55 Kenosia Avenue
Danbury, CT 06810
Phone: 203.744.0100
Toll Free: 1.800.999.6673
http://rarediseases.org

Congenital Central Hypoventilation Syndrome

NORD is very grateful to Samantha C. Gordon, BS, Center for Autonomic Medicine in Pediatrics (CAMP), Ann & Robert H. Lurie Children's Hospital of Chicago; Casey M. Rand, BS, Center for Autonomic Medicine in Pediatrics (CAMP), Ann & Robert H. Lurie Children's Hospital of Chicago; and Debra E. Weese-Mayer, MD, Professor of Pediatrics at Northwestern University Feinberg School of Medicine and Chief, Center for Autonomic Medicine in Pediatrics (CAMP), Ann & Robert H. Lurie Children's Hospital of Chicago, for assistance in the preparation of this report.

Synonyms of Congenital Central Hypoventilation Syndrome

- autonomic control, congenital failure of
- CCHS
- CCHS with Hirschsprung disease, included

- Ondine curse, congenital

Disorder Subdivisions

- No subdivisions found.

General Discussion

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of respiratory control and autonomic nervous system (ANS) regulation. Respiratory control is the automatic function of breathing in response to varied activities of daily living (ex. exercise, concentration, sleep, eating), so within the context of the ANS. The ANS is the portion of the nervous system that controls or regulates many involuntary body functions including heart rate, blood pressure, temperature regulation, bowel and bladder control, breathing, and more. Impaired breathing regulation (respiratory control) is the hallmark of CCHS. Individuals with CCHS typically present in the newborn period with inadequate shallow breathing (alveolar hypoventilation) during sleep and, in more severely affected individuals, during wakefulness and sleep. Breathing complications occur despite normal lungs and a normal airway, because of the abnormal control of breathing. A growing number of individuals are now being identified whose symptoms were not apparent until later infancy, childhood, or even adulthood and are called later onset congenital central hypoventilation syndrome (LO-CCHS).

All individuals with CCHS have a mutation in the PHOX2B gene. The PHOX2B gene plays an important role in the prenatal development of the ANS. The normal PHOX2B gene has a region with 20 repeats of a code for the amino acid, alanine. For those individuals with CCHS, the majority (~90%) have a mutation causing an increase in the number of these alanine repeats above the normal 20 alanines. This is called a polyalanine repeat expansion mutation (PARM). The expansion can be from 24 to 33 alanines, so the genotype for CCHS patients will be 20/24-20/33 (reflecting the normal number of alanines on the normal gene (n=20) and the number of alanines on the abnormal gene (n==24-33). The remaining individuals with CCHS have a different type of abnormality in the PHOX2B gene. These other mutations in the PHOX2B gene are called non-polyalanine repeat expansion mutations (NPARM). They can be missense, nonsense, frameshift, or stop codon mutations and they will typically severely alter the protein coded by the PHOX2B gene.

Symptoms

The symptoms and severity of CCHS vary from one individual to another, though for many features of the clinical presentation the type of mutation in the PHOX2B gene

and the repeat length (number of alanines in the affected region) are related to CCHS disease severity. A rapidly expanding understanding of the risks specific to the PHOX2B mutation is allowing physicians and parents to anticipate risks for continuous ventilation, pauses in the heart rhythm, Hirschsprung disease, and tumors of neural crest origin in individuals with CCHS (this is referred to as anticipatory management).

The hallmark of CCHS is duskiness or a bluish discoloration of the skin and mucous membranes (cyanosis), resulting from very shallow breathing, and a general decrease in breathing (hypoventilation) during sleep (nap and night). Because of the innate control of breathing abnormality, the individual with CCHS will not increase her/his breathing or awaken to abnormal oxygen and carbon dioxide levels. In more severely affected patients with CCHS, the hypoventilation is apparent awake and asleep. In all patients with CCHS, a lack of normal responsivity to low oxygen and elevated carbon dioxide occurs during wakefulness as well as sleep, even when awake breathing is adequate. So individuals with CCHS will not increase their rate or depth of breathing, nor will they "sense" the low oxygen/high carbon dioxide awake or asleep (they will not become short of breath). Consequently, they are at increased risk for organ damage and neurocognitive delay if not conservatively managed to optimize oxygenation and ventilation.

