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Original Article

Sleep-disordered breathing, craniofacial development, and neurodevelopment in premature infants: a 2-year follow-up study

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ABSTRACT

Introduction: Sleep problems, neuro-developmental development, and sleep-disordered-breathing (SDB), are reported as more prevalent in premature infants than in full-term infants. We investigated the relationship between neuro-development, and SDB in preterm infants at 24 months corrected age (CA) with a narrow palatal presentation over time.
Methods: We enrolled infants 40 weeks or younger at birth collecting obstetric and birth data. Participants were followed up at 6, 12, 18, and 24 months CA. We evaluated craniofacial development by inspecting and photo documenting hard palate; sleep using sleep diary, actigraphy and night-time polysomnography-PSG-; and development using Bayley- Scales-of-Infant-Development and Denver-Developmental-Screening-Test (DDST) at each visit and comparing results at six months and two years.
Results: 244 premature infants [139 (57.0%) boys, [at birth: mean gestational age-GA- 31.5 ± 3.2 weeks, 1691.9 ± 593.9 g, 40.2 ± 5.2 cm], and 30 full term infants (50% boys), [mean GA 39.3 ± 1.0 weeks, 3131.0 ± 390.0 g, and 49.38 ± 2.0 cm] were enrolled in the study. At 6 and 24 months, 65.2% premature infants had a narrow hard palate (NHP). At 24 months, 79% had an apnea–hypopnea- index (AHI) > 1 events/hour at PSG, with a mean AHI of 3.00 ± 2.95. Only 10% of full term infants had NHP at birth and the mean AHI was 0.5 ± 0.2 event/hour at 24 months.
Conclusion: Preterm infants have a higher occurrence of NHP at birth. At two years of age they have more sleep problems, most commonly associated with obstructive-SDB, and a higher rate of development delays. Frequency of NHP is still abnormally high, suggesting not only abnormal orofacial growth over-time, but also impact of this abnormal growth in the genesis of the obstructive-SDB.

1. Introduction

Since obstructive-sleep-apnea-OSA-was first identified in full-term children by Guilleminault et al. in 1976 [1], sleep-disordered-breathing-SDB- and OSA have been associated with many morbidities such as cardiovascular and metabolic (eg, hypertension) [2], growth (eg, failure to thrive) [3], neurocognitive (eg, low academic performance) [4,5], and neurobehavioral (eg, inattention, hyperactivity, impulsivity, aggressivity, and poor executive functions, communication, and adaptive skills) [5,6] during childhood or adolescence.

Recently, preterm birth has been recognized as a risk factor for both SDB (at age 8–11) [7] and OSA (at age 2.5–6) [8] in prepubertal children. Our previous prospective studies have reported that premature infants are at a great risk of developing SDB [9]. Meanwhile, OSA has been reported not only to be more severe in adults with a past history of prematurity, but also to be associated with a clear narrow hard palate-NHP- and a very narrow upper airway [10]. How does this risk develops, what is

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the frequency of such risk, is there an association between SDB and poor sleep, is there an association between early SDB and early development of premature infants are questions incompletely resolved [10–12].

Adenotonsillar hypertrophy has been the first-line treatment target for childhood SDB and OSA [13]. However, craniofacial anomalies, not adenotonsillar hypertrophy, are the primary cause of OSA in syndromic infants [10,13,14]. These craniofacial anomalies include hypoplasia or displacement of the maxilla or mandible, such as midface hypoplasia, micrognathia, glossoptosis [15], Pierre Robin sequence [16], and changes associated with NHP [17]. However, orofacial dysfunction in non-syndromic infants such as present in premature infants may be associated with orofacial growth problem that may result in OSA [14,17–19].

