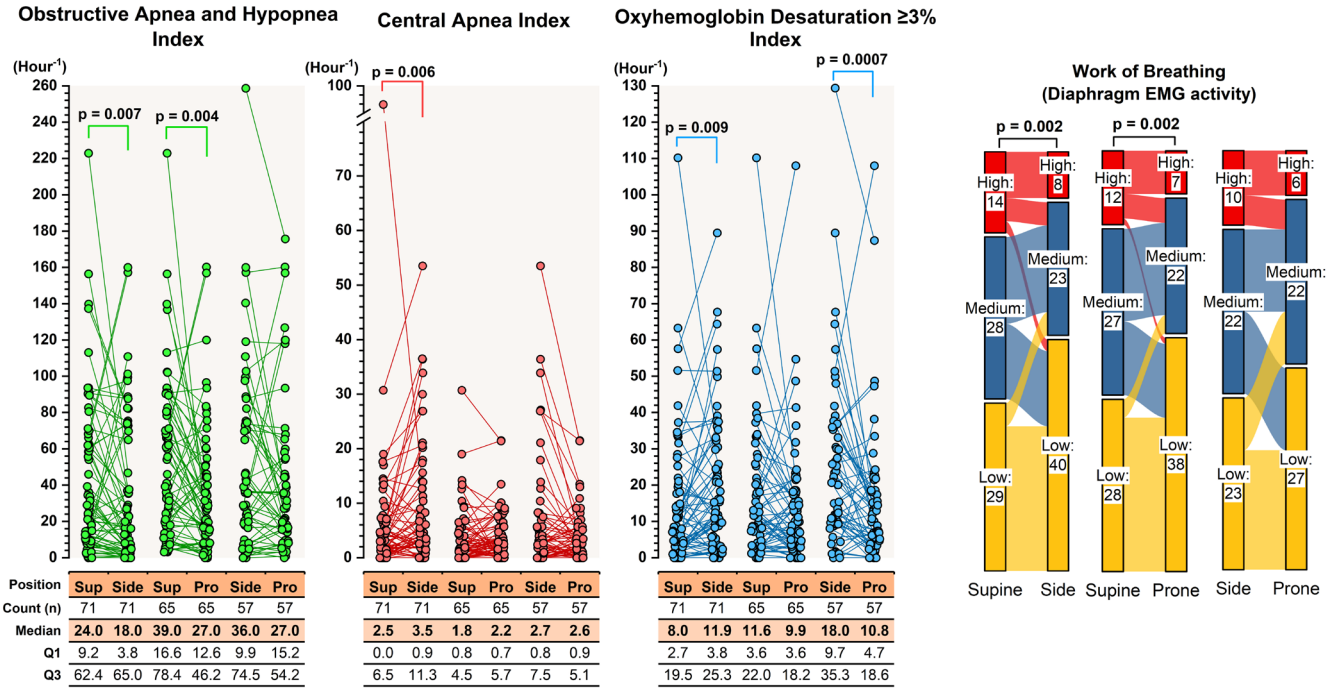
Micrognathia appeared as a key factor causing breathing difficulty in this study cohort (Figure 3). In contrast to the RS group, only one infant (3%) with cleft palate without micrognathia had OAHI over $20\,h^{-1}$ and none of these infants had $ODI_{\geq 3}$OAH over $5\,h^{-1}$. Despite this, most infants with cleft palate without micrognathia showed a number of upper airway obstructions, including 14 infants (44%) with OAHI over $5\,h^{-1}$. On average, obstructive apnoea and hypopnea index (OAHI; $p < 0.0001$), frequency of oxygen desaturations ($ODI_{\geq 3}$OAH; $p < 0.0001$) and work of breathing ($p = 0.02$) all were higher in infants with micrognathia (RS) than in those with cleft palate alone without micrognathia (Figure 3).

