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CASE REPORTS

Carbamazepine Improves Apneic Episodes in Congenital Central Hypoventilation Syndrome (CCHS) With a Novel *PHOX2B* Exon 1 Missense Mutation

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Pathogenic variants in Paired-Like Homeobox 2B (*PHOX2B*) gene cause congenital central hypoventilation syndrome (CCHS), a rare disorder of the nervous system characterized by absent or reduced ventilatory response to hypoxia and hypercapnia. The focus of management in CCHS is optimizing ventilation. Thus far, no medication has proved effective in improving ventilation. Most CCHS cases are caused by polyalanine repeat expansion mutations. Non-polyalanine repeat expansion mutations are the cause in 8% of cases and result in a more severe clinical presentation. *PHOX2B* has 3 exons. Exon 3 of *PHOX2B* is the most common location for CCHS-causing mutations. Thus far, only 9 CCHS-causing mutations have been reported in exon 1, 8 of which were nonsense mutations. We report a child with CCHS who was found to have a novel heterozygous missense variant in exon 1; c.95A > T. Improvement in his apneic episodes was observed following treatment with carbamazepine.

Keywords: apnea, carbamazepine, CCHS, congenital central hypoventilation syndrome, PHOX2B

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INTRODUCTION

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder that affects the nervous system and results in impaired respiratory and autonomic regulation. The presentation is typically during the neonatal period with hypoventilation or apnea during sleep and sometimes while awake. Rarely, CCHS can present later in life. Other manifestations of CCHS may include arrhythmias, Hirschsprung disease, ophthalmologic abnormalities, and neuroblastoma.[1] Management of CCHS requires a multidisciplinary approach to provide ventilatory support and monitor for complications.

Breathing is controlled by a complex network of receptors responding to changes in PO_2, PCO_2, and pH, in addition to other factors, such as lung compliance. Normally receptors in the central nervous system stimulate breathing in response to hypercapnia and peripheral receptors respond to acidemia, transient hypercapnia, or hypoxia in arterial blood. Although the exact pathophysiology of CCHS is unknown, research evidence suggests that defects in multiple physiological processes underlie the breathing and autonomic dysregulations caused by CCHS. There is a lack of physiological response to hypercapnia, hypoxia, challenges of exercise, effect of reduced body temperature on breathing, and respiratory-cardiovascular interactions.[1] Ventilatory support is the cornerstone in the management of CCHS. Cardiac pacemakers may be used for prolonged sinus pauses. Hirschsprung disease and neural crest tumors are treated in the usual manner.[1] Respiratory stimulant drugs are ineffective in patients with CCHS. Medications are used only to treat associated complications.[2]

CCHS is suspected in patients with hypoventilation with no evidence of an underlying primary neuromuscular, cardiopulmonary disease, or brainstem lesion and confirmed by identifying the pathogenic mutation in *PHOX2B* gene. *PHOX2B* gene plays a significant role in the process of nerve cell differentiation into sympathetic, parasympathetic, and enteric nerves.[3] CCHS is inherited in an autosomal dominant manner. The most common mutations are heterozygous expansions of a 20-alanine repeat sequence in exon 3 of *PHOX2B* gene to 24 to 33 alanines, which accounts for 90% to 92% of cases. Heterozygous missense, nonsense, or frameshift mutations in *PHOX2B* gene accounts for up to 8% of CCHS cases. These are usually associated with a severe respiratory phenotype and an increased prevalence of autonomic dysregulation, Hirschsprung disease, and neuroblastoma. In almost 2% of CCHS cases there is a deletion of all or part of the *PHOX2B* gene. Most CCHS-causing *PHOX2B* variants are found in exon 3 of the gene.[1,2] There are only 7 families reported with exon 1 mutations, of which most had nonsense mutations, as summarized in **Table 1**.[4–9] Only one had a missense mutation in exon 1 at position c.202G > T, which results in a substitution from glycine to cysteine (Gly68Cys) in the *PHOX2B* protein.[9] That child reportedly had CCHS phenotype associated with profuse sweating, profound swallowing dysfunction, and hyperinsulinism.

Table 1—A list of case reports of individuals with CCHS and mutation in exon 1 of *PHOX2B*.

