Congenital Central Hypoventilation Syndrome

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Congenital central hypoventilation syndrome (CCHS) is a disorder that affects normal breathing.

Keywords: genetic conditions

1. Introduction

People with this disorder take shallow breaths (hypoventilate), especially during sleep, resulting in a shortage of oxygen and a buildup of carbon dioxide in the blood. Ordinarily, the part of the nervous system that controls involuntary body processes (autonomic nervous system) would react to such an imbalance by stimulating the individual to breathe more deeply or wake up. This nervous system reaction is impaired in people with CCHS. They must be supported with a machine to help them breathe (mechanical ventilation) or a device that stimulates a normal breathing pattern (diaphragm pacemaker). Some affected individuals need this support 24 hours a day, while others need it only at night.

Symptoms of CCHS usually become apparent shortly after birth when affected infants hypoventilate upon falling asleep. In these infants, a lack of oxygen in the blood often causes a bluish appearance of the skin or lips (cyanosis). In some milder cases, CCHS may not become apparent until later in life.

In addition to the breathing problem, people with CCHS may have difficulty regulating their heart rate and blood pressure, for example, in response to exercise or changes in body position. They also have decreased perception of pain, low body temperature, and occasional episodes of heavy sweating.

People with CCHS may have additional problems affecting the nervous system. About 20 percent of people with CCHS have abnormalities in the nerves that control the digestive tract (Hirschsprung disease), resulting in severe constipation, intestinal blockage, and enlargement of the colon. (Some researchers refer to the combination of CCHS and Hirschsprung disease as Haddad syndrome.) Some affected individuals develop learning difficulties or other neurological problems. People with CCHS are also at increased risk of developing certain tumors of the nervous system called neuroblastomas, ganglioneuromas, and ganglioneuroblastomas.

Additionally, individuals with CCHS usually have eye abnormalities, including a decreased response of the pupils to light. People with CCHS, especially children, may have a characteristic appearance with a short, wide, somewhat flattened face often described as "box-shaped."

In CCHS, life expectancy and the extent of any intellectual disabilities depend on the severity of the disorder, timing of the diagnosis, and the success of treatment.

2. Frequency

CCHS is a relatively rare disorder. More than 1,000 individuals with this condition have been identified. Researchers believe that some cases of sudden infant death syndrome (SIDS) or sudden unexplained death in children may be caused by undiagnosed CCHS.

3. Causes

Mutations in a gene called *PHOX2B* cause CCHS. The *PHOX2B* gene provides instructions for making a protein that is important during development before birth. The PHOX2B protein helps support the formation of nerve cells (neurons) and regulates the process by which the neurons mature to carry out specific functions (differentiation). The protein is active in the neural crest, which is a group of cells in the early embryo that give rise to many tissues and organs. Neural crest cells migrate to form parts of the autonomic nervous system, many tissues in the face and skull, and other tissue and cell types.

PHOX2B gene mutations that cause CCHS are believed to interfere with the PHOX2B protein's role in supporting neuron formation and differentiation, especially in the autonomic nervous system. As a result, bodily functions that are controlled by this system, including regulation of breathing, heart rate, blood pressure, and body temperature, are inconsistent in CCHS.

3.1. The Gene Associated with Congenital Central Hypoventilation Syndrome

- PHOX2B

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

More than 90 percent of cases of CCHS result from new mutations in the *PHOX2B* gene. These cases occur in people with no history of the disorder in their family. Occasionally an affected person inherits the mutation from one affected parent. The number of such cases has been increasing as better treatment has allowed more affected individuals to live into adulthood and start families.

About 5 to 10 percent of affected individuals inherit the altered gene from an unaffected parent who has a *PHOX2B* gene mutation only in their sperm or egg cells. This phenomenon is called germline mosaicism. A parent with mosaicism for a *PHOX2B* gene mutation may not show any signs or symptoms of CCHS.

5. Other Names for This Condition

- CCHS
- congenital central hypoventilation
- congenital failure of autonomic control
- Haddad syndrome
- Ondine syndrome
- Ondine-Hirschsprung disease

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