Estimated work of breathing using diaphragm EMG activity behaved parallel to our observation with OAHI and SpO_2 desaturations. In the RS group, 25 (20%) infants showed a high level of EMG activity, 62 (50%) a medium level of activity and 36 (29%) a normal low level of diaphragm activity.[20] In contrast to the RS group, of 32 infants with cleft palate without micrognathia, only 3 (9%) showed high-level diaphragm EMG activity.

The difference in OSA severity between the study groups was also reflected in the implementation of the PSG study: the infants with cleft palate without micrognathia were studied more often only on the supine position (first and preferred position on study onset) whereas the RS-group infants underwent study more often in several sleeping positions to obtain optimal sleeping position for breathing (Table 1; $p = 0.003$). No co-existing syndrome or gene defect correlated with frequency of airway obstructions or with OSA severity (Figure 1); OAHI ($p = 0.09$), $ODI_{\geq 3}$OAH ($p = 0.46$).

3.2 | Sleep positioning and degree of OSA

Obstructive sleep apnoea and sleep efficiency (SE) showed sleep-position dependency in RS-group infants (Table S1), the lowest OAHI and highest SE occurred in the prone sleeping position (Figure 4). A similar trend appeared in infants with cleft palate without micrognathia, but only the supine-side comparison was possible to perform with reasonable accuracy. Prone sleep positioning was applied for only six infants, providing only five (16%) values for comparisons (supine vs. prone; side vs. prone).



	Sup	Side	Sup	Pro	Side	Pro
Position						
Count (n)	71	71	65	65	57	57
Median	24.0	18.0	39.0	27.0	36.0	27.0
Q1	9.2	3.8	16.6	12.6	9.9	15.2
Q3	62.4	65.0	78.4	46.2	74.5	54.2

	Sup	Side	Sup	Pro	Side	Pro
	71	71	65	65	57	57
	2.5	3.5	1.8	2.2	2.7	2.6
	0.0	0.9	0.8	0.7	0.8	0.9
	6.5	11.3	4.5	5.7	7.5	5.1

	Sup	Side	Sup	Pro	Side	Pro
	71	71	65	65	57	57
	8.0	11.9	11.6	9.9	18.0	10.8
	2.7	3.8	3.6	3.6	9.7	4.7
	19.5	25.3	22.0	18.2	35.3	18.6

FIGURE 4 Obstructive apnoea and hypopnoea index (OAHI), central apnoea index (CAI), frequency of oxygen desaturations ($ODI_{>3}$) and work of breathing in different sleep positions in infant with Robin sequency (infants with micrognathia). OAHI was significantly lower in the side (Side) and prone (Pro) positions than when supine (Sup). However, in the side position, the frequency of central apnoea episodes was increased, leading to an increase in oxygen desaturation frequency. The prone sleeping position showed lowest values of OAHI, $ODI_{>3}$ and work of breathing.

3.3 | Treatment

The patient clinical flow is presented in Figure S2. Infant group correlated with OAHI, $ODI_{\geq 3}$OAH, need for and choice of treatment, recommended sleep positioning and use of home oximeter monitoring ($p < 0.0001$). On the other hand, the OAHI observed on PSG correlated with $ODI_{\geq 3}$OAH, need for and choice of treatment, recommended sleep positioning and home oximeter monitoring ($p < 0.0001$). Similarly, $ODI_{\geq 3}$ OAH correlated with choice of treatment, recommended sleep positioning and home oximeter monitoring ($p < 0.0001$). Moreover, the estimated level of work of breathing correlated with the choice of or need for treatment ($p = 0.0005$) and the use of home oximeter monitoring ($p < 0.0001$) but failed to correlate with our recommendation of infant sleep positioning ($p = 0.08$).

Pulse oximeter home monitoring was used in 72 (59%) infants with RS but in only four (13%) infants with cleft palate without micrognathia ($p < 0.0001$). In automatic linear regression modelling, treatment invasiveness in RS-group infants correlated only with the OAHI observed in the best position with lowest OAHI ($R^2 = 0.25$).

The RS-group infants clinical flow chart is presented in Figure S3.

