Sleep Medicine 48 (2018) 93–100

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Phenotypes of sleep-disordered breathing symptoms to two years of age based on age of onset and duration of symptoms

Muna Kamal [a, 1], Sukhpreet K. Tamana [a, 1], Lisa Smithson [a, 1], Linda Ding [a], Amanda Lau [a], Joyce Chikuma [a], Jennifer Mariasine [a], Diana L. Lefebvre [b], Padmaja Subbarao [c, d], Allan B. Becker [e], Stuart E. Turvey [f], Malcolm R. Sears [b], Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators[2], Jacqueline Pei [g], Piush J. Mandhane [a, *]

[a] Department of Pediatrics, University of Alberta, Alberta, Canada
[b] Division of Respirology, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[c] Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada
[d] Respiratory Medicine, Hospital for Sick Children, Canada
[e] Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada
[f] Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada
[g] Department of Educational Psychology, University of Alberta, Alberta, Canada

ARTICLE INFO

Article history:
Received 26 September 2017
Received in revised form
23 March 2018
Accepted 4 April 2018
Available online 3 May 2018

Keywords:
Pediatric
Sleep-disordered breathing
Birth cohort
Population-representative

ABSTRACT

Objective: Childhood sleep-disordered breathing (SDB) symptoms may comprise multiple phenotypes depending on craniofacial anatomy, tonsil and adenoid growth, body habitus, and rhinitis symptoms. The primary objective of this study is to identify and characterize the different SDB phenotypes to two years of age.

Methods: Data from 770 infants in the Edmonton sub-cohort of the Canadian Healthy Infant Longitudinal Study (CHILD) were analyzed to identify SDB phenotypes based on age of onset and duration of symptoms. Parents completed the 22-item sleep-related breathing disorder (SRBD) scale. Children with a SRBD ratio greater than 0.33 were considered positive for SDB at each quarterly assessment between three months and two years. The STATA Proc trajectory extension identified SDB phenotypes based on their age of onset and duration of symptoms and attributed the percentage chance of a participant being assigned to each phenotype. Multivariate linear regression identified factors associated with increased risk of being assigned to each SDB phenotype.

Results: Trajectory analysis identified four phenotypes: no SDB (65.7%), early-onset SDB (15.7%) with peak symptoms at nine months, late-onset SDB (14.2%) with peak symptoms at 18 months, and persistent SDB (5.3%) with symptoms from 3 to 24 months. Rhinitis was associated with all three SDB symptom trajectories ($p < 0.05$). Children with gastroesophageal reflux disease presented with early ($p = 0.03$) and late SDB ($p < 0.001$). Maternal obstructive sleep apnea syndrome (OSAS) was associated with persistent ($p = 0.01$) and late SDB ($p < 0.001$). Atopy (positive skin prick test at one year) was associated with persistent SDB ($p = 0.04$). Infants born prior to 36.5 weeks gestational age were more likely to present with late SDB ($p = 0.03$).

Conclusion: Childhood SDB symptoms, rather than being a homogenous disorder, may comprise multiple overlapping phenotypes each with unique risk factors.

1. Introduction

Sleep disordered breathing (SDB), which may range from habitual snoring to obstructive sleep apnea, affects up to 10% of children, with a peak prevalence between two and eight years of

* Corresponding author. 1050 Research Transition Facility, 8308-114 Street, Edmonton, Alberta, T6G 2V2, Canada.
E-mail address: mandhane@ualberta.ca (P.J. Mandhane).
[1] These authors contributed equally to this manuscript.
[2] A complete list of active investigators in the CHILD study is provided in the Supplementary Material.

https://doi.org/10.1016/j.sleep.2018.04.008
1389-9457/

age [1–3]. An increased risk of snoring has been observed among first-born children [4] and children of mothers who smoked during pregnancy [5], while children who were breastfed for more than two months were less likely to develop SDB [6]. Several studies have shown that SDB is more common among atopic children [7,8] although one study has reported that inner-city snoring children referred for a laboratory sleep study (polysomnography; PSG) were less likely to have asthma [9]. Self-reported proximity to road traffic was associated with self-reported habitual snoring in preschool children although the strength of the association was reduced when controlling for single-parent families and socioeconomic deprivation [8].

We present findings from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study where we sought to determine patterns of SDB symptoms (SDB phenotypes) based on age of onset and duration of symptoms. Childhood SDB may comprise multiple overlapping phenotypes depending on a child's craniofacial anatomy, tonsil and adenoid growth, body habitus, and presence of rhinitis symptoms [10]. We hypothesized that the different symptom phenotypes may be distinguished by age of onset and duration of symptoms.