Currently, an abundant literature has also demonstrated the association of pediatric SDB and OSA with cognitive (mental) and behavioral (psychomotor) problems [4–6,20–23]. One study suggested that OSA may lead to neuronal damage in the hippocampus and prefrontal cortex, which could permanently alter the cognitive potential of a developing child [23]. We hypothesized that the presence of a NHP in premature infants and impairment of orofacial growth may play a major role in the development of SDB and thus, may play a role in the observed neurodevelopmental deficits. Our study aimed to further investigate the development of SDB in premature infants, its relations with the orofacial development based on clinical information, and the potential impact on neurodevelopment.

2. Method

This cohort study was approved by the institutional review board of Chang Gung Memorial Hospital.

2.1. Subjects

Women who delivered in our obstetric department were asked to enroll their neonates prior to being discharged from the neonatal intensive care unit from 2010 till 2013.

2.1.1. Inclusion criteria

(1) All infants born in our hospital before completing 37 gestational weeks, without any of the exclusion criteria, and with a signed parental consent form during the study period were included and form the preterm infants ie group A.
(2) All infants delivered from 37 to 40 weeks of gestational age with birth body weight of more than 2500 g, without presentation of exclusion criteria, and with a signed parental consent form during the study period were included and form the full-term infants ie group B. We included the first 10 infants/year with signed informed consent.

2.1.2. Exclusion criteria

(1) Neonates with severe physical impairments due to perinatal injuries or severe hypoxic ischemic encephalopathy.
(2) Neonates with confirmed severe congenital malformations.
(3) Indication that systematic follow-up over time will not be possible, and infants with long-term intubation were also excluded form out study.
(4) A very small group of premature infants (n = 5) that were submitted to intensive myofunctional therapy from birth as part of another study, was excluded from the analysis.

2.2. Procedure

All infants meeting the inclusion criteria were enlisted during the first 3 days of life and were considered as “participant” in our prospective study. We collected basic obstetric and birth data on all infants.

The planned follow-up points were as follows:

- **Every 3 months:** (a) clinical evaluation by the initial team of specialists, including pediatric, ear-nose-throat (ENT) and oro-maxillo-facial and developmental specialists with photo-documentation [24–26] and questionnaires. (b) development assessment using the Denver Developmental Screening Test – second edition (Denver-II).
- **Every 6 months**: (a) development assessment with the addition of the Bailey-Scales of Infant Development (BSID-II) administered by child psychologists, (b) followed by nocturnal PSG.
- The 30 full-term infants constituting our control group underwent similar investigations at the same pre-determined follow-up points.

2.3. Assessment

- Infants received a pediatric and sleep clinical evaluation that included visual evaluation of the oro-pharynx with systematic photograph documentation of the shape and width of the palate arch, pediatric evaluation with nasal endoscopy with photo, and orofacial surgical specialist evaluation. The definition of narrow hard palate [NHP] was considered present if the internal distance edge to edge at the middle of the palate was less than 20 mm [24–26].
- The parents of each participant were asked to fill out a validated questionnaire, the “Brief Infant Sleep Questionnaire-Chinese version,” (CBISQ) [9,27], which was derived from the Brief Infant Sleep Questionnaire (BISQ) of Avi Sadeh [24]. [The original BISQ had 13 variables included “evaluating sleep duration, night awakenings, and method of falling asleep of infants” aged 29 months or younger, while the CBISQ has three additional questions that consider “time spent with mouth breathing”, “severity of loud noisy breathing”, and “time spent crying during the night”]. Both BISQ and CBISQ have been validated for infants up to three years of age.
- Neurodevelopmental assessments: (i) Denver Developmental Screening Test–II(DDST-II): Items that can be completed by 75%–90% of children but are failed are called “cautions”; those that can be completed by 90% of children but are failed are called “delays”. Normal: No delays and a maximum of 1 caution. Suspect delay: two or more Cautions and/or One or more Delays [28]. (ii) Bayley Scales of Infant Development–II (BSID–II); mental development index (MDI); psychomotor development index (PDI). The mean ± standard deviation (SD) of the standardization sample is 100 ± 15, and a score of less than 70, which is more than 2 SDs below the mean, is defined as a significant delay for the BSID-II Mental and Motor scales [29].
- All infants were evaluated with an actigraph (Philips Respironics actiwatch 2, with a small size well-suited for use with younger subjects or those sensitive to wrist-worn devices) on the left leg or arm (24 months) of the non-dominant side. The equipment measured body movements and light exposure. It was placed on the infant at the time of the visit and kept for 7–10 days, and was analyzed with commercially available software with one point every 2 min and indicated activity/non-activity. The

