https://doi.org/10.5664/jcsm.9636

JCSM | Journal of Clinical Sleep Medicine

REM: A PUBLICATION FOR RESIDENTS AND FELLOWS

IMAGES: Sleep-disordered breathing and hypoventilation in a child with obesity and hypothalamic dysfunction

Radhika Ghosh, MD[1]; Manisha Malik, MD[1]; Tanicia C. Daley, MD[2]; Ajay S. Kasi, MD[1]

[1]*Division of Pediatric Pulmonology and Sleep Medicine, Emory University, Children's Healthcare of Atlanta, Atlanta, Georgia;* [2]*Division of Pediatric Endocrinology, Emory University, Children's Healthcare of Atlanta, Atlanta, Georgia*

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare and potentially lethal disorder of respiratory control, autonomic, and hypothalamic dysfunction of unknown etiology. We report a 15-year-old girl with ROHHAD who developed hyperphagia and rapid weight gain of 16 kg between 2.5 and 4 years of age and cardiorespiratory arrest at 4 years. Initial polysomnography showed central sleep apnea and severe oxygen desaturations without hypoventilation. Mild obstructive sleep apnea and intermittent hypoxemia were identified at 4.5 years, following which nocturnal bilevel positive airway pressure therapy was initiated. At 6 years, she developed sleep-related hypoventilation, and subsequent polysomnograms continued to show obstructive sleep apnea and hypoventilation requiring bilevel positive airway pressure. Clinicians interpreting polysomnograms should become familiar with the evolution of sleep-disordered breathing in ROHHAD and that hypoventilation may develop over time. Our case highlights the importance of serial polysomnography in patients with ROHHAD and optimal ventilatory management.

Keywords: ROHHAD, noninvasive positive pressure ventilation, hypoventilation

Citation: Ghosh R, Malik M, Daley TC, Kasi AS. Images: Sleep-disordered breathing and hypoventilation in a child with obesity and hypothalamic dysfunction. *J Clin Sleep Med*. 2022;18(1):339–342.

INTRODUCTION

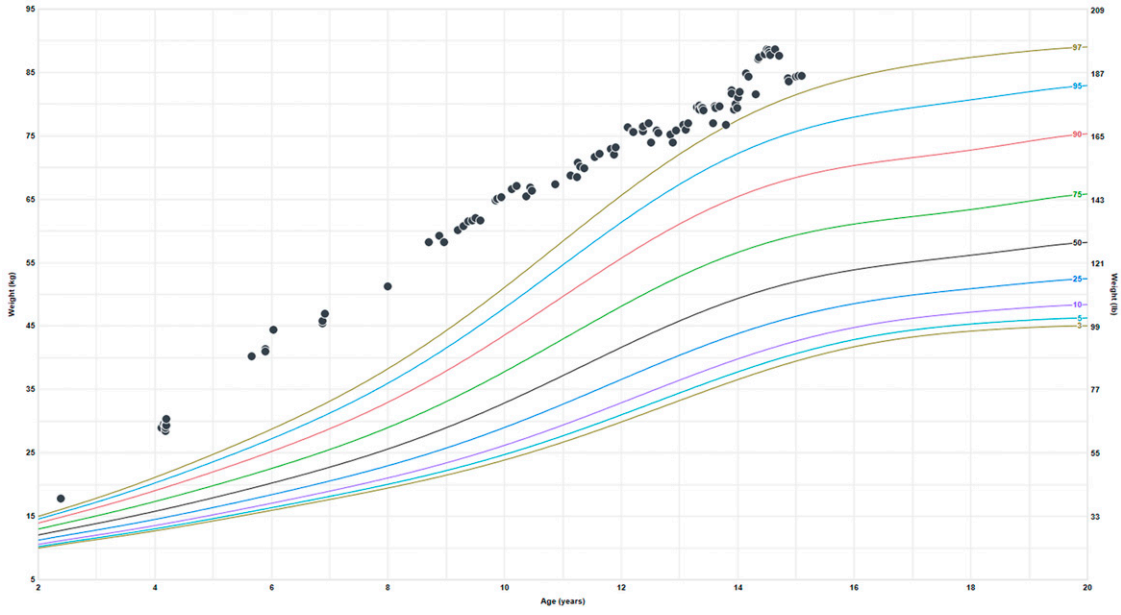
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare life-threatening disorder of respiratory control, autonomic, and hypothalamic dysregulation of unclear etiology.[1] Patients with ROHHAD present in childhood with rapid weight gain (20–30 lb over 3–12 months), followed by features of hypothalamic dysfunction (hypothyroidism, adrenal insufficiency, growth hormone deficiency, altered pubertal onset, disordered water balance), hypoventilation, and autonomic dysregulation (abnormalities in heart rate, temperature, blood pressure, gastrointestinal motility, and neural crest tumors).[2–4] Respiratory manifestations include obstructive sleep apnea (OSA), hypoventilation, reduced carbon dioxide ventilatory response, central pauses and desaturations during wakefulness, and cardiorespiratory arrest.[1,5–7] Children with ROHHAD may initially present with OSA and develop hypoventilation at a later age. Unrecognized or inadequately treated hypoventilation can be fatal with increased risk of cardiorespiratory arrest (up to 60% patients).[1,7,8] Therefore, patients require assisted ventilation that may range from sleep-only to continuous assisted ventilation delivered by noninvasive positive pressure ventilation (NPPV) or mechanical ventilation via tracheostomy.[1,8] ROHHAD is diagnosed based on clinical features. Due to the variable ages of clinical presentation, evolving phenotype, and potentially fatal outcomes, early recognition and treatment is vital for ensuring optimal outcome.[1,5]

