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CASE REPORTS

A novel case of central hypoventilation syndrome or just heavy breathing?

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With the growing prevalence of obesity in the pediatric population, reports of its severe complications are increasing. Obesity hypoventilation syndrome is an uncommon disorder in children with altered respiratory mechanics, sleep-disordered breathing, and impaired ventilatory responses leading to persistent hypercapnia. Presentation is varied, and children may remain relatively asymptomatic until challenged with a respiratory infection, when they may present with acute respiratory failure. With increasing use of genetic testing in pediatric patients, our knowledge of potential contributors to hypoventilation syndromes is growing. Although mutations in the paired-like homeobox 2B gene are known to be causative of congenital central hypoventilation syndrome, other genes may also contribute to hypoventilation phenotypes. We report one of the youngest reported patients with obesity hypoventilation syndrome in pediatrics, with a proposed congenital predisposition for central hypoventilation derived from a deletion in the brain-derived neurotrophic factor gene.

Keywords: obesity hypoventilation syndrome, congenital hypoventilation syndromes, nocturnal hypoventilation

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INTRODUCTION

Cardiopulmonary compromise in patients with obesity has been studied for decades. In 1959, the first reported case in pediatrics was published. A 6-year-old child with obesity, presenting with dyspnea, somnolence, cyanosis, and congestive heart failure, with no intrinsic pulmonary disease, died after a prolonged hospitalization with cyanosis and apnea.[1] Altered ventilatory responsiveness during sleep and wakefulness is now a well-described respiratory complication of obesity, although its mechanism is not well understood.

In pediatrics, obesity hypoventilation syndrome (OHS) is defined by the combination of obesity (body mass index [BMI] > 30 kg/m^2, BMI > 95th percentile for age and sex or weight > 95th percentile for age and sex), daytime hypercapnia (P_aCO_2 > 45 mm Hg), and absence of known neurological, cardiac, or pulmonary causes of hypoventilation.[2] Clinical presentation is varied and may include patients who are asymptomatic and those presenting with sleep-disordered breathing, hypersomnolence, heart failure, or even acute respiratory failure.

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant disorder secondary to mutations in the paired-like homeobox 2B (*PHOX2B*) gene, categorized into polyalanine repeat expansion mutations and nonpolyalanine repeat expansion mutations. It was first described in 1970, and since then more than 1,000 patients with CCHS have been identified, with an estimated incidence of 1 in 148,000.[3,4] CCHS is characterized by alveolar hypoventilation stemming from impaired response to hypercarbia and hypoxemia, and it has been associated with anatomic and physiologic dysregulation of the autonomic nervous system, including Hirschsprung's disease, tumors of neural crest origin, breath-holding spells, and lack of physiologic responsiveness to exercise.[3] Although mutations in *PHOX2B* are known to be the cause of CCHS, it remains plausible that other genetic mutations may lead to impaired ventilatory responsiveness, and thus extended CCHS panels include a variety of other candidate genes, including *ASCL1, BMP2, EDN3, PHOX2A, RET,* and *BDNF.*

REPORT OF CASE

A 4-year-old boy presented with cyanosis and decreased level of consciousness in the context of a 2-day history of cough and fever. His past medical history was remarkable for obesity, mild developmental delay, and adenotonsillectomy that was performed at age 3 years after clinical diagnosis of obstructive sleep apnea. Weight for age and BMI were greater than 3 standard deviations above the median, with a BMI of 47.5 kg/m^2. Previous genetic testing had revealed a maternally inherited deletion of 1.543 Mbs in chromosome region 11p14.1, Arr[hg19]11p14.1 (27,623,610-29,166,110)x1 that included the following OMIM genes: *BDNF-AS, BDNF, KIF18A,* and *MIR610.* Maternal inheritance of the abnormality was discovered after parental genetic testing was pursued to aid in the interpretation of his initial microarray that had identified a copy number variant of uncertain significance.