Each phenotype may be associated with different genetics (eg, parental history of SDB) and environmental exposures. Increased lymph-adenoid tissue can be triggered by respiratory syncytial virus [11], environmental tobacco smoke [12,13], and environmental pollutants [14]. We have identified individual factors (eg, atopy, body mass index [BMI], gestational age [GA]) and environmental exposures (eg, breast-feeding, socioeconomic status (SES), daycare attendance) associated with the development of each SDB symptom.

2. Methods

2.1. Study participants

CHILD is a longitudinal birth cohort study designed to assess the influence of gene–environment interactions on the development of allergy and asthma. CHILD Edmonton families ($N = 822$) participated in an add-on study examining the longitudinal relationship between sleep and neurodevelopment. The sleep-related breathing disorder (SRBD) scale, the Brief Infant Sleep questionnaire (BISQ), parental history of obstructive sleep apnea syndrome (OSAS) based on the global sleep assessment questionnaire (GSAQ), and home PSG were collected specifically for the ancillary study. Mothers aged 18 years and over were recruited during the second or third trimester of pregnancy, and seen at delivery, when their children were 3–4 months of age, and then annually. Parents completed questionnaires regarding their children's sleep and SDB symptoms every three months. Family and child characteristics (ie, SES, ethnicity), maternal and infant nutrition, and maternal stress were assessed longitudinally throughout the study. Informed consent was obtained from all mothers and from consenting fathers. Approval for this research study was obtained from the Research Ethics Board (REB) at the University of Alberta (Pro00002099).

2.2. Study variables

2.2.1. SDB symptom trajectories (primary outcome variable)

The 22-item item SRBD scale, based on the pediatric sleep questionnaire (PSQ), was completed quarterly by parents from three months to two years of age. The SBRD scale uses the 22-item yes/no SBRD [15] questionnaire which includes items on snoring, excessive daytime sleepiness, and attention deficit hyperactivity disorder (ADHD) symptoms. The SRBD ratio is obtained by dividing the sum of all 'yes' responses by the total number of non-missing items (yes or no). Infants with an SRBD ratio greater than 0.33 were considered to have SDB at that quarterly assessment [15].

The STATA Proc Traj [16,17] extension uses a finite mixture model to simultaneously estimate multiple longitudinal trajectories using maximum likelihood. We used STATA Traj (05/2017) [18,19] (logistic) to identify and assign phenotypes to each child based on a positive or negative SRBD at each time point between three months and two years of age. Participants had to have at least one SRBD ratio to be included in the trajectory analysis. Linear, quadratic, and cubic trajectory models were considered for model development [20]. The optimal number of trajectories was selected based on the lowest Bayesian Information Criteria (BIC). The STATA Traj plug-in provides the probability of an individual being included in each of the SDB trajectories (0–100%). Participants are also assigned to a trajectory based upon the group trajectory for which they have the highest probability of membership.

2.2.2. Atopy (primary exposure variable)

Atopy was assessed at one year of age using skin-prick testing (SPT) with highly standardized ALK allergens. Atopy was defined as having at least one positive SPT (wheal $\geq$2 mm greater than negative control) to any of the tested allergens at age one year.

2.2.3. Assessment of potential confounding variables previously associated with SDB

Details of all the confounding variables are available in the Supplementary Material.

2.2.4. Daycare/Dayhome

Parents were asked whether their child regularly went to a location away from home (eg, daycare, babysitter, activities with mom) for at least 1 h per day on average, or at least 7 h total in a week at 3, 6, 12, 18, and 24 months.

2.2.5. Rhinitis symptoms

Infants were classified as having rhinitis at 3, 6, 9, and 12 months of age if parents reported yes to at least one of the following questions: (1) dry mouth during the day, (2) dry mouth on waking up in the morning, (3) child has a stuffy nose that is congested at night, or (4) mouth breathes most of the time.

2.2.6. Rhinitis treatment

Infants were classified as having rhinitis treatment at 3, 6, 12, 18, and 24 months of age if they were treated with any of the following nasal steroid or sprays: fluticasone propionate, fluticasone furoate, mometasone furoate, budesonide, beclomethasone, ciclesonide, flunisolide or polyethylene glycol/propylene glycol.

2.2.7. Gastroesophageal reflux disease

Infants were classified as having gastroesophageal reflux disease (GERD) if they were treated with any of the following medications: ranitidine, omeprazole, lansoprazole, or pantoprazole at 3, 6, 12, 18, and 24 months of age.

2.2.8. Treatment with inhaled corticosteroids

Infants were classified as being treated with inhaled corticosteroids if they were treated with any of the following medications: fluticasone propionate, beclomethasone, fluticasone propionate, and salmeterol, at 3, 6, 12, 18, and 24 months of age.

Apnea Hypopnea Index: A single-night home PSG study (NOX-T3) was completed at 12 months of age [21]. Scoring was completed by Sleep Strategies using a modified AASM pediatric scoring rubric [22] based on the channels available (Supplementary Material: Appendix 1).