# Ondine's Curse – Never Too Late

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> "You swore faithfulness to me with every waking breath, and I accepted your oath. So be it. As long as you are awake, you shall have your breath, but should you ever fall asleep, then that breath will be taken from you and you will die"
>
> Ondine's curse (German folk epic)

Classic congenital central hypoventilation syndrome, known also as "Ondine's curse," is characterized by hypoventilation with normal respiratory rates and shallow breathing during sleep with adequate ventilation during wakefulness. Severely affected individuals hypoventilate also while awake. Most patients present in the newborn period and require assisted ventilatory support for life, at least during sleep. CCHS represents an increasingly recognized group of conditions characterized by respiratory and autonomic nervous system dysregulation [1,2]. A subset of patients will have altered development of neural crest-derived structures manifested as Hirschsprung disease and tumors of neural crest origin including neuroblastoma, ganglioneuroma, and ganglioneuroblastoma. Many individuals with CCHS who have been successfully ventilated are now in their twenties or thirties, suggesting the potential for a normal life span. It has recently been shown that CCHS confers risk for adverse neurocognitive outcome [3]. Visuoperceptual reasoning and clerical/visuographic speed appear particularly vulnerable.

In this issue of *IMAJ*, Cohen-Cymberknoh and colleagues [4] present an interesting and unusual case of a 12 year old girl with late-onset CCHS that was suspected and diagnosed only after she failed extubation from assisted ventilation that was initiated due to respiratory failure caused by pneumonia. Extubation failure resulted from central hypoventilation. Pneumonia is a common disease in children. However, it uncommonly results in respiratory failure necessitating assisted ventilatory support in healthy school-aged children. Hence, it is possible that central hypoventilation contributed to impaired gas exchange and respiratory failure before the intubation and precipitated intubation similarly to its contribution to extubation failure. Indeed, the patient had high $CO_2$ levels before intubation. We cannot conclude that the pneumonia changed the respiratory drive of the patient and initiated the expression of CCHS. Hence, the hypoventilation during sleep was probably present before the ventilatory assist. A significant difference in arterial blood gas and oxygen saturation between sleep and awake states during an acute respiratory disease (pneumonia in this case) could be an early clue.

The present case is also interesting in that hypoxemia during sleep was not continuous as expected in central hypoventilation, but episodic – described as "several events of hypoxemia with $SpO_2$ on room air decreasing to 78%." We do not know what the baseline $SpO_2$ and end-tidal $CO_2$ were during sleep apart from these episodes. Since the authors do not provide these data, one can assume that these were normal or close to normal during most of sleep time. This is the most important message of this case report, namely, that a mild type of CCHS may not only present later in life, but may be associated with normal (or close to normal) gas exchange and blood gases during a significant part of the sleep time. Unfortunately, no data are provided on whether the hypoventilation episodes were confined to specific sleep stages. This may be important, as suspected mild cases do require a polysomnogram that contains all sleep stages and REM (rapid eye movement) sleep in sufficient amounts for scoring and evaluation. Ideally, in future cases, arterial blood gas should be monitored through an arterial line during polysomnography. Obviously, this can be performed only in sleep laboratories in pediatric medical centers or hospitals and not in outside facilities. It should be emphasized that the diagnosis should be based on arterial blood gases and not on polysomnography alone since the proof of alveolar hypoventilation requires calculation based on the alveolar gas equation.

The diagnostic approach to CCHS has changed dramatically since the *PHOX2B* gene was identified in 2003 [5]. Until then, the diagnosis of CCHS was based on the exclusion of a variety of neurologic and metabolic diseases and other syndromes, necessitating an extensive clinical and laboratory investigation in the presence of hypoventilation during sleep. Today, a typical simple

CCHS = congenital central hypoventilation syndrome

presentation of hypoventilation during sleep that resolves during the wake state in the presence of an otherwise normal neurologic examination is a sufficient condition for running a genetic test. The results of this test are confirmed within 2–3 weeks, obviating the need for an extensive workup. The gene test can now be performed in Israel (Wolfson Medical Center, Holon).