The patient presented in the evening to a community hospital secondary to a decreased level of consciousness with a 2-day

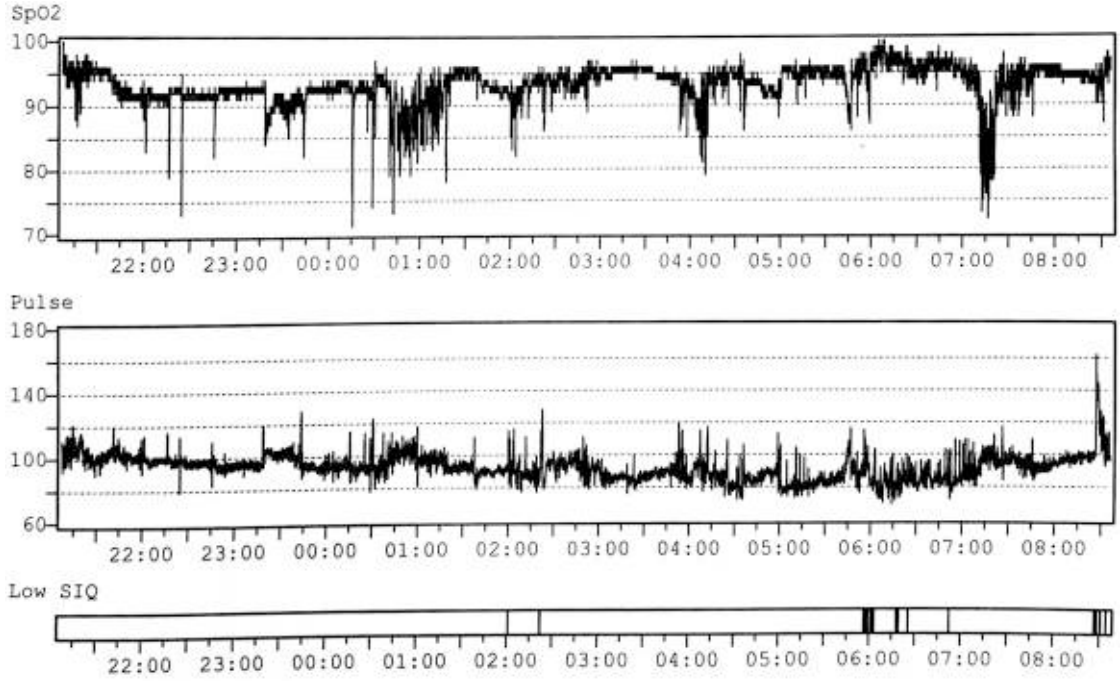
history of fever and cough. He awoke from a 3-hour nap after rolling off the couch and was noted to be confused, unsteady, and cyanotic. He was cyanotic at triage with tachypnea, but he had no other signs of increased work of breathing. He was hypoxemic, with an oxygen saturation in the 70s (%), with an initial venous blood gas revealing pH 7.20, pCO_2 90 mm Hg, and HCO_3 35 mmol/L.

The patient was transferred to the pediatric intensive care unit of a nearby tertiary care hospital for acute hypercarbic respiratory failure. He was empirically treated with ceftriaxone and azithromycin. Viral testing was positive for respiratory syncytial virus subgroup A. The pediatric intensive care unit team noted considerable difficulty ventilating the patient and in particular noted worsening hypercarbia with any attempts to wean his rate or inspiratory pressures. Bronchoscopy revealed normal airway anatomy. On day 8 of the pediatric intensive care unit admission he self-extubated and, given adequate oxygenation, without significant work of breathing, he was placed on a high-flow nasal cannula with supplemental oxygen of 40%. He was gradually weaned to room air over the following 72 hours and was discharged home off all respiratory support. His last capillary blood gas before discharge was done less than 8 hours post extubation while on the high-flow nasal cannula and showed a pH 7.48, pCO_2 49, and HCO_3 38.

Six months later, the patient presented to a community hospital. He had been well the day before but awoke from sleep groggy and requested his "puffers." His parents noted perioral cyanosis and found him difficult to rouse, which prompted them to call the emergency medical services. A venous blood gas in the community hospital showed hypoventilation and pH 7.23, pCO2 81 mm Hg, and HCO3 38 mmol/L. He was readmitted to the pediatric intensive care unit and started on bilevel positive airway pressure (BPAP). He was treated empirically with ceftriaxone. No infectious etiology was determined for this admission. Within 3–4 days of his initial presentation, his parents reported that he was back to his normal baseline. Although the patient clinically tolerated a wean off all respiratory supports, blood gases showed a persistent high pCO_2 during the day at 50–60 mm Hg, with a compensated normal pH. There was a documented episode of cyanosis with activity several days after coming off all acute respiratory support, and after more than a week off of respiratory support, a 6-minute walk test could not be completed because of significant desaturation events. Overnight oximetry (**Figure 1**) and transcutaneous CO_2 recording (**Figure 2**) performed more than 1 month after this presentation showed low baseline saturations, clusters of desaturation suggestive of obstructive sleep apnea, and nocturnal hypoventilation.