We report a 15-year-old girl with ROHHAD using NPPV during sleep who presented in early childhood with rapid weight gain followed by cardiorespiratory failure and central sleep apnea.

REPORT OF CASE

Our patient, now 15 years of age, developed hyperphagia and weight gain of approximately 16 kg between 2.5 and 4 years of age following an uncomplicated infancy (**Figure 1**). At 4 years, weight, and body mass index were 30.3 kg and 26.3 kg/m^2 (> 99th percentile), respectively. She was hospitalized with cardiorespiratory failure when she developed apnea and bradycardia requiring resuscitation and mechanical ventilation. Arterial blood gas showed pH of 7.18 and partial pressure of carbon dioxide (PCO_2) of 79 mm Hg. Chest radiograph showed patchy right middle and left lower lobe airspace densities. Labs showed hyponatremia (122 mmol/L), hypokalemia (3.2 mmol/L), hypochloremia (84 mmol/L), and elevated serum bicarbonate (33 mmol/L). Electrocardiogram, echocardiogram, and brain magnetic resonance imaging were normal. The cardiorespiratory failure was attributed to a respiratory infection, and she received intravenous antibiotics. She was subsequently extubated but continued to require oxygen during sleep. Capillary blood gas showed improved PCO_2 of 41 mm Hg. Polysomnography showed central sleep apnea with central apnea-hypopnea index of 12 events/h. There was no OSA. The baseline oxygen saturation was 98%, with nadir to 53% associated with central apneas requiring initiation of supplemental oxygen. End-tidal carbon dioxide ranged from 21 to 45 mm Hg. Capillary blood

Figure 1—Growth chart showing weight-for-age percentiles with rapid-onset weight gain at 2.5 years of age.

