Short Communication

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The Physiology of Ondine's curse – An Untold Story

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Abstract

Ondine's curse is a classical myth story which is also called Central Hypoventilation syndrome. In this ancient mythical story, a young nymph named Ondine falls in love with a handsome knight, Palemon and marries him. Later she discovers that her husband had been unfaithful to her, she uses her supernatural powers to set a curse on her disloyal husband in which he retains the ability to breathe, but only when he is awake and conscious. Hence the victim cannot breathe if he falls asleep and therefore must choose between sleeping and remaining alive. Patients with central hypoventilation syndrome do not have the ability to maintain regular respiration during sleep or may stop breathing during sleep. Interruption of breathing can cause a decrease in oxygen supply to the body and symptoms usually can range from fatigue to organ damage to death. Damage to the lateral medulla caused by stroke, tumors, and trauma accounts for acquired conditions of central hypoventilation syndrome. Discovery in mutations of PHOX2B gene is responsible for this condition and it is not likely to be hereditary. There are two types namely Classical Congenital Hypoventilation Syndrome (CCHS) and isolated congenital central hypoventilation syndrome. Children with PHOX2B gene frame shift mutations, also have Hirschsprung's disease and Neuroblastoma and are described as having Classical Congenital Hypoventilation Syndrome (CCHS) and the another PHOX2B mutation, a polyalanine expansion which has been described in children with isolated congenital central hypoventilation syndrome. CCHS is a neurocristopathy caused primarily by the mutation of the paired like homeobox PHO2XB gene. Despite advances in diagnosis of PHOX2B, treatment of Ondine's curse continues to rely on respiratory support with mechanical ventilation, and sometimes tracheostomy, as the cornerstones of treatment. Depending on the severity of the condition, life expectancy is expected to be shortened, although supportive measures are extending the survival.

Keywords: central hypoventilation syndrome, Ondine's curse, PHOX2B mutation

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Every human soul born in this universe is under the curse of a sin. Even though the individuals are responsible for their own deeds, humans are not always the victims of curses placed on them either by no wrong deed of their own or by doing erroneous actions of past generations. Hence, their sins are their own errors not anybody else's. Physiologists and Physicians even now like to understand that practicing medicine requires the constant gaining of new knowledge, though they often assume their existing medical beliefs do not need re-examination. These medical myths are a light hearted reminder that we can be wrong and need to question what other falsehoods we unwittingly propagate as we practice medicine. One such curse and a myth still requires further understanding of its basic pathophysiology is the Ondine's curse, or Central Alveolar Hypoventilation Syndrome, a very rare medical condition characterized by loss of breathing mechanisms during sleep.[1]
Ondine's curse syndrome was originally based on the

German and French mythology stories written by Friedrich La Motte Fouque (1811). According to Paracelsus proposed theory, an Ondine is a water nymph or the water element, which tells the story of a nymph who falls in love with a handsome knight – Palemon and he promised her by exchanging vow with the nymph and said, "My every waking breath shall be my pledge of love and faithfulness to you." A year after their marriage, Ondine gave birth to his son and she lost her usual physical attractive beauty and hence he lost interest in his wife. Later she found that she was betrayed and hence she uttered a curse: "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!"[2]