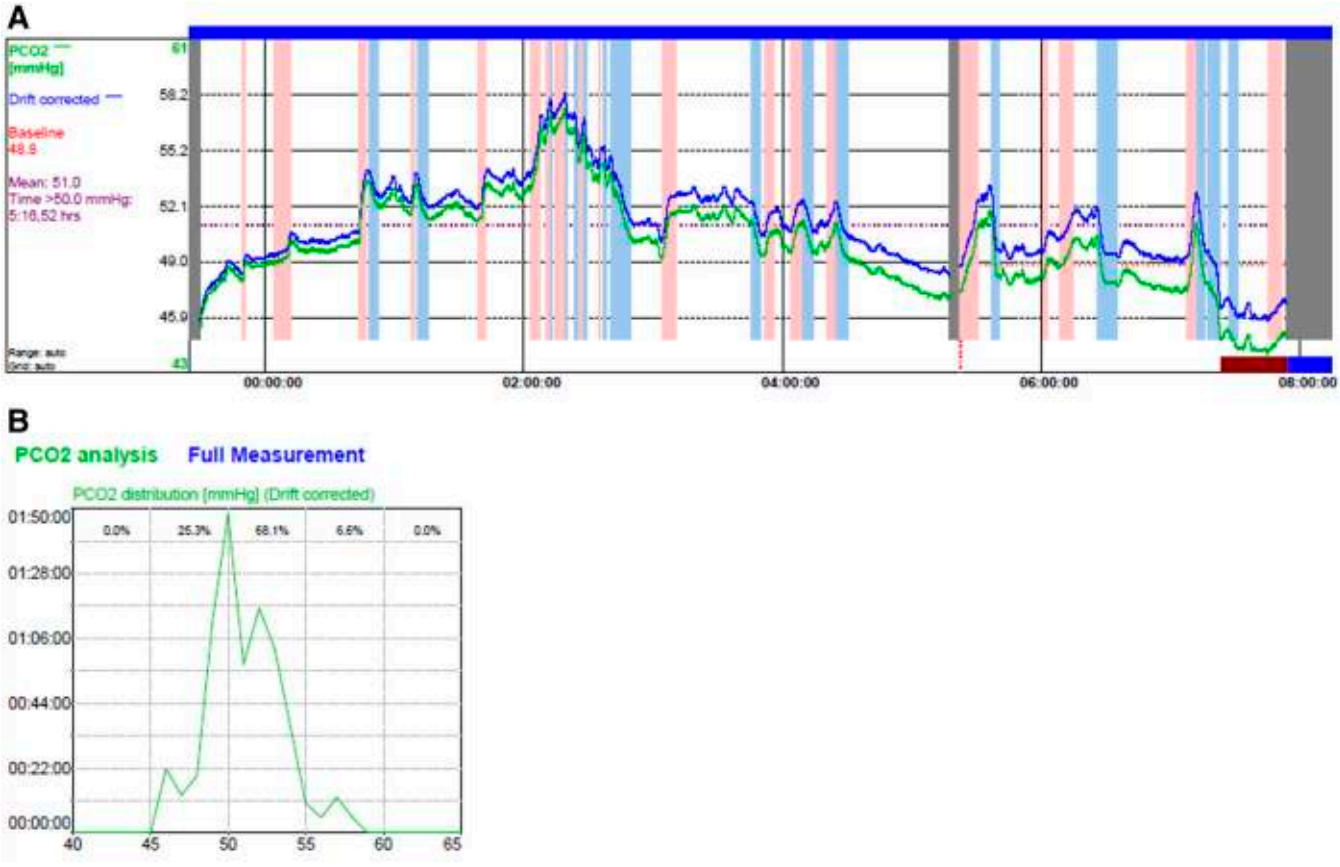
An extensive workup was conducted during the course of the patient's 2 admissions. His head magnetic resonance imaging was normal. Chest computed tomography showed dependent symmetric volume loss, which could be consistent with atelectasis vs resolving pneumonia. An echocardiogram showed no evidence of pulmonary hypertension, and the Holter monitor was normal. An endocrine workup including pituitary function, cortisol, prolactin, and thyroid function was normal, aside from evidence of insulin resistance. There was no polycythemia. Abdominal ultrasound and urine homovanillic acid and vanillylmandelic acid (HVA/VMA) were normal. He had no clinical signs or symptoms of autonomic dysfunction including a normal ophthalmologic examination. Genetic testing for congenital central hypoventilation was negative for a

Figure 1—Overnight oximetry conducted on room air.