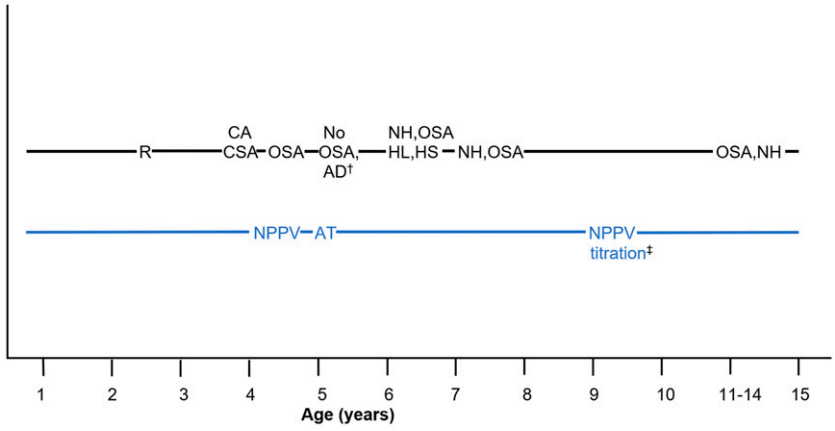


Source: Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. http://www.cdc.gov/growthcharts/. May 30, 2000.

gas obtained in the morning after the polysomnography showed pH of 7.45 and PCO_2 of 37 mm Hg. Evaluation by an endocrinology established the following diagnoses: diabetes insipidus, adrenal insufficiency, and hypothyroidism requiring hormone replacement with hydrocortisone, levothyroxine, and desmopressin. Based on the constellation of clinical features, she was clinically diagnosed with ROHHAD.

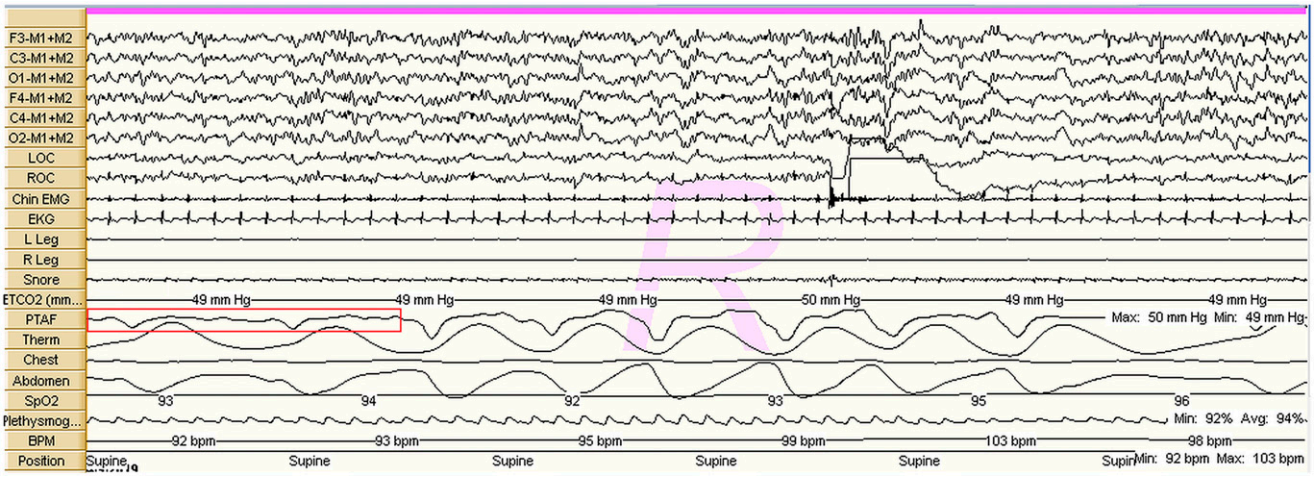
At 4.5 years, polysomnography showed mild OSA, fewer central apneas (central apnea-hypopnea index 1.2 events/h), baseline oxygen saturation of 97% with nadir to 79%, and end-tidal CO_2 between 30 and 56 mm Hg. Capillary blood gas was performed a few days before the polysomnography and showed pH of 7.35 and PCO_2 of 41 mm Hg. Based on the diagnosis of ROHHAD and prior cardiorespiratory arrest, nocturnal bilevel

Figure 2—Onset of clinical features.



Blue line represents interventions such as adenotonsillectomy, noninvasive positive pressure ventilation, and noninvasive positive pressure ventilation titration. †Thermal dysregulation, strabismus, and gastrointestinal dysmotility. ‡Polysomnography at 9 and 10 years of age were performed only as bilevel positive airway pressure titration without a diagnostic portion. AD = autonomic dysfunction, AT = adenotonsillectomy, CA = cardiorespiratory arrest, CSA = central sleep apnea, HL = hyperlipidemia, HS = hepatic steatosis, NH = nocturnal hypoventilation, NPPV = noninvasive positive pressure ventilation, OSA = obstructive sleep apnea, R = rapid-onset obesity.