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equipment was correlated with a sleep diary simultaneously kept by care-givers.

- A nocturnal polysomnogram (PSG) (using Embla N7000 PSG recording-sleep- system) were performed in the pediatric sleep laboratory at the planned follow-up points (6,12,18 and 24 months), with monitoring of the following variables: electro-encephalography, electromyography, electrocardiography, and electro-oculography. Respiration was monitored with a nasal cannula pressure transducer, oral thermistor, thoracic and abdominal inductive plethysmography bands, and pulse-oximetry. The infants were continuously video-monitored during the recording. For PSG scoring, the recommendations of the AASM-2007 were followed [30,31]. PSG was scored blind on the status of the infant/child.

2.4. Analyses

We collected demographic data and performed ANOVA and t tests to compare follow-up data with their initial values and Chi-square statistics for percentage comparison. All statistics were performed using the software PASW Statistics (SPSS-18). Variables are presented as either mean ± standard deviation (SD) or frequency. The statistical significance was defined at the 0.05 level.

3. Results

We recruited 30 full-term and 244 premature infants (see Table 1 for demographic and initial information at enrollment and differences between full-term and premature infants). With aging, four groups of premature infants could be identified from an initial NHP + group consisting of 152 (62.3%) children; and an initial NHP- group of 92 (37.7%). 181 children did not change their anatomic attribute between birth and six months of age, ie. stayed in Group NHP+ and NHP-. These 181 children were subdivided in 2 subgroups and form “group 1” and “group 2”. However 63 children had a different palatal presentation at six months compared to the one observed at birth. Our report does not consider children that switched categories but only reports on Group-1 and Group-2, which presented the same orofacial anatomy as the one noted at birth till two years of age.

3.1. At birth

According to our definition of NHP, 62.3% of premature infants had such presentation [NHP+], compared to only 3 (10%) of full term infants. As can be seen premature infants have significant difference in many variables compared with full-term group (Table 1). The overall NHP + group has a trend of younger gestational age (31.23 ± 3.31 and 32.03 ± 3.01, p = 0.06) than non-NHP [NHP-] premature infants and control group. Two variables, however, were significantly associated with NHP: the head circumference (p = 0.05) was smaller in infants with NHP+, and parents reported more difficulty feeding (p = 0.025) in association with presence of NHP+.

3.2. At six months of age

Considering the premature infants and the two subgroups [NHP+] and [NHP−], obstructive-AHI is not only significantly higher in the overall premature group compared to the controls (p < 0.001) but also in the NHP + group (p = 0.001) than in the NHP- group at six months. Furthermore, the NHP + infants have more sleep problems of any type (84.7%) than the NHP- premature infants (68.7%) (p = 0.001) (Tables 1 and 2a).

The results of the 181 premature infants with same orofacial anatomy as the one noted at birth and at 6 months of age are presented. Of these 181 children, 118 (**65.2%)** presented with a NHP (NHP+) and 63 (**34.8%** NHP−) were considered to have a normal palate at the clinical evaluation performed by the evaluating team (Table 2a). At the same time, the developmental assessment results showed that only one full-term infant has language developmental delay (MDI) < 70 by BSID-II and Denver-II tests (mean MDI = 96.59 + 18.19; PDI = 99.50 + 12.79 in mature infants). Premature infants present more neurodevelopmental deficits than full-term infants.