*PHOX2B*, located on chromosome 4p12, encodes a protein that contains two polyalanine repeat sequences of 9 and 20 residues in length. Polyalanine expansions in the 20 residues region are the major mutations responsible for CCHS. Over 90% of confirmed *PHOX2B* expansion mutations occur *de novo* in CCHS probands, while up to 10% of unaffected parents are somatic mosaics for the expansion mutation seen in their child. The size of the *PHOX2B* polyalanine expansion mutation in children with CCHS varies from an additional 5 to 13 nucleotide triplets, resulting in repeat expansion of 25–33 repeats on the affected allele [6]. The number of alanine repeats correlates with the phenotypic expression. Patients carrying the shortest alanine expansions display a less severe phenotype. The wide range of presentations associated with the size of the expansion mutation, which extends from the newborn period to adulthood, raises the possibility that some individuals with short expansions may remain undiagnosed throughout life.

The *PHOX2B* screening test is a polymerase chain reaction assay that directly amplifies and sizes the second polyalanine-coding triplet repeat sequence in exon 3 of the *PHOX2B* gene. The test is highly sensitive and specific for detection of the triplet repeat polyalanine expansion mutations. This triplet repeat is expanded in 92% of individuals with CCHS. The remaining individuals with CCHS (8%) will have mutations that can be identified by follow-up sequencing of the coding regions of the *PHOX2B* gene. Therefore, children suspected to have CCHS should ideally be tested by the PCR assay *PHOX2B* Screening Test, with follow-up sequencing if no mutation is found.

Although most individuals with CCHS are new *PHOX2B* mutations, CCHS is inherited in an autosomal dominant manner in approximately 5% of individuals, i.e., they have an asymptomatic parent with a somatic mosaicism for a *PHOX2B* mutation. Because mosaic parents can pass the same *PHOX2B* mutation on to other children, it is necessary to test *all* parents of CCHS probands for mosaicism. Physiologic respiratory testing and Holter recordings should be performed on any parent who has a *PHOX2B* mutation (either mosaic or classic mutation). Prenatal testing for pregnancies at increased risk is possible if the causative mutation has been identified in an affected family member.

It was recently recognized that some individuals with nocturnal alveolar hypoventilation and a polyalanine expansion mutation in *PHOX2B* characteristic of CCHS do not present until childhood or adulthood [7]. All individuals with *PHOX2B* mutations who present after the newborn period appear to have the 20/25 genotype (i.e., 20 repeats on one allele and 25 repeats on the other allele). These individuals exhibit the characteristic alveolar hypoventilation during sleep and symptoms of autonomic nervous system dysregulation; thus, these individuals who present at an older age still have CCHS.

Later-onset CCHS needs to be distinguished from a disorder described more than 40 years ago termed "late-onset central hypoventilation with obesity and hypothalamic dysfunction" [8,9] that was recently termed "rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation" (ROHHAD) [9]. Children with ROHHAD do not have mutations in the *PHOX2B* gene, thereby distinguishing ROHHAD from CCHS.

With the introduction of clinically available molecular genetic testing for *PHOX2B* mutations, it has become apparent that CCHS may no longer be as rare as previously thought. It is estimated that more than 500 cases of genetically confirmed CCHS have been identified. This is almost certainly an underestimate. I have personally encountered three cases over the last 20 years in the center of Israel when no genetic analysis was available. I have, however, been familiar with two new cases over the last year and one case with the combination of Hirschsprung disease, not including the present case. Increased awareness regarding milder presentations will likely lead to identification of more cases in the future.

CCHS needs to be considered in individuals who do not have the characteristic CCHS phenotype, including individuals with apparent life-threatening events and cyanosis during sleep, unexplained seizures, respiratory depression after anti-seizure medication, sedation or anesthesia, unexplained neurocognitive delay with any history of prior cyanosis, unexplained nocturnal hypercarbia and hypoxemia, seeming unresponsiveness to conditions of apparent hypercarbia or hypoxemia (prolonged underwater swimming, pneumonia), and infants and children who die suddenly and unexpectedly. Because it is anticipated that a growing number of children and adults presenting with symptoms compatible with mild versions of CCHS will be found to be heterozygous for a *PHOX2B* mutation, a differential diagnosis as thorough as that considered in infancy should be applied.

PCR = polymerase chain reaction
ROHHAD = rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation

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