Ondine's Curse – Never Too Late

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CCHS = congenital central hypoventilation syndrome

"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/visual perceptual 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. Exubation 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 CO₂ 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 SpO₂ on room air decreasing to 78%.” We do not know what the baseline SpO₂ and end-tidal CO₂ 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...
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.

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Temporal changes in dendritic cell subsets, cross-priming and co-stimulation via CD70 control CD8+ T cell responses to influenza

The question of which dendritic cells (DCs) respond to pulmonary antigens and cross-prime CD8+ T cells remains controversial. Ballesteros-Tato and co-authors show that influenza-specific CD8+ T cell priming was controlled by different DCs at different times after infection. Whereas early priming was controlled by both CD103−CD11bhi and CD103−CD11bhi DCs, CD103−CD11bhi DCs dominated antigen presentation at the peak of infection. Moreover, CD103−CD11bhi DCs captured exogenous antigens in the lungs and directly cross-primed CD8+ T cells in the draining lymph nodes without transferring antigen to CD8α+ DCs. Finally, the authors show that CD103−CD11bhi DCs were the only DCs to express CD70 after influenza infection and that CD70 expression on CD103−CD11bhi DCs licensed them to expand CD8+ T cell populations responding to both influenza and exogenous ovalbumin.

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Salt-sensitive hypertension in circadian clock-deficient mice involves dysregulated adrenal dehydrogenase

Malfunction of the circadian clock has been linked to the pathogenesis of a variety of diseases. Doi and co-scientists show that mice lacking the core clock components cryptochrome-1 (Cry1) and cryptochrome-2 (Cry2) (Cry-null mice) show salt-sensitive hypertension due to abnormally high synthesis of mineralocorticoid aldosterone by the adrenal gland. An extensive search for the underlying cause led us to identify type VI 3β-hydroxysteroid dehydrogenase (Hsd3β6) as a new hypertension risk factor in mice. Hsd3β6 is expressed exclusively in aldosterone-producing cells and is under transcriptional control of the circadian clock. In Cry-null mice, Hsd3β6 messenger RNA and protein levels are constitutively high, leading to a marked increase in 3β-hydroxysteroid dehydrogenase-isomerase (3β-HSD) enzymatic activity and, as a consequence, enhanced aldosterone production. These data place Hsd3β6 in a pivotal position through which circadian clock malfunction is coupled to the development of hypertension. Translation of these findings to humans will require clinical examination of human HSD3β1 gene, which the authors found to be functionally similar to mouse Hsd3β6.

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“The machine has got to be accepted, but it is probably better to accept it rather as one accepts a drug – that is, grudgingly and suspiciously. Like a drug, the machine is useful, dangerous, and habit-forming. The often one surrenders to it the tighter its grip becomes”

George Orwell (1903-1950), English novelist and journalist, whose work is marked by keen intelligence and wit, a profound awareness of social injustice, an intense, revolutionary opposition to totalitarianism and a belief in democratic socialism. He is best known for the dystopian novel Nineteen Eighty-Four and the satirical novella Animal Farm.