3.3. At two years of age

- *PSG data* (see Tables 2a and 2b and Fig. 1): PSG data showed that the total premature group still had abnormal breathing during sleep with an apnea-hypopnea-index-AHI- of 3.00 ± 2.95, with 79% of the children having an AHI> 1. When the children were categorized based on the presence/absence of NHP: 100 (84.7%)

Table 1
Demographic data of full-term and premature infants, with and without narrow hard palate (NHP) at birth.

	Full-term infants	Premature infants (n = 244)			
	(n = 30)	Total (n = 244)	NHP n = 152 (62.3%)	No NHP n = 92 (37.7%)	*p* value
Male gender, n (%)	15 (50.0)	139 (57.0)	84 (55.3)	55 (59.8)	0.490
Birth history					
Gestational age (weeks), mean ± SD	$39.27 \pm 1.01^{A/B;a/c,d}$	$31.54 \pm 3.22^{A/B}$	$31.23 \pm 3.31^{a/c}$	$32.03 \pm 3.01^{a/d}$	<0.001*
Body weight (grams), mean ± SD	$3131.0 \pm 390.0^{A/B;a/,c,d}$	$1691.9 \pm 593.9^{A/B}$	$1665.0 \pm 625.3^{a/c}$	$1736.3 \pm 538.2^{a/d}$	0.001*
Body height (cm), mean ± SD	$49.38 \pm 2.03^{A/B;a/c,d}$	$40.54 \pm 5.26^{A/B}$	$40.19 \pm 5.56^{a/c}$	$41.11 \pm 4.72^{a/d}$	0.001*
Head circumference (cm), mean ± SD	$34.07 \pm 1.21^{A/B;a/c,d}$	$29.41 \pm 3.42^{A/B}$	$29.07 \pm 3.53^{a/c/d}$	$29.97 \pm 3.18^{a/d/c}$	0.050*
Cesarean section, n (%)	$9\ (30.0)^{A/B;a/d}$	$172\ (70.5)^{A/B}$	104 (68.4)	$68\ (73.9)^{a/d}$	0.424
Short-term Intubation,n (%)	$2\ (6.7)^{A/B;a/c}$	$134\ (54.9)^{A/B}$	$91\ (59.9)^{a/c}$	43 (46.7)	0.062
Difficulty feeding, n (%)	$3\ (10.0)^{A/B;a/c,d}$	$114\ (46.7)^{A/B}$	$80\ (52.6)^{a/c/d}$	$34\ (37.0)^{a/d/c}$	0.020†
NHP at birth, n (%)	$3\ (10.0)^{A/B}$	$152\ (62.3)^{A/B}$			<0.001†
Polysomnographic data (at six months of age)	(n = 30)	(n = 181)	(n = 118)	(n = 63)	
AHI (events/hour), mean ± SD	$0.5 \pm 0.2^{A/B;a/c,d}$	$3.00 \pm 2.95^{A/B}$	$3.52 \pm 3.32^{a/c/d}$	$2.02 \pm 1.73^{a/d/c}$	0.001*

ANOVA test for three groups: Full-term infants (a), premature NHP+(c) and premature NHP-(d). *Significant difference ($p < 0.05$); Post hoc (Scheffe test) analysis: “a,c,d” showed a significant difference (p < 0.05) between different groups.
Independent t test for two groups: Full-term infants (A) and total premature (B). Significant difference: p < 0.05.
Chi-square test for three groups. †Significant difference between groups ($p < 0.05$); “A/B” and “a,c,d” showed a significant difference (p < 0.05) between different groups.
AHI, apnea-hypopnea index. Narrow hard palate: NHP.

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Table 2a
Polysomnographic characteristics of premature infants, with and without NHP at six months.