Some individuals with CCHS have anatomic/structural malformations including Hirschsprung disease (absent ganglion cells of the distal intestine). Overall, 16-20% of individuals with CCHS have Hirschsprung disease, but the risk is higher for those who have longer PARMs (increased alanine number; genotypes 20/26-20/33) or who have NPARMs (more than 50% of these patients). Likewise, tumors of neural crest origin have been described in patients with CCHS. Ganglioneuromas and ganglioneuroblastomas are rare but have been identified in a small subset of individuals with large polyalanine repeat expansion PARMs (specifically genotypes 20/29 and 20/33), though recently one infant with the 20/33 genotype has been identified with a neuroblastoma). Neuroblastoma has been described in up to 40% of individuals with NPARMs.

Individuals with CCHS may also have characteristic facies, heart rhythm abnormalities such as brief episodes when the heart stops beating (cardiac asystole), abnormalities affecting the normal contractions of the digestive system (altered gut motility) even in the absence of Hirschsprung disease, altered temperature regulation and pain perception, decreased anxiety, altered pupillary response to light, and other eye abnormalities. Many of these characteristics of ANS dysregulation (ANSD) have been related to the specific PHOX2B genotype, allowing for anticipatory management.

Causes

PHOX2B, the disease-defining gene for CCHS, is located on chromosome 4 (specifically, 4p12). Chromosomes, which are present in the nucleus of human cells, carry the genetic information for each individual. Human body cells normally have 46 chromosomes. Pairs of human chromosomes are numbered from 1 through 22 and the sex chromosomes are designated X and Y. Males have one X and one Y chromosome and females have two X chromosomes. Each chromosome has a short arm designated "p" and a long arm designated "q". Chromosomes are further sub-divided into many bands that are numbered. For example, "chromosome 4p12" refers to band 12 on the short arm of chromosome 4. The numbered bands specify the location of the thousands of genes that are present on each chromosome. Genes contain the instructions for creating proteins which perform vital functions in the body.

The vast majority of individuals (90%) with CCHS are heterozygous for a polyalanine repeat expansion mutation (PARM) in exon 3 of the PHOX2B gene: the normal allele will have the normal 20 alanine repeats and the expanded allele will have anywhere from 24 all the way up to 33 repeats. Heterozygous means that patients with CCHS have one normal PHOX2B gene (with the normal 20 alanines) and one abnormal PHOX2B gene (with the expanded number of alanines). So the PHOX2B genotype range for an individual with a PARM will be 20/24-20/33. The remaining ~10% of individuals with CCHS have a non-polyalanine repeat expansion mutation (NPARM) typically between the end of exon 2 and into exon 3 of the PHOX2B gene. The altered DNA sequences resulting in the PARMs and NPARMs cause the protein resulting from the PHOX2B gene to function improperly. Fewer than 1% of children with CCHS will be missing most of exon 3 or potentially missing the entire PHOX2B gene on one chromosome.

The PHOX2B mutation results in malregulation of involuntary or automatic body functions primarily by abnormal development of early embryonic cells that form the neural crest. Individuals with the NPARMs will typically be more severely affected than individuals with the PARMs, and individuals with the greater number of alanine repeats (higher genotype number) will typically be more severely affected than those with the fewer number of repeats (at least among the more common PHOX2B genotypes: 20/25, 20/26, 20/27).

Genetic diseases are determined by the combination of genes for a particular trait that are on the chromosomes received from the father and the mother. CCHS and the PHOX2B mutations are inherited in an autosomal dominant manner. Autosomal dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from

either parent, or can be the result of a new mutation (gene change) in the affected individual (this is called a de novo mutation). Though 70-75% of the CCHS-related PHOX2B mutations are not inherited (new mutations or de novo), up to 25% of parents of children with CCHS are mosaic (somatic mosaicism) for the same mutation. That means that these mosaic parents have the PHOX2B mutation in some of the cells of their body, but presumably not in their brains as among those tested to date they breathe normally and do not appear to have CCHS. A subset of parents may have germline mosaicism, meaning that the PHOX2B mutation is apparent in a subset of either the ovum or the sperm.

The risk of passing the abnormal gene from an affected parent to her/his offspring is 50% for each pregnancy regardless of the sex of the resulting child or of the affected parent. The risk of passing the abnormal gene from mosaic parent to offspring is up to 50% for each pregnancy regardless of the sex of the resulting child. An individual with CCHS can have either a totally healthy normal child or a child with CCHS. Likewise, a mosaic parent can have either a totally healthy normal child or a child with CCHS. A mosaic parent cannot have a mosaic child. When inherited, the PHOX2B mutation (repeat number in the PARMs or the specific NPARM) will be identical in the parent and the child (so no change from one generation to the next as reported in other inherited diseases like Huntington's disease).