Figure 3—Diagnostic portion of split-night polysomnography during rapid eye movement sleep performed at 13 years of age showing obstructive sleep apnea and mild hypoventilation.



Electroencephalogram derivations = F3-M1+M2, F4-M1+M2, C3-M1+M2, C4-M1+M2, O1-M1+M2, O2-M1+M2 (F = frontal, C = central, O = occipital, M = mastoid). BPM = heart rate in beats per minute, Chest and Abdomen = piezo-electric respiratory belts for chest and abdomen, respectively, EKG = electrocardiogram, EMG = electromyography, ETCO2 = end-tidal carbon dioxide, L leg and R leg = electromyogram of left and right leg, respectively, LOC = left electrooculogram, Plethysmog = plethysmography, PTAF = pressure transducer airflow, ROC = right electrooculogram, SpO2 = oxygen saturation, Therm = thermistor.

positive airway pressure in spontaneous-timed mode was initiated. Following adenotonsillectomy at 5 years, the diagnostic portion of split night polysomnography showed resolved OSA, central apneas (central apnea-hypopnea index 3.5 events/h), baseline oxygen saturation of 97% and nadir to 84% associated with central apneas, and no hypoventilation. At 6 years, she developed sleep-related hypoventilation (average end-tidal CO_2 55 mm Hg) and mild OSA (**Figure 2**). Subsequent polysomnograms continued to show mild to moderate OSA with hypoventilation and bilevel positive airway pressure was titrated[9] (**Figure 3** and **Figure S1** and **Figure S2** in the supplemental material). *PHOX2B* (paired-like homeobox2B) gene sequence analysis was normal. Serial echocardiograms, Holter monitor studies, and imaging for neural crest tumors were normal.

DISCUSSION

We present the case of a 15-year-old girl with ROHHAD using NPPV during sleep who presented with rapid-onset obesity, cardiorespiratory failure, central sleep apnea with severe desaturations, followed by later manifestation of OSA and hypoventilation. Children with ROHHAD may develop OSA early in the course and eventually develop hypoventilation.[4,7] Although our patient had elevated PCO_2 upon presentation with cardiorespiratory failure, this was transient, and sleep-related hypoventilation was identified at 6 years of age. Therefore, serial polysomnograms should be performed to identify hypoventilation and titrate NPPV.[7]

ROHHAD is a rare disease, and approximately 160 cases have been reported worldwide. The prevalence of ROHHAD is unknown.[5,10] The underlying etiology of ROHHAD is unknown, and possible genetic abnormalities, epigenetic changes, autoimmune, and paraneoplastic syndrome have been suggested as potential etiologies.[3,4] Children with ROHHAD are apparently normal until presentation after 1.5 years of age with rapid-onset obesity followed by hypothalamic dysfunction, autonomic dysfunction, and hypoventilation at median ages of 3, 3.6, and 6–7 years, respectively.[1,3,7,8] Other clinical features associated with ROHHAD include behavioral disorders, seizures, developmental disorders such as developmental delay and developmental regression, and recurrent respiratory infections.[1,10] However, there is wide variation in the age and interval between onset of different clinical features and hypoventilation. Other diagnostic challenges include the growing prevalence of childhood obesity, lack of a confirmatory diagnostic test, and later onset of hypoventilation.[2,3] Since the diagnosis of ROHHAD is based on clinical criteria, evaluations in patients with suspected ROHHAD include comprehensive respiratory physiologic assessments during sleep and wakefulness, magnetic resonance imaging or computed tomographic scan of the chest and abdomen for neural crest tumors, brain imaging, genetic studies for diseases with overlapping features such as congenital central hypoventilation syndrome and Prader-Willi syndrome, and evaluation by a pediatric endocrinologist.[1,3] Once the diagnosis of ROHHAD is established, multispecialty collaborative care with a pediatric pulmonologist, sleep medicine physician, cardiologist, endocrinologist, psychiatrist, and neurologist may be beneficial.[4] Unless promptly diagnosed and adequately treated, cardiorespiratory arrest and/or death can occur.[1,7,8] In a systematic review on ROHHAD, Lee et al[10] reported 12 deaths (9 due to sudden cardiac arrest) in 110 patients.

