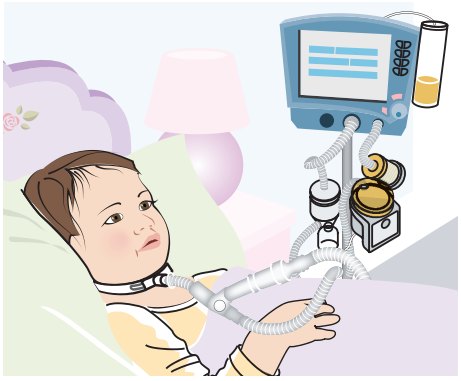
Congenital Central Hypoventilation Syndrome (CCHS)

Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder of the Autonomic Nervous System (ANS) and control of breathing. CCHS is caused by a mutation in the PHOX2B gene. The abnormal gene leads to problems in ANS development. The ANS is part of the body's nervous system that controls body functions that happen automatically (that is without thinking) to keep us alive. The ANS controls regulation of breathing, heartbeat, blood pressure, intestinal motility, temperature regulation and more. All organ systems are served by the ANS.



The key feature of CCHS is shallow breathing while sleeping, and if severe, shallow breathing awake and asleep, resulting in low oxygen and elevated carbon dioxide. With CCHS, the lungs, airways (breathing tubes) and the heart are normal, but the body does not adequately respond to these signals to normalize breathing and heart rate.

CCHS is a rare condition that has affected more than 1,300 people world wide. CCHS is being diagnosed more often now because of increased knowledge about its varying presentation and the availability of clinical genetic testing to confirm the PHOX2B gene mutation.

How is breathing control a problem in CCHS?

Both low oxygen levels and high carbon dioxide levels normally stimulate control of breathing to "kick in" and automatically cause us to breathe deeply or more often. People with severe CCHS, do not sense the need to breathe more deeply or to increase the rate of breathing when they develop hypoxemia or hypercarbia. For this reason, people with CCHS may be able to hold their breath for a long period of time without knowing the potential harm this can cause. Swimming therefore, is a dangerous sport for individuals with CCHS.

What kinds of signs or symptoms might I (or my child) have with CCHS?

CCHS is a life-long disease. Newborns with CCHS are often diagnosed soon after birth because they do not breathe effectively. Ineffective shallow breathing can cause low oxygen levels (called hypoxemia) and elevated carbon dioxide levels (called hypercarbia). The infant's shallow breathing or (rarely) pauses in breathing (called apnea) can result in the baby turning blue (called cyanosis).

In milder cases, older infants, children, and adults may not be diagnosed until they have problems in situations that require the body to adjust breathing automatically (LO-CCHS). Therefore, a person may be discovered to have CCHS only after having hypercarbia during sedation for surgery, when taking medications that cause sleepiness (such as seizure or sedation medications), or when they have pneumonia or another severe respiratory illness).

How do I know if I have (or my child has) CCHS?

CCHS is typically diagnosed during the newborn period when the shallow breathing, hypoxemia, and hypercarbia may be immediately identified. Milder forms of CCHS, however, may go undiagnosed through infancy, childhood or even adulthood. These forms are referred to as later onset CCHS (LO-CCHS).

A simple blood test can be done to check if you or your child has CCHS. The most common gene mutations (changes in the gene) can be found with the "PHOX2B Screening Test". If the results from this test are normal and there is still a concern that you or your child has CCHS, then the "PHOX2B Sequencing Test" should be done to look for rare mutations in the PHOX2B gene. And if the "PHOX2B Sequencing Test" is negative but the clinical features strongly suggest CCHS or LO-CCHS, then the "PHOX2B MLPA Test" should be performed. Because PHOX2B gene mutations can be inherited in up to 35% of cases, direct family members (parents and children) of people with CCHS, should have testing for PHOX2B mutations and work closely with their physician and a genetic counselor. It is important that the correct genetic test is performed for parents of a child with CCHS and their physician should request the "PHOX2B Screening Test" as a start. Most often, though, a PHOX2B gene mutation occurs as a new mutation in a person with CCHS and is not inherited from someone else in the family.

How is a person's breathing monitored in CCHS

Because people with CCHS do not sense changes in oxygen and carbon dioxide well, these levels need to be watched closely. Oxygen saturation levels can be measured either using a probe attached to a finger or toe (called a pulse oximeter) or by a blood test (called an arterial blood gas). Carbon dioxide levels can be measured by a monitor that measures the air you exhale or breath out (called capnography) or by a blood test (arterial blood gas). A sleep study (polysomnogram) or more sophisticated physiologic recordings awake and asleep can be used to look at breathing, oxygen saturation, and exhaled carbon dioxide levels during sleep and wakefulness. Often, other testing is done as well to be sure that the breathing abnormality is not due to abnormalities with the lungs,

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heart, brain or conditions which cause muscle weakness. For more information on Pulse Oximetry and Sleep studies see ATS Patient Information handouts at www.thoracic.org/patients.