Some individuals affected with CCHS have been found to have mutations in other genes, but these mutations do not cause CCHS.

Affected Populations

Congenital central hypoventilation syndrome (CCHS) is a rare disorder that affects females and males in equal numbers. Though the mutation is already present before birth, in milder cases the diagnosis may be missed until after the newborn period. Some affected individuals will not be identified until after receiving sedation, anesthesia, or anti-seizure medications, making it especially important to educate health care personnel about CCHS and to have a high index of suspicion for considering a diagnosis of CCHS. As of 2013, more than 1,000 cases are known worldwide. The birth prevalence of CCHS has been extrapolated from incidence figures and general birth rates, but the true prevalence is unknown as culturally diverse large population based studies have not been reported. Because the milder cases of CCHS may go unrecognized or misdiagnosed, it is difficult to estimate the true frequency of CCHS in the general population, though the anticipation is far greater than the current estimate.

Related Disorders

The following disorders might be considered in the differential diagnosis of CCHS: Before the opportunity for genetic testing to confirm CCHS, and the description of the characteristic facies in CCHS, the diagnosis was essentially one of exclusion. CCHS was diagnosed in the absence of primary lung, cardiac, neuromuscular, or causative brainstem abnormalities. Even those diagnoses listed below do not have the anticipated phenotype of CCHS including symptoms of autonomic dysregulation and PHOX2B mutation.

Congenital myopathy is a term for any muscle disorder present at birth. By this definition the congenital myopathies could include hundreds of distinct neuromuscular syndromes and disorders. In general, congenital myopathies cause loss of muscle tone and muscle weakness in infancy and delayed motor milestones, such as walking, later in childhood. Three distinct disorders are definitively classified as congenital myopathies: central core disease, nemaline rod myopathy, and centronuclear (myotubular) myopathy.

Congenital myasthenia usually occurs in infants but may become evident in adulthood. Associated features may vary in severity from case to case. Such abnormalities may include feeding difficulties, periods with absence of spontaneous breathing (apnea), failure to grow and gain weight at the expected rate, muscle weakness and fatigue, weakness or paralysis of eye muscles (ophthalmoplegia), and/or other abnormalities.

Moebius syndrome is a rare developmental disorder that may have a number of different causes and is characterized by facial paralysis present at birth (congenital). Facial nerve development is absent or diminished causing abnormalities of the facial muscles and jaw. Additional symptoms may include numerous abnormalities of the mouth and face (orofacial region) and potentially malformations of limbs. Mental retardation occurs in approximately 10 percent of cases. (For more information on this disorder, choose "Moebius" as your search term in the Rare Disease Database.)

When CCHS occurs in adults it may be confused with other more common respiratory diseases such as obstructive sleep apnea unresponsive to traditional management. Notably individuals with CCHS, regardless of age at presentation/diagnosis, will not have shortness of breath as they do not perceive low oxygen or elevated carbon dioxide. After the airway obstruction has been treated, the hypoventilation becomes more apparent. Among adults in whom a diagnosis of CCHS is considered, a careful family tree asking about offspring with CCHS should be obtained.

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a related but separate disorder. Children with ROHHAD

typically present between the ages of 1.5 and 7 years of age with a rapid weight gain of 20 or more pounds over a 6 month period. They are then noted to have symptoms of hypothalamic dysfunction such as water imbalance, growth insufficiency, hypothyroidism, cortisol abnormalities, and more. A subset of the cases of ROHHAD will experience a respiratory arrest early in their course but subsequent to an intercurrent illness. Many of the children with ROHHAD will have antecedent obstructive sleep apnea. Once the obstructive sleep apnea is treated, the children will be noted to have hypoventilation, even among those who did not endure a cardiorespiratory arrest. Soon thereafter the children will be noted to have other symptoms of ANSD including dramatically low body temperatures, icy cold hands and feet, and very slow heart rates. Many of the children will have tumors of neural crest origin (ganglioneuromas and ganglioneuroblastomas). Children with ROHHAD do not have CCHS-related mutations in the PHOX2B gene. The genetic basis for ROHHAD is not yet known. (For more information on this disorder, choose "ROHHAD" as your search term in the Rare Disease Database.)

The following disorders may be associated with CCHS as secondary characteristics. They are not necessary to confirm a diagnosis of CCHS, though in an infant/child with cyanotic spells during sleep they will heighten the suspicion of the physician that an individual has CCHS.