It was first characterized by Robert Mellins et al (1970) as central apnea which is due to dysfunction of autonomic nervous system.[3] Hypoventilation is accentuated during sleep, especially in the non-REM phase of sleep, in which our autonomic control of breathing predominates and probably for this reason it was called Ondine's curse syndrome. Gabriel Haddad (1978) described the association between CCHS (Classical Congenital Hypoventilation syndrome) and Hirschsprung's disease which are due to tumors derived from the neural crest with the familial character of the disease. During embryogenesis, after the induction of the neural crest, the newly formed neural crest cells (NCC) delineate from their tissue of origin and migrate from the entire neural axis of the vertebrate embryo to specific locations where they will give rise to different cell derivatives which requires an interplay of inter- and intra-cellular signals. An alteration in the occurrence and timing of these signals leads to a set of syndromes called Neurocristopathies (NCP). CCHS is a neurocristopathy caused primarily by the mutation of the paired like homeobox PHO2XB gene.[4] It has been recognized as a congenital disorder for a long time and about 200 to 500 cases reported worldwide each year. Mostly 15-20% of cases of CCHS have Hirschsprung's disease. PHOX2B gene mutations was identified as responsible for CCHS.[5] The PHOX2B gene which is located on chromosome 4p12, encodes a transcription factor responsible for the regulation of genes involved in the development of the autonomic nervous system. The most frequently found mutation is a polyalanine expansion in exon 3. More than 90% of affected persons are heterozygous for this mutation. The normal genotype has a sequence of 20 alanines (20/20 genotype) whereas CCHS occurs from four extra alanines in one of the alleles (20/24 genotype).[6] There is a correlation between genotype and phenotype, i.e., the higher the number of alanines, the greater the severity of clinical findings. The mutation has been best demonstrated by polymerase chain reaction and other types of mutations such as missense or frameshift mutation are demonstrated by gene sequencing.[7] Most of the individuals with CCHS have PHOX2B mutations, and it is inherited in an autosomal dominant manner in approximately 5% of individuals. They have an asymptomatic parent with a somatic mosaicism for this PHOX2B mutation and because these 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 parents who have 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.

The central chemical regulatory mechanism depends on chemoreceptors which are located in the retro-trapezoid nucleus of the brainstem. These neurons are sensitive to carbon dioxide levels in Cerebrospinal Fluid (CSF). Retro - trapezoid nucleus neurons (RTNN) expresses the PHOX2B gene and they are integrated into the neuronal circuitry which stimulates the phrenic nerve and, consequently, promotes diaphragm movement and controls ventilation in order to maintain homeostasis.[8]

The acquired form of the disease results from medullary tumors, infections especially poliomyelitis, upper cervical trauma with Duret hemorrhage, some mitochondrial diseases, degenerative diseases such as multiple system atrophy, demyelinating diseases like multiple sclerosis or nonspecific anoxic-ischemic insults.[9] Late-onset central hypoventilation with hypothalamic dysfunction is a disorder of the central control of ventilation. It can be diagnosed if sleep related hypoventilation develops after the first few years of life. The patients usually present with obesity, endocrine abnormalities of hypothalamic origin, severe emotional or behavioral disturbances or a tumor of neural origin.[10] In most of the aberrant ventilatory patterns,

particularly causing death in the acute phase of stroke, Ondine's curse is the cause, which typically occurs in the lower brainstem and involves the lateral portion of the medulla. This lesion causes a selective interruption of the descendent anterolateral medullocervical pathway, which in its turn is responsible for automatic breathing.[11]

Bogousslavsky et al., in their clinicopathological correlation of brainstem strokes with loss of automatic breathing, have detected unilateral ischemia in most of the cases, which suggests that bilateral lesions are not required for the occurrence of significant hypoventilation.[12] Laboratory criteria for the diagnosis of Ondine's curse are prolonged and persistent periods of apnea associated with desaturation and hypercapnia during non-REM sleep should be demonstrated, while other authors mention some criteria such as normal pulmonary and mediastinal anatomy, pO2 normalization through voluntary breathing when awake and precipitation of alveolar hypoventilation with diminished voluntary control.[13] The goal of treatment is to activate the remaining respiratory nuclei through the induction of metabolic acidosis. Drugs such as trazodone, acetazolamide, medroxiprogesterone, protyptilin, clomipramine, tiroxine and caffeine have been used. [14] The other therapeutic interventions are the use of positive airway pressure and the placement of a diaphragmatic pacemaker which is responsible for a 50- 70% success rate in these cases.[15] These patients usually respond well to tracheostomy and nocturnal assisted ventilation until spontaneous recovery occurs. Deaths usually occur during sleep due to complete apnea. Therefore, the prognosis of the disease is variable, depending on the specific location of the lesion, and recovery, although frequent, is usually unpredictable.[16] Although CCHS is a life-long condition, complications can be avoided with early diagnosis and specialist management. Life expectancy for children with CCHS has improved greatly with technological advances, particularly in ventilatory support, and most will grow up to adulthood, with a near normal work and family life.[17-20]

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