Recording time: 11 hours, 28 minutes. Mean SpO_2: 93.2%. Time SpO_2 < 90%: 49 minutes, 12 seconds (7.1%). Longest continuous desaturation ≤ 89%: 2 minutes, 50 seconds. Desaturation index (4%): 16.1 events/h.

Figure 2—Transcutaneous CO_2.



(A) Transcutaneous CO_2 vs time graph. **(B)** Drift corrected transcutaneous CO_2 distribution. Mean: 51.0 mm Hg. Maximum: 58.3 mm Hg. Time > 50.0 mm Hg: 5 hours, 16 minutes, 52 seconds (63%). Time > 55.0 mm Hg: 28 minutes, 36 seconds (5.7%).

PHOX2B mutation; however, it did confirm the homozygous deletion of the brain-derived neurotrophic factor (*BDNF*) gene, which had been identified previously because the *BDNF* gene was encompassed by his maternally inherited 11p14.1 deletion.

Nocturnal BPAP was initiated for a presumptive hypoventilation syndrome. Once the patient was established on nocturnal BPAP, morning capillary pCO_2 ranged from 36–46 mm Hg and there was resolution of diurnal hypoventilation. He was ultimately discharged on the following BPAP settings: mode spontaneous/timed, inspiratory positive airway pressure (IPAP) 20 cm H_2O, expiratory positive airway pressure (EPAP) 10 cm H_2O, rate 26/min, inspiratory time (Ti) 0.1–1.1 seconds, rise 200, trigger medium, and cycle medium.

Several months after discharge, a BPAP titration polysomnogram was performed. A prestudy capillary blood gas suggested persistent mild diurnal hypoventilation despite good compliance with nocturnal BPAP therapy: pH 7.34, pCO_2 49 mm Hg, HCO_3 27 mmol/L. The polysomnogram did show some residual obstructive events on lower BPAP pressures. The patient continues on nocturnal BPAP with close follow-up by respiratory medicine. The parents report that daytime functioning is much improved on BPAP with improved daytime energy and function, along with tolerance of viral respiratory illnesses without further episodes of cyanosis or a decreased level of consciousness.

DISCUSSION

We are presenting a novel case of a 4-year-old patient with obesity and a known *BNDF* mutation with impaired ventilatory response to viral illness and diurnal hypoventilation. His acute-on-chronic respiratory failure was responsive to nocturnal BPAP therapy, which is consistent with a diagnosis of a hypoventilation syndrome. Notably, he did not have evidence of dysregulation of the autonomic nervous system, and endocrinologic workup was negative for hypothalamic dysfunction, arguing against a diagnosis of rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation and neuroendocrine tumor.

Acute-on-chronic hypercarbic respiratory failure is a common presentation of hypoventilation syndromes and may be the first opportunity for diagnosis. In a cohort of adult patients with OHS, Kessler et al[5] determined that approximately half of patients had been hospitalized in the intensive care unit for acute respiratory insufficiency at least once before a definitive diagnosis was made. Patients with late-onset CCHS and rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysregulation and neuroendocrine tumor may also remain relatively asymptomatic until challenged with a respiratory infection, at which time they may present with acute hypercarbic respiratory failure.[6,7]

With the combination of obesity and daytime hypercapnia, this patient meets the clinical criteria for OHS, making him one of the youngest patients to be reported. This presentation of OHS in a young child emphasizes the severe consequences of an elevated BMI on respiratory mechanics. Wang et al[8] reported OHS in a 4-year-old child, with a BMI of 32 kg/m^2, nocturnal hypoxia, daytime end-tidal CO_2 of 47 mm Hg, and pulmonary hypertension. Altered chest wall mechanics, upper airway dysfunction, leptin resistance, and ultimately alterations in the central respiratory drive with blunted hypoxic and hypercarbic ventilatory responses likely contribute to the multifactorial and complex pathophysiology of OHS.[9] Although there is increasing evidence available on OHS in adults, there is limited research available in pediatrics.