Author	Year	Sex	Phenotype	Genotype
Current case		M	• Hypoventilation at birth • Breath-holding episodes • Feeding difficulty • Gastroesophageal reflux • Constipation	Heterozygous for missense variant c.95A > T in exon 1 of *PHOX2B*, which results in a substitution from aspartic acid to valine (Asp32Val)
Lombardo et al.[5]	2017	M	• Hirschsprung disease • Self-resolving Neonatal onset hypoventilation • Mildly dysmorphic • Anisocoric • No neuroblastoma	Heterozygous for nonsense mutation c.234C > G in the coding region of exon 1 of *PHOX2B* which replaces a tyrosine residue producing premature stop codon
		F	• Hirschsprung disease • Desaturations at 4 hour of life needed O_2 therapy	
		M	• Mother of the above sib-pair • Reportedly has sleep apnea (not evaluated) • No constipation • Congenital malformation of aorta	
Cain et al.[4]	2017	M	• Hypoventilation at birth • No Hirschsprung disease • No neuroblastoma	Heterozygous for nonsense variant c.13G > T (p.Glu5*) in the exon 1 of *PHOX2B*
		F	• Neonatal onset hypoventilation • Severe constipation	Heterozygous for nonsense variant c.18T > C (p.Tyr6*) in the exon 1 of *PHOX2B*
Magalhães et al.[8]	2015	N/A	• Hypoventilation requiring sleep-time NIV	Heterozygous variant c.23dupA, resulting in a premature stop codon (p.Y8*) in exon 1 of the *PHOX2B*
Trochet et al.[7]	2009	N/A	• Late onset-CCHS	Heterozygous nonsense variant c.42C > A resulting in a premature stop codon (p.Y14*) in exon 1 of *PHOX2B*
Parodi et al.[6]	2008		• CCHS (no further clinical data)	Heterozygous nonsense variant c.18T > G producing stop codon (p.Y6*) in exon 1 of PHOX2B
Hennewig et al.[9]	2008		• Hypoventilation at birth required intubation • Profuse sweating • Feeding difficulty • Hyperinsulinism	Heterozygote missense variant c.202G > T, which results in a substitution from glycine to cysteine (Gly68Cys) in exon 1 of *PHOX2B*

CCHS = Congenital central hypoventilation syndrome, *PHOX2B* = Paired-Like Homeobox 2B, N/A = not available, NIV = noninvasive ventilation.

We report the case of a 3-year-old child with CCHS who presented with hypoventilation and apnea from birth. Our case helps provide better insight into both etiology and management of CCHS.

REPORT OF CASE

A male infant was born at term to nonconsanguineous Caucasian parents. His mother had pregnancy-induced hypertension and was treated with labetalol. The infant was delivered by forceps-assisted vaginal birth due to fetal distress following spontaneous onset of labor; birth weight was 2680 g (0.4th centile). He was hypotonic with poor respiratory effort and bradycardia. Apgar scores were 5 at 1 minute and 7 at 5 minutes, and cord arterial pH was 7.25 and venous pH 7.3. He received bag and mask ventilation, which improved his slow heart rate but he remained hypotonic with poor respiratory effort. The patient was transferred to the neonatal care unit and supported with continuous positive airway pressure (CPAP). He was commenced on antibiotics and investigated for sepsis, meningitis, and metabolic causes of apnea.

Multiple attempts to wean him off CPAP failed, as recurrent episodes of apnea and desaturation occurred, particularly during sleep. He was also noted to have awake apneic episodes associated with crying or handling. These episodes were preceded by abnormal body posturing with stiff arms and legs and nonrhythmic jerks of upper and lower limbs, similar to breath-holding episodes. This was associated with pallor and central cyanosis lasting for about 30 to 60 seconds. He remained hypotonic with head lag but had reasonable antigravity movements. Overnight oxygen saturation in the neonatal period, including transcutaneous CO_2 monitoring, showed multiple desaturations and mild elevation of CO_2. During the first 2 months of

life, he was dependent on respiratory support via noninvasive ventilation (NIV) and high-flow oxygen therapy. A trial of caffeine citrate did not result in any improvement. After this initial period, the patient was able to maintain a normal gas exchange while awake but required respiratory support during sleep. Most of the apneic episodes were brief and self-correcting but some episodes required stimulation and occasionally bag and mask ventilation.

Initial neurology review considered the possibility of a diagnosis of congenital myotonia, which is an inherited myopathy of the skeletal muscles characterized by rigidity and slow muscle relaxation. Electromyography, at 3 months of age, demonstrated findings consistent with myotonia. However, examination revealed normal muscle tone and strength. Because of the possible congenital myotonia diagnosis, carbamazepine was administered (5 mg/kg in 2 divided doses). This improved the patient's daytime apneic episodes and resolved the episodes of limb stiffness and jerky movements. He later had an episode of nonrhythmic jerky movement and limb stiffness associated with a drop in his carbamazepine level in line with weight gain and improvement was noticed on increasing the carbamazepine dosage. Both the clinical team and the patient's parents observed an improvement in the apneic episodes in association with carbamazepine. He had feeding difficulties, which required nasogastric tube feeding, and he later underwent a fundoplication and formation of a gastrostomy due to severe gastroesophageal reflux.

Investigations including routine blood tests, metabolic screening, creatinine kinase, 24-hour electrocardiography, heart scan, and magnetic resonance imaging of the brain were all normal. Short synacthen test, which is a test of adrenal insufficiency that involves measuring serum cortisol level before and after injection of synthetic adrenocorticotropic hormone, was normal. Multichannel electroencephalogram, including during sleep, was unremarkable. Testing of the genes associated with nondystrophic myotonia including *SCN4A*, *CLCN1*, *CACNA15*, and *KCN12* was normal. Bronchoscopy demonstrated normal airway anatomy. Polysomnography at 4 months of age was consistent with the diagnosis of CCHS. The study, which was performed in room air, showed central hypoventilation mainly noted during sleep. On the basis of the study, overnight NIV was started.