4 | DISCUSSION

Our study shows that severe OSA is common in infants with RS prior to 6 months of age, with OSA severity related to micrognathia, not to cleft palate. Our rationale is based on the frequency of obstructive events (OAHI) in infants with cleft palate without micrognathia having been much lower than in RS-group infants. None of the infants with cleft palate without micrognathia had OSA that could be regarded as severe in a clinical context with frequent SpO_2 desaturations. We also showed in this study that the degree of OSA in RS-group infants is position dependent; OSA is more severe in the supine than in the side- or prone sleeping positions. Although altering sleep positioning from the supine to the side or prone reduced the frequency of obstructive events (OAHI) and reduced the related SpO_2 desaturations, the frequency of obstructive events remained high (OAHI >20 h^{-1}) in half of the RS-group infants.

4.1 | Micrognathia and cleft palate as a cause of OSA

Infants with RS frequently had severe OSA irrespective of the presence of cleft palate. In contrast to the RS group, while most infants with cleft palate without micrognathia showed some tendency for upper airway obstructions, none of these infants had frequent SpO_2 desaturations and $ODI_{\geq 3}$OAH over 5 h^{-1}. A similar difference between these study groups was observed in the levels of estimated work of breathing.

Previously, Macclean and associates[17] studied infants with cleft palate in a similar study setup as in our study. Their study included

21 infants with isolated hard and soft cleft palate, 6 infants with lip palate, 17 infants with combined lip and cleft palate and 8 infants with RS. RS-group infants presented similar PSG findings as observed in our study. However, cleft palate group showed significantly more obstructive events than observed in our isolated cleft palate group infants. The differences in the study results are likely to reflect patient selection and definition of RS. However, the clinical conclusions of these two studies are clearly different as our study do not support systematic PSG screening for infants with isolated cleft palate.

4.2 | Effect of sleep positioning on OSA

In the RS infant group, upper airway obstruction showed a clear position dependency. Upper airway obstructions, SpO_2 desaturations were more frequent and the estimated work of breathing higher in the supine than in the side- or prone sleeping positions (Figure 4 and Table S1). Despite the decrease in the number of obstructive events from the supine to either the side- or prone sleeping positions, in the majority of infants, the frequency of obstructive events remained high (Figure 4). This high frequency may, however, lead to overestimation of the clinical significance of OSA, because the number of SpO_2 desaturations ($ODI_{\geq 3}$OAH) was much lower than was OAHI. This notification is also supported by others; airway obstruction appears often more severe in PSG than in the clinical assessment.[19] Obstructive events also interfere with sleep much less in infants than in older children and adults.[33] We included in our PSG assessment no arousal analysis.

The current literature concerning sleep positioning is summarised by Waters.[19] This study confirms earlier studies in a large cohort of 123 infants with RS. We have reported earlier our preliminary results concerning RS-group infants.[18] For this study, all PSG recordings were reanalysed for systematic, uniform approach. This study confirms our preliminary results in a significantly larger RS cohort. This study also enabled the comparison of two RS-group subcohorts, infants with and without cleft palate. The appearance of OSA was similar between these two subgroups.

As an unexpected co-finding, we observed an increased tendency for periodic breathing and a higher number of central apnoea episodes in the side sleeping position when compared to the supine sleeping position. This increase was followed by a higher $ODI_{\geq 3}$ in the side than in the supine sleeping position (Figure 4). In the light of PSG variables only, the prone sleeping position showed the most favourable indexes in the RS infant group.

4.3 | Treatment

The natural course of OSA in RS is not well-established, although OSA is clearly age-dependent.[34] Our clinical observation is that OSA in infants with RS seems to be most severe at an approximate age of 6–8 weeks, becoming significantly alleviated during the following few weeks to months. This notion is supported also by the literature.[16,35,36] The strong spontaneous tendency toward OSA resolution makes it difficult to evaluate the long-term benefits of any treatment.