	Total (n = 181)	NHP+: 65.2% (n = 118)	NHP−:34.8% (n = 63)	*p* value
AHI (1/hour) in sleep, mean ± SD	3.00 ± 2.95	3.52 ± 3.32	2.02 ± 1.73	<0.001**
AHI > 1, n (%)	143 (79.0)	100 (84.7)	43 (68.25)	0.011†
AI (1/hour), mean ± SD	1.03 ± 1.05	1.03 ± 1.00	1.01 ± 1.15	0.924
HI (1/hour), mean ± SD	2.21 ± 2.73	2.62 ± 3.10	1.44 ± 1.58	<0.001**
RDI (1/hour), mean ± SD	3.99 ± 3.76	4.30 ± 4.05	3.37 ± 3.07	0.163
RERA (counts), mean ± SD	3.41 ± 6.73	3.30 ± 7.35	3.62 ± 5.31	0.786
Sleep latency (min), mean ± SD	15.51 ± 27.06	15.39 ± 22.84	15.80 ± 33.52	0.934
Sleep efficiency (%), mean ± SD	83.9 ± 13.8	83.3 ± 14.5	84.8 ± 12.4	0.485
N1 sleep (%), mean ± SD	15.3 ± 8.9X	15.5 ± 9.2X	15.0 ± 8.4	0.716
N2 sleep (%), mean ± SD	40.3 ± 10.6	39.1 ± 10.8	42.7 ± 9.7X	0.027*
N3 sleep (%), mean ± SD	18.2 ± 11.4	19.2 ± 12.7	16.3 ± 8.2X	0.107
REM sleep (%), mean ± SD	23.7 ± 6.5X	24.0 ± 6.9X	23.1 ± 5.6X	0.400
PLMS index (1/hour), mean ± SD	3.19 ± 7.97	3.89 ± 9.18	1.96 ± 5.17	0.294
Mean SaO_2 (%), mean ± SD	97.60 ± 0.84X	97.54 ± 0.92X	97.70 ± 0.66X	0.152

*Significant difference (independent *t* test $p < 0.05$); **Highly significant difference (independent *t* test, $p < 0.001$).
Chi-square test for groups. †Significant difference between two groups (NHP+ and NHP−) ($p < 0.05$);
AHI, apnea-hypopnea index; AI, apnea index; HI, hypopnea index; RDI, respiratory disturbance index; RERA, respiratory effort related arousal; PLMS index, periodic leg movements in sleep index; Mean SaO2, mean oxygen saturation. NHP: narrow hard palate.
Legend: Infants with narrow hard palate(NHP) have a much greater likelihood of obstructive-sleep-disordered breathing.

Table 2b
PSG data followed for two years in premature infants.

Corrected age, years (n = 181)	6 months	12 months	18 months	24 months
AHI, mean ± SD	3.00 ± 2.95	5.41 ± 4.16	3.54 ± 4.98	4.03 ± 1.67
AHI > 1/hr, n (%)	79.0%	90.2%	86.2%	88.2%
AI, mean ± SD	1.03 ± 1.05	1.59 ± 1.63	1.29 ± 1.56	1.49 ± 0.85
HI, mean ± SD	2.21 ± 2.73	3.78 ± 3.72	2.37 ± 3.94	1.58 ± 1.55
RDI, mean ± SD	3.99 ± 3.76	6.70 ± 5.38	5.07 ± 6.89	4.39 ± 4.42
Efficiency%, mean ± SD	83.9 ± 13.8	83.71 ± 9.19	82.17 ± 14.99	86.5 ± 10.78
Awake%, mean ± SD	12.01 ± 6.35	12.19 ± 7.77	12.83 ± 15.27	8.30 ± 8.60
REM%, mean ± SD	23.7 ± 6.5	25.43 ± 5.90	26.29 ± 14.11	24.15 ± 3.79
TST, mean ± SD	383.2 ± 35.8	378.2 ± 34.6	371.0 ± 61.4	400.3 ± 45.3
PLMS Index, mean ± SD	3.19 ± 7.97	3.03 ± 6.07	5.00 ± 10.85	2.50 ± 5.74
MeanSaO2%, mean ± SD	97.60 ± 0.84	97.58 ± 1.45	97.62 ± 0.82	97.59 ± 0.66
NHP (+), n (%)	118 (65.2%)	101 (55.8%)	108 (59.7%)	96 (53.0%)