Although some patients with severe ROHHAD phenotypes require continuous assisted ventilation, our patient did not develop hypoventilation during wakefulness and uses NPPV only during sleep.[1,4] Serial monitoring in ROHHAD includes respiratory assessments during sleep and wakefulness, Holter monitoring for cardiac dysrhythmia, imaging studies for neural crest tumors, and multispecialty care.[1,4] Our case is limited by the lack of weight data between 2.5 and 4 years of age, and the rapid-onset of weight gain could not be reliably established. Our case highlights the spectrum and evolution of sleep-disordered breathing in ROHHAD and emphasizes the importance of serial polysomnography and management with NPPV.

ABBREVIATIONS

NPPV, noninvasive positive pressure ventilation
OSA, obstructive sleep apnea
PCO_2, partial pressure of carbon dioxide
ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation

REFERENCES

1. Ize-Ludlow D, Gray JA, Sperling MA, et al. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation presenting in childhood. *Pediatrics.* 2007;120(1):e179–e188.
2. Barclay SF, Rand CM, Nguyen L, et al. ROHHAD and Prader-Willi syndrome (PWS): clinical and genetic comparison. *Orphanet J Rare Dis.* 2018; 13(1):124.
3. Patwari PP, Wolfe LF. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation: review and update. *Curr Opin Pediatr.* 2014;26(4):487–492.
4. Patwari PP, Rand CM, Berry-Kravis EM, Ize-Ludlow D, Weese-Mayer DE. Monozygotic twins discordant for ROHHAD phenotype. *Pediatrics.* 2011;128(3): e711–e715.
5. Selvadurai S, Benzon D, Voutsas G, et al. Sleep-disordered breathing, respiratory patterns during wakefulness and functional capacity in pediatric patients with rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation syndrome. *Pediatr Pulmonol.* 2021;56(2):479–485.
6. Carroll MS, Patwari PP, Kenny AS, Brogadir CD, Stewart TM, Weese-Mayer DE. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD): Response to ventilatory challenges. *Pediatr Pulmonol.* 2015;50(12):1336–1345.
7. Reppucci D, Hamilton J, Yeh EA, Katz S, Al-Saleh S, Narang I. ROHHAD syndrome and evolution of sleep disordered breathing. *Orphanet J Rare Dis.* 2016;11(1):106.
8. Chew HB, Ngu LH, Keng WT. Rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD): a case with additional features and review of the literature. *BMJ Case Rep.* 2011; March 1, 2011: bcr0220102706.
9. Berry RB, Chediak A, Brown LK, et al. NPPV Titration Task Force of the American Academy of Sleep Medicine. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. *J Clin Sleep Med.* 2010;6(5):491–509.
10. Lee JM, Shin J, Kim S, et al. Rapid-Onset Obesity with Hypoventilation, Hypothalamic, Autonomic Dysregulation, and Neuroendocrine tumors (ROHHADNET) syndrome: a systematic review. *BioMed Res Int.* 2018;2018: 1250721.

ACKNOWLEDGMENT

The authors thank the patient and her mother for their participation in this report.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February 23, 2021
Submitted in final revised form August 4, 2021
Accepted for publication August 19, 2021
Address correspondence to: Radhika Ghosh, MD, Fellow in Pediatric Pulmonology, Emory University School of Medicine, 1400 Tullie Road NE, Atlanta, GA 30329; Tel: (404) 785-5437; Fax: (404) 785-9087; Email: rnghosh@emory.edu

DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at Children's Healthcare of Atlanta at Egleston Hospital. The authors report no conflicts of interest.