Hirschsprung disease is a rare gastrointestinal disorder characterized by absence at birth of certain cells (autonomic ganglia) in the lower segment of the large bowel. The ability of the colon to push intestinal contents along the length of the bowel (peristalsis) is absent or impaired. The lower bowel is typically in continuous spasm and is abnormally dilated (megacolon). The symptoms of Hirschsprung disease appear soon after birth and may include constipation, abdominal distention and vomiting. Older infants may have a profound loss of appetite (anorexia), failure to thrive and severe constipation. Some individuals will have unresolved constipation at an older age, suggesting short segment Hirschsprung disease. (For more information about this disease, choose "Hirschsprung" as your search term in the Rare Disease Database.)

Epilepsy is a group of disorders of the central nervous system characterized by repeated convulsive electrical disturbances in the brain. In CCHS the cause of seizures is most often due to suboptimal ventilatory management, resulting in low oxygen. The major symptoms may include loss of consciousness, convulsions and spasms. The symptoms of a grand mal seizure may include loss of consciousness, violent muscle spasms, gnashing of teeth, loss of bladder and/or bowel control, confusion, and/or drowsiness. (For more information on these disorders, choose "epilepsy" as your search term in the Rare Disease Database).

Standard Therapies

Diagnosis and Clinical Testing

The diagnosis of CCHS is based on the clinical presentation, the related clinical features, documentation of an absence of other potentially confounding diagnoses, and confirmation with clinically available PHOX2B testing. The 2010 American Thoracic Society (ATS) Statement on CCHS advises stepwise PHOX2B testing to identify specific mutations in this disease-defining gene for CCHS. The PHOX2B Screening Test is the first step in making the genetic diagnosis of CCHS. This test will diagnose all of the polyalanine repeat expansion mutations (PARMs), mosaicism, polyalanine repeat contraction mutations (fewer than the normal 20 alanines on the affected chromosome), and the large deletion non-polyalanine expansion mutations (NPARMs). Another name for the PHOX2B Screening Test is fragment analysis (see www.genetests.org). If the PHOX2BScreening Test is normal and the subject has the clinical presentation of CCHS, then the sequel PHOX2B Sequencing Test should be performed. The PHOX2B Sequencing Test will detect the PARMs, the contractions, and the NPARMs but it will not detect mosaicism, so this test is rarely useful in asymptomatic parents of children with CCHS. Because the PHOX2B Screening Test is less expensive with a more rapid turnaround time than the PHOX2B Sequencing Test, and it will detect the vast majority of the cases of CCHS, the two-step testing process is least costly, most expeditious, and most efficient for nearly all patients in whom CCHS is considered. A third step of testing was introduced subsequent to the 2010 ATS Statement on CCHS. This is called MLPA PHOX2B testing and will identify large deletions and duplications involving the PHOX2B gene and potentially neighboring genes. The actual phenotype for individuals with these large deletions is variable (likely because many genes including the PHOX2B gene are deleted, rather than an isolated segment of the PHOX2B gene).

As recommended in the 2010 ATS Statement on CCHS, physiologic evaluation should include annual comprehensive assessment during spontaneous breathing awake (in varying levels of concentration and activity) and during sleep in a pediatric respiratory physiology laboratory with extensive expertise in CCHS (often referred to as Centers of Excellence). Responses to endogenous (the result of the child's own hypoventilation) and exogenous (ventilatory challenges from inhaled gas mixtures) hypercarbia, hypoxemia, and hyperoxia should be assessed, ideally awake and asleep. 72 hour Holter recording should be performed annually to evaluate for asystoles (prolonged sinus pause) that might require a cardiac pacemaker. A head up tilt test should be performed annually to better understand the autonomic response to positional changes. An echocardiogram should be performed annually to rule out cor pulmonale or right ventricular hypertrophy (response to low oxygen from insufficient ventilator management). Neurocognitive testing should be performed annually to

determine the effectiveness of the ventilatory management and compliance. In infants under the age of three years, the above-described testing should be performed every 6 months. Gastrointestinal motility studies and, if indicated, a rectal biopsy should be performed in the event of severe constipation. All of the above described tests are part of routine standard of care for individuals with CCHS. Efforts are underway to create an expanded comprehensive testing profile for autonomic regulation in children which will also be considered standard of care for children with CCHS (testing of temperature regulation, vasomotor tone, integration of breathing, heart rate, and blood pressure, cerebrovascular regional blood flow, and pupillometry have already been integrated into care). These comprehensive evaluations are typically performed inpatient to optimize safety and assure the test results are representative of the patient's condition.