AHI, apnea-hypopnea index; AI, apnea index; HI, hypopnea index; RDI, respiratory disturbance index; RERA, respiratory effort related arousal; PLMS index, periodic leg movements in sleep index; Mean SaO2, mean oxygen saturation. NHP = narrow hart palate.

NHP + children had a mean pediatric AHI>1, while 43 (68.25%) NHP- had an AHI>1 ($p = 0.011$). The presence of an abnormal AHI was associated with a non-significant trend of lower sleep efficiency: 83.3 ± 14.5% versus 84.8% ± 12.4 ($p = 0.485$), with both groups having decreased sleep efficiency; with the NHP + having a significant decrease in stage-2 NREM sleep: 39.1% ± 10.8 versus 42.7% ± 9.7 ($p = 0.027$). The following two years PSG data are displayed in Table 2b, indicating that a high proportion of premature children still had both a narrow palate (53%) and AHI>1/hour (88.2%) at two years of age.

- *Relationship between NHP and developmental delays (DDST-II and Bayley−II)*: Table 3 shows the proportion of premature infants with developmental delays, as identified with the Denver-II and BSID-II at the follow-up assessments. When comparing groups 1(NHP+) and 2(NHP-), a higher proportion of group 1 infants had significant developmental delays, identified with all Denver-II items at all time points. Fig. 2 demonstrates the proportion of infants with Denver-II total score (ie, suspect delay). Regarding BSID-II, using 70 as cutoff value, a higher proportion of group 1 infants has a low psychomotor development index (PDI); however, the proportions with a low mental development index (MDI) displayed no difference.

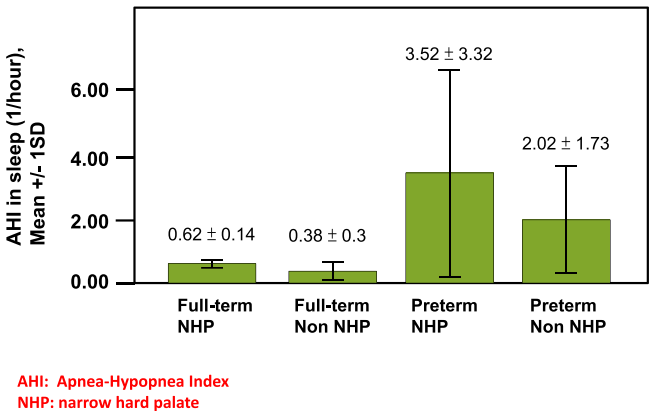

Fig. 1. Proportion of NHP of full-term and preterm infants at six months of corrected age. AHI: Apnea-Hypopnea index, NHP: narrow hard palate.

4. Discussion

The study-results showed that the presence at birth, and persistence overtime, of a NHP in premature infants is associated with persistence of obstructive-SDB and sleep problems (Tables 2a and 2b) and may thus worsen neurodevelopmental deficits (Table 3). Although, the sample size of our premature infant group is not very large, in this prospective study, we observed in our premature infants, how narrow hard palates, sleep problems, and neurodevelopment evolved and interacted during the first two

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Table 3
Relationship between NHP and developmental delays (DDST and Bayley–II).