What other problems can people with CCHS have?

There are other health problems that can co-occur in CCHS due to abnormalities with the ANS. The risk of developing these problems varies by the type of PHOX2B mutation present. Some people with CCHS have structural problems such as Hirschsprung disease and/ or neural crest tumors. With Hirschsprung disease, certain nerve cells (ganglion cells) are not present so that a section of the intestines (gut) will not work properly. This abnormal section will not move stool properly through the intestines, so it needs to be surgically removed. The tumors (abnormal growths of neural crest tissue), are made up of cells that are usually seen very early in the development of the body. These tumors can appear at any age and include tumors called neuroblastoma, ganglioneuroma, or ganglioneuroblastoma. When present, they are found in the chest or abdomen. Other types of ANS abnormalities can lead to loss of "automatic" function of many other parts of the body. For example, people with CCHS may have heart rhythm abnormalities (such as prolonged pauses in the heart beat, called asystoles), abnormal temperature regulation with low body temperatures (hypothermia), altered pupillary response to light, and decreased sense of pain and anxiety. Some people have problems with slow movement of food and stool in the gut causing constipation even without Hirschsprung disease.

What is the treatment for CCHS?

At present, there is no cure for CCHS. Treatment depends on supportive artificial ventilation and attention to specific symptoms of ANS dysregulation. Most importantly, everyone with CCHS will need help with breathing during sleep (whether a daytime nap or nighttime sleep). In severe cases, help with breathing is needed when the individual is awake and asleep (day and night). Infants with CCHS usually require a machine (called a mechanical ventilator) to help them breath. This machine helps the infant breathe by blowing air through a surgically made hole in the airway (tracheostomy). In some cases, older children and adults who only have problems breathing during sleep, may be able to be treated with a machine that blows air with a mask over the nose or nose/mouth (called non-invasive ventilation). In some cases, a special device called phrenic nerve-diaphragm pacers can be used to assist breathing. This requires a surgical procedure for placement of electrodes onto the phrenic nerves that stimulates the diaphragm. The diaphragm is the large, thin muscle that lies just under the lungs that is used for breathing. The diaphragm pacemaker works by stimulating the nerves that cause the diaphragm to move, causing air to be pulled into the lungs. For more information on home ventilators and diaphragmatic pacing see ATS Patient Information Handouts at www.thoracic.org/patients.

If a person with CCHS has asystoles (long pauses in the heart beat), a cardiac pacemaker may be needed. Medicines taken by mouth and dietary changes can be used to treat constipation. Neural crest cell tumors and parts of the intestine with Hirschsprung disease need to be removed with surgery.

Because CCHS can involve many body functions, and the amount of involvement differs from person to person, it is important for people with this rare condition to be followed at a specialty center with a team experienced in diagnosing and treating large numbers of patients with CCHS. The goal of this team is to provide a person with CCHS the best quality of life and to work closely with your local physicians.

How will CCHS affect my lifestyle or that of my child?

Early diagnosis and treatment can limit complications from CCHS. New technology has offered many options to children and families with CCHS. Home mechanical ventilators, portable oxygen saturation and carbon dioxide monitors, home care registered nurses and other support have allowed infants and children to go home from the hospital and to stay out of the hospital. The result is that children with CCHS now have an excellent chance of growing up with their families, taking part in normal activities such as going to school (including college and graduate school), and living well into adulthood as productive members of society.

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Rx *Key Points*

If you/your child have CCHS,

- ✔ To confirm the diagnosis of CCHS, get stepwise PHOX2B genetic testing from a specialist in CCHS (www.genetests.org).
- ✔ Use the ventilator or diaphragm pacers as directed by your healthcare provider.
- ✔ Make sure you tell every healthcare provider that you or your child has CCHS, especially every time a new medicine is prescribed or if you need sedation/anesthesia for a test or surgery.
- ✔ Avoid swimming and breath holding as you will be at risk for drowning.
- ✔ Do not drink alcohol as it may cause you to not breathe adequately.
- ✔ Do not use recreational drugs or any drugs like sleeping pills or narcotic pain medicines that may reduce your breathing effort or cause you to stop breathing.

Healthcare Provider's Contact Number:

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Resources:

CCHS Registry on clinicaltrials.gov
https://clinicaltrials.gov/show/NCT03088020

CCHS Publications:
https://www.luriechildrens.org/en-us/care-services/specialties-services/center-for-autonomic-medicine/training-education/Pages/index.aspx

General CCHS Description:
https://www.luriechildrens.org/en-us/care-services/conditions-treatments/congenital-central-hypoventilation-syndrome/Pages/index.aspx