In the RS infant group, PSG results (OAHI, $ODI_{\geq 3}$OAH, WOB) significantly guided our decision for treatment, for recommended sleep positioning and for recommendation of home pulse oximeter monitoring (Figure S2). Because the improvement in breathing from supine to side and prone sleeping positions occurred not only in OAHI but also as a reduction in SpO_2 desaturations ($ODI_{\geq 3}$ OAH), in work of breathing and in sleep efficiency, the improvement gave an impression of more significant clinical changes than would be justified by merely the change in OAHI. As the number of SpO_2 desaturations was also much lower than the number of obstructive events, two-thirds of infants with RS received positional treatment (60%) or were regarded as requiring no clinical intervention (16%) (Figure S2). During the study period, all infants treated with CPAP, NPA, SGP, TLA or tracheostomy had OAHI $>10\,h^{-1}$, most for $>20\,h^{-1}$. Among 29 infants who received CPAP, NPA, SGP, TLA or tracheostomy, 25 (86%) exhibited either frequent SpO_2 desaturations, hypoventilation, laborious breathing or a clear failure to improve with sleep-positioning treatment.

Since the response for sleep positioning is variable, our results support the use of PSG in making the treatment plan for OSA in RS-group infants as suggested earlier.[25]

We may have undertreated the RS-group infants, especially during the early years of the study period. As the HFNC treatment is well tolerated and easy to obtain also in the home environment, our threshold for treating RS-group infants with a combination of HFNC and side- or prone sleep positioning has, during the last few years, become lower. This combination of sleep positioning and other forms of therapy such as HFNC, palatal plate, NPA or TLA calls for further research. Despite our conservative approach in interpretation of PSG results during the study period, the approach chosen agrees with the traditional RS management approach.[2,22,28]

4.4 | Study limitations

We recognise several limitations concerning our study. We used daytime PSG recording instead of overnight PSG. The total recording times and total sleep times were shorter than would have been obtained by standard overnight PSG. In most cases, the time spent in each sleeping position represents only one cycle of non-REM and REM sleep. The short recording times most likely increased the inaccuracy of the respiratory indexes presented. Some infants had very severe OSA with continuous obstructions and with deep SpO_2 desaturations especially in the supine sleeping position. In these infants, the sleep recording would not have been continued in this position much longer, regardless of available recording time.

Based on our clinical experience, it is easy to unintentionally block small nostrils with the nasal pressure cannula used for measurement. If obstructive events occurred at high frequency, the effect of measuring with a mini cannula was tested by replacement of the cannula and shortening of the measuring cannula parts intended for nostrils if necessary.

5 | CONCLUSIONS

Obstructive sleep apnoea is common in infants with RS who are under 6 months of age. In RS, micrognathia seems to be the key factor for OSA, and in this study, those infants with cleft palate without micrognathia had a significantly lower tendency toward upper airway obstructions than RS-group infants had. Moreover, the degree of OSA in RS-group infants was often severe, whereas none of the infants with cleft palate without micrognathia showed similarly severe OSA with frequent SpO_2 desaturations. In most of our infants with RS, OSA was sleep-position dependent, and most of these infants experienced a reduced number of obstructive events, SpO_2 desaturations and lower work of breathing in the side- or prone sleeping positions compared with supine sleeping. Although sleep positioning may not be a sufficient treatment alone for those infants with RS, our study supports the use of sleep positioning as a part of OSA treatment.

AUTHOR CONTRIBUTIONS

Turkka Kirjavainen: Conceptualization; methodology; software; data curation; validation; formal analysis; project administration; visualization; writing – review and editing; writing – original draft; funding acquisition; investigation; resources. **Pia Vuola:** Conceptualization; methodology; writing – review and editing; validation; resources. **Janne Suominen:** Conceptualization; writing – review and editing; validation; resources. **Anne Saarikko:** Conceptualization; writing – review and editing; supervision; validation; resources.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicting of interest to disclose.

DATA AVAILABILITY STATEMENT

Data is available on anonymous form upon reasonable request.

ETHICS STATEMENT

The local ethics committee (87/13/03/03/2015) and New Children's Hospital Institutional Review Board (Project #4980) approved the study protocol.

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SUPPORTING INFORMATION

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

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