Age	6 months				12 months			
	Total	NHP+	NHP–	p	Total	NHP+	NHP–	p
Denver–II								
suspect delay	14.8%	17.6%	1.5%	0.001	27.8%	34.3%	17.5%	0.02
Personal-social delay	2.5%	1.9%	1.5%	0.96	10.3%	10.5%	7.9%	0.65
Fine-motor adaptive delay	2.5%	3.7%	0.0%	0.15	5.1%	8.6%	1.6%	0.08
Language delay	2.9%	1.9%	0.0%	0.30	20.9%	28.6%	9.5%	0.01
Gross motor delay	12.3%	16.7%	1.5%	0.001	15.4%	16.2%	7.9%	0.17
BSID–II				p				p
MDI <70	6.4%	4.8%	5.4%	0.93	9.7%	8.2%	8.7%	0.91
PDI <70	19.1%	25.8%	2.7%	0.001	18.5%	24.6%	8.7%	0.021
Age	18 months				24 months			
	Total	NHP+	NHP–	p	Total	NHP+	NHP–	p
Denver–II								
suspect delay	28.3%	28.8%	25.4%	0.71	16.6%	19.5%	11.1%	0.22
Personal-social delay	8.1%	10.6%	3.4%	0.09	5.5%	9.1%	0.0%	0.02
Fine-motor adaptive delay	6.3%	9.6%	1.7%	0.06	5.5%	7.8%	02.2%	0.11
Language delay	23.8%	25.0%	18.6%	0.44	11.7%	10.4%	11.1%	0.86
Gross motor delay	10.8%	12.5%	8.5%	0.38	8.0%	11.7%	0.0%	0.01
BSID–II				p				p
MDI <70	20.0%	13.8%	13.3%	0.87	19.4%	18.2%	18.8%	0.95
PDI <70	7.3%	6.9%	0.0%	0.03	8.3%	9.1%	0.0%	0.01

NHP+(group 1): children with persistent presence of narrow palate till two years corrected age.
NHP–(group 2): children with continuous absence of narrow palate till two years corrected age.
Denver–II, Denver Developmental Screening Test–II; The definition of of Denver II Test: Items that can be completed by 75%–90% of children but are failed are called "cautions"; those that can be completed by 90% of children but are failed are called "delays". Normal: No delays and a maximum of 1 caution. Suspect delay: two or more Cautions and/or One or more Delays [28].
BSID–II, Bayley Scales of Infant Development–II; MDI, mental development index; PDI, psychomotor development index. The mean ± standard deviation (SD) of the standardization sample is 100 ± 15, and a score of less than 70, which is more than 2 SDs below the mean, is defined as a "significant delay" based on the BSID-II Mental and Motor scales [29].

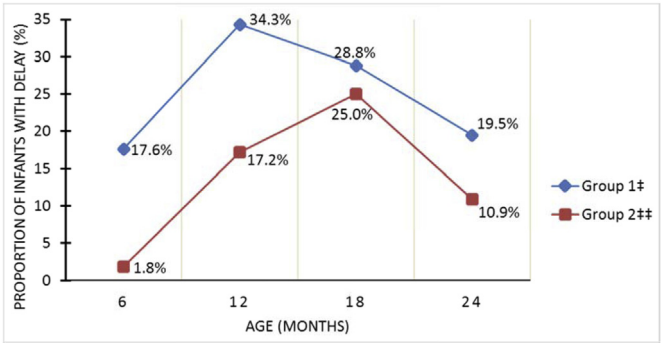

Fig. 2. The relationship between developmental delays (Denver-II: any delay) and NHP in premature infants. Group 1: Children with persistent presence of narrow hard palate [NHP+] till two years corrected age. Group 2: children with continuous absence of narrow palate [NHP–] till two years corrected age. NHP: narrow hard palate.

years of life. Compared to normal controls, premature infants had significantly higher amount of sleep disorder breathing, significantly higher frequency of abnormal orofacial anatomy [NHP], and more delays as shown in neuropsychometric testing. Our study indicates that premature infants with presence of NHP [NHP+] at birth, have more abnormal breathing during sleep, more sleep problems and more developmental delays when this clinical indicator of abnormal orofacial growth is still present at two years of age compared to findings obtained on premature infants without presence of such finding with aging.