Microdeletions of 11p14.1, inclusive of the *BDNF* gene, have been previously associated with the development of significant obesity in children and thus may contribute to a diagnosis of OHS in this fashion.[10] Although the patient meets the criteria for OHS, his presentation is complicated by his known *BDNF* mutation. This factor uniquely shows the complexities of hypoventilation syndromes in patients with multiple hits against the normal control of breathing. Although genetic testing revealed no abnormalities in *PHOX2B,* making a classic diagnosis of CCHS unlikely, *BDNF* has been previously studied as a potential candidate gene for CCHS and likely plays a role in normal ventilatory responses. *BDNF* is a neurotrophin that supports the survival of primary somatic and visceral sensory neurons. The *BDNF* gene is located at 11p13-14. *BDNF* knockout mice, both homozygotes and heterozygotes, have shown a dose-dependent loss of chemo-afferent neurons in the nodose–petrosal ganglion complex, leading to resultant depressed and irregular breathing pattern and reduced chemosensory drive.[11] Balkowiec and Katz[12] also discovered that the loss of one or both *BDNF* alleles in mice led to an approximate 50% decrease in central respiratory frequency compared with wild-type mice. In a case study of 19 patients with CCHS, Weese-Mayer, Bolk, et al[13] discovered 1 patient with a paternally inherited *BDNF* mutation with associated dysregulation of the autonomic nervous system; however, this patient was later found to have a mutation of *PHOX2B*. *BDNF* is now included in some extended genetic panels for congenital hypoventilation syndromes.

Abnormalities in *BDNF* expression have also been implicated in sudden infant death syndrome. Tang et al[14] showed that the expression of mature recombinant human *BDNF* was lower in the caudal medulla of infants who had sudden infant death syndrome compared to infants who did not, with a higher expression of the *BDNF* receptor tyrosine kinase receptor B. Lavezzi et al[15] also discovered a lower expression of *BDNF* in the pontine Kölliker-Fuse nucleus of infants who had sudden infant death syndrome and sudden infant intrauterine syndrome compared with age-matched controls. This finding suggests that reduced *BDNF* expression in infants may alter ventilatory responsiveness with potentially fatal consequences.

Even as a case of a patient with simple OHS, this is an important presentation to describe because it documents one of the youngest reported patients with OHS and one presenting with severe respiratory compromise and hypercarbia on 2 distinct occasions. However, this patient has multiple risk factors for hypoventilation, with the combination of morbid obesity leading to altered respiratory mechanics and sleep-disordered breathing and a 1.5 Mb deletion encompassing the *BDNF* gene. Thus, we postulate a 2-hit hypothesis in our patient involving a dire combination of significant obesity and congenital predisposition for central hypoventilation derived from his *BDNF* deletion, a candidate gene for non-*PHOX2B*-related CCHS, leading to further impairment in ventilatory control. Though limited, the existing literature on *BDNF* function suggests that his *BDNF* gene deletion could contribute to a depressed and irregular breathing pattern with reduced response to hypercarbia and hypoxia.

This poses the following question: Might other candidate genes beyond *PHOX2B* predispose pediatric patients to hypoventilation syndromes? Do such genes require the presence of additional risk factors such as obesity, sleep-disordered breathing, or respiratory illness to manifest the phenotype of a central hypoventilation syndrome? With the increasing use of CCHS genetic panels and whole-exome sequencing to work up patients presenting with suspected hypoventilation syndromes, our knowledge of potential contributing genes may continue to grow.

In summary, this case report highlights the multifaceted and complex pathophysiology involved in ventilatory control and the potential for additional genetic contributions to be considered when children present with hypercapnia.

ABBREVIATIONS

BMI, body mass index
BPAP, bilevel positive airway pressure
CCHS, congenital central hypoventilation syndrome
OHS, obesity hypoventilation syndrome

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DISCLOSURE STATEMENT

All authors have reviewed and approved of the final manuscript as submitted. Work for this study was performed at Western University, Children's Hospital, London Health Sciences Centre, London, Ontario, Canada. The authors report no conflicts of interest.