A screen of the 3 exons of *PHOX2B* gene by direct sequence analysis revealed a heterozygous novel missense variant in exon 1; c.95A > T. This is a highly reserved site and results in the substitution of valine from aspartic acid (Asp32Val). The physiochemical difference between the 2 amino acids is large. Bioinformatics analysis predicts that this variant is likely to be pathogenic by affecting normal protein function. This mutation could not be found on testing *PHOX2B* gene in the parents. Therefore, it is likely to be a de novo mutation, although germline mosaicism cannot be excluded. Both parents are in good health. There is a family history of sudden infant death in 2 infants on the paternal side (father's cousins) of the family nearly 2 decades ago.

At 6 months of age, the patient was discharged home on overnight NIV via face mask. Polysomnography at one year of age showed effective ventilation with good synchrony. Measurements when off the ventilator demonstrated central hypoventilation, with 3 desaturations with CO_2 peaks of 9kPa in one night. Each of these was effectively managed with mask ventilation.

The patient is now 3 years of age and making normal developmental progress. At night, he continues to receive NIV via facemask. He has 3 to 4 brief desaturations at night, which are mainly self-correcting, but occasionally he needs minimal stimulation. When the patient is sleepy or tired during the day, he has occasional desaturations that require ventilator support. He is very much dependent on his gastrostomy for feeding but takes some pureed food by mouth. He struggles with constipation, which is effectively managed medically. Abdominal ultrasound scan and gastrointestinal contrast studies did not detect any abnormality.

DISCUSSION

We report a child who presented with classic features of CCHS and was found to have a novel pathogenic missense mutation in exon 1 of *PHOX2B* gene. Carbamazepine was noted to improve daytime apneic episodes but not the sleep-related hypoventilation in this patient. This effect of carbamazepine has never been previously reported in CCHS.

Carbamazepine has been successfully used to treat certain types of seizure, neuralgia, mood disorders, and congenital myotonia. Carbamazepine produces a wide variety of biochemical effects on channels, receptors, and signaling pathways. It mainly acts by reducing the ability of neurons to fire at high frequency by blocking voltage-gated sodium channels. It also acts on synaptic transmission and neurotransmitter receptors including noradrenaline, adenosine, dopamine and gamma-aminobutyric acid receptors.[10]

Carbamazepine has not been used for management of CCHS or central sleep apnea. There is, however, a single case in the medical literature[11] in which the use of carbamazepine for seizures reportedly improved central sleep apnea, although there is very little clinical information on that patient.

In CCHS, ventilation is profoundly depressed during sleep, especially during non-rapid eye movement sleep, but generally, some degree of residual ventilatory activity is retained and passive peripheral limb movement during sleep stimulates ventilation.[3] There are possible pathways through which carbamazepine could affect the interaction between sleep, wakefulness, and ventilation. One possibility is that carbamazepine may modulate ventilation through neurotransmitter receptors. The association between elevated plasma noradrenaline levels and sleep apnea has been recognized for years. Studies measuring noradrenaline levels in patients with sleep apnea receiving CPAP show lower nocturnal levels of norepinephrine after a CPAP trial.[12] This effect could be explained by the inhibitory effect of improved ventilation on the sympathetic nervous system while desaturations stimulate the sympathetic nervous system and increase norepinephrine levels. It is also possible that norepinephrine directly inhibits ventilation.[13] Carbamazepine inhibits both synaptic uptake and release of noradrenaline in the brain and this is, at least partly, its mode of action as a mood

stabilizer.[14] Therefore, it is plausible that carbamazepine may affect ventilation through blocking noradrenaline receptors.

Carbamazepine is an antagonist for both A1 and A2 adenosine receptors but with lower potency at A2 receptors. Adenosine is an inhibitory neurotransmitter. In the central nervous system adenosine acts as a respiratory depressant. Adenosine antagonists such as caffeine are efficient respiratory stimulants and used to treat neonatal apnea.[14] The effect of carbamazepine on adenosinergic receptors could, in theory, explain the clinical improvement observed in our patient. However, despite the similarities in actions of carbamazepine and caffeine on adenosine receptors, they appear to produce paradoxical pharmacological effects, with anticonvulsant and sedative effects of carbamazepine compared to the stimulant effect of caffeine.[14] On the surface, the sedative effect of carbamazepine appears to contradict the purpose of treatment in CCHS. However, a number of sedative-hypnotic agents such as zolpidem and triazolam have been trialed in the treatment of adults with central sleep apnea. The limited available data show improvement in apnea-hypopnea index and sleep quality.[15]

Currently, it is not possible to determine the contribution of carbamazepine to symptomatic improvement in our patient. The clinical relevance of our observations therefore remains to be determined but carbamazepine could be an exciting therapeutic agent for CCHS. Our patient also proves that exon 1 missense mutations can cause CCHS and that sequencing of the entire coding region should be performed when the diagnosis is strongly suspected and no non-polyalanine repeat expansion mutation is detected.

ABBREVIATIONS

CCHS, congenital central hypoventilation syndrome
CPAP, continuous positive airway pressure
NIV, noninvasive ventilation
PHOX2B, Paired-Like Homeobox 2B

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.