Premature infants are known to have more developmental delay risks than full-term babies [20–23]. Previous studies in the recent past showed that sleep disturbances could lead to daytime impairment of neurocognitive functions and behavior during wakefulness. One of the factors that disturbs sleep on a chronic basis is obstructive-SDB: Not only the typical obstructive-apnea-and-hypopnea- syndrome, but also more subtle forms of SDB such as abnormal amount of "flow limitation" that has been associated with abnormal increased in upper-airway resistance when using esophageal manometry in nocturnal PSG [30,31]. Such subtle forms of SDB have also been associated with abnormal amount of mouth-breathing during sleep, also previously related to abnormal orofacial growth in children [30]. Abnormal orofacial anatomy has been related to abnormal breathing during sleep: Modest changes in the orofacial skeleton supporting the upper airway [UA] increase the risk of UA collapsibility during sleep as these changes decrease the size of the upper-airway lumen increasing the risks of upper airway partial or complete collapse during sleep [10,14]. Sleep per se is a more vulnerable state than wakefulness due to the reduction or elimination of reflexes involved in maintaining normal airway patency [10,14,17–19,32]. The more premature the infant is at birth, the greater the risk of generalized hypotonia at birth (including hypotonia of upper-airway muscles); and the less time the fetus also has training specific brain-stem reflexes [14]. It is during the last three months of pregnancy that the fetus organized and "train" reflexes involved in the normal functioning of activities such as sucking, swallowing, chewing, and nasal breathing that have to be appropriate at birth [14]. These functions have been shown to play an active role in the growth of the face through osteochondral ossification involving the intermaxillary cartilage [9,14]. A persistent NHP over-time has been shown to be one of the clinical indicators of abnormal orofacial development over-time, and an "indicator" of maxillary growth that can be studied with aging [10,14].

The results of our study showed that NHP + premature infants have lower gestational age, more short-term intubation and more difficulty feeding at birth than NHP- premature group (Table 1) confirming prior information [9,14]. The persistence of NHP after birth, is an indicator of persistence of abnormal orofacial growth;

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and this persistence of abnormal orofacial growth increase the risk of on the collapsibility of the UA during sleep, leading to more SDB-related sleep problems and secondary impacting the normal neurodevelopmental functioning where sleep is critical. Even if we properly understand the development of abnormal orofacial structures in premature infants and the associated risks of collapsibility of UA during sleep, many questions remain unanswered, such as: can the fundamental functions of sucking-swallowing-chewing and nasal breathing progressively become sufficient over time to stimulate orofacial growth and allow for normal sleep and the improvement of cognitive functions? Are there stages when infants will not spontaneously be able to induce such normal evolution, and will a persistence of the abnormal chain of events lead to an increase in obvious behavioral and cognitive problems with aging? Are clinical approaches available for enhancing normal orofacial development and stopping the series of known vicious cycles? Some of these questions may be considered through longer-term follow-up of our premature cohort, but further studies are clearly required, as our study is only reporting longitudinal findings to two years.

5. Conclusion

Our data have shown the following: Premature infants present with a NHP, more SDB-related sleep problems, and more neurodevelopmental deficits than full-term infants and premature infants without NHP. Until two years old, premature infants with continuous presence of NHP have more SDB-related sleep problems and more neurodevelopmental deficits than those without. These findings are in support our hypothesis that a NHP in premature infants participates in the development of SDB-related sleep problems and neurodevelopmental delays.

CRediT authorship contribution statement

Yu-Shu Huang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Jen-Fu Hsu:** Data curation, Project administration. **Teresa Paiva:** Conceptualization. **Wei-Chih Chin:** Writing - original draft, Writing - review & editing. **I-Chia Chen:** Data curation, Project administration. **Christian Guilleminault:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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Conflicts of interest

All authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.015.

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