Treatment

Most importantly, individuals with CCHS will require artificial respiratory support asleep and in more severe cases awake and asleep. The safest way to deliver this is with a mechanical ventilator via a tracheostomy. The tracheostomy requires a surgical procedure in which an opening is surgically created in the throat (tracheostomy) into which a small tube (cannula) is inserted. The patient requires a mechanical ventilator at home (with a back-up ventilator, pulse oximeter, end tidal carbon dioxide monitor, generator and ventilator batteries) as well as experienced registered nursing (R.N.) care for 12-24 hours/day (depending upon the patient's ventilatory needs and fragility). In older children and adults, non-invasive (mask) ventilation may be considered. This technique is discouraged in infants and young children because of the risk of facial deformation from the mask and inadequate stability of mask ventilation at a time of rapidly progressing neurodevelopment. The goal is to optimize oxygenation and ventilation in order to optimize neurocognitive outcome. CCHS is a life-long disease and children with CCHS will always require artificial ventilation during sleep. Ventilatory needs will vary with the specific PHOX2B mutation. For example, individuals with small repeat expansions will typically require ventilator support during sleep only, whereas individuals with large repeat expansions and those with an NPARM will typically require artificial ventilation 24 hours/day (though exceptions have been identified). Supplemental oxygen alone is not adequate for treating the individual with CCHS. In select cases, other assistive breathing apparatus and/or techniques may be used such as diaphragm pacing. This technique may be used for 24 hour ventilator-dependent patients such that diaphragm pacing is used awake and mechanical ventilation during sleep. In older patients who are ventilator-dependent during sleep only, a subset might benefit from diaphragm pacing (but with knowledge that the pacer transmitter has no alarms to alert the patient or caregivers to pacer dysfunction). Those patients using diaphragm pacers during sleep will continue to require continuous monitoring with pulse oximetry and end tidal carbon dioxide

monitoring, and ideally an awake RN to intervene in the event of physiologic compromise or diaphragm pacer dysfunction.

Some individuals with CCHS develop prolonged sinus pauses (asystoles) which require a cardiac pacemaker to correct the heart rhythm. The risk for asystoles varies with the specific PHOX2B mutation. Among children with the most common PARMs (20/25, 20/26, 20/27), those with the PHOX2B 20/27 genotype are at greatest risk (more than 80% of 20/27 patients will have a sinus pause of 3 seconds or longer). To date children with the 20/25 genotype have not been noted to have sinus pauses in childhood, but adults with the 20/25 genotype whose diagnosis was missed at an earlier age have documented prolonged sinus pauses.

Treatment of Hirschsprung disease usually consists of surgery to remove the non-functional segment of bowel and relieve obstruction. First, a temporary bowel opening of the colon in the abdominal wall (colostomy) is usually performed. The second operation consists of removing the diseased parts of the colon and rectum and connecting the normal bowel to the anus. In some centers with extensive expertise in Hirschsprung disease, the above-described procedures can be performed in one surgery.

Neuroblastomas, ganglioneuromas, and ganglioneuroblastomas are removed surgically, followed by chemotherapy in some neuroblastoma cases. The non-neuroblastoma neural crest tumors are often detected anecdotally. Per the 2010 ATS Statement on CCHS children with the 20/28-20/33 PARM genotypes and the NPARMs should be screened at diagnosis of CCHS and with advancing age for neural crest tumors.

Multidisciplinary care from a Center of Excellence with long-term comprehensive experience in the care of children and adults with CCHS, in collaboration with each patients' medical team closer to home, is key to the successful management of these patients. This team may include pediatricians, med-peds physicians, pulmonologists, cardiologists, intensivists, ENT physicians, surgeons, sleep medicine physicians, gastroenterologists, endocrinologists, neurologists, ophthalmologists, psychologists, psychiatrists, respiratory therapists, nurses, social workers, speech and language therapists, special education teachers, and more.

A high index of suspicion, early detection, and aggressive conservative intervention are critical to optimizing neurocognitive outcome and quality of life for individuals with CCHS. If inadequately treated, the affected individuals will likely suffer neurocognitive compromise and potentially sudden death. If treated conservatively and followed comprehensively, individuals with CCHS can have a good quality of life

and an anticipated normal life span, as evidence from increasing numbers of children with CCHS graduating from college, graduate school, and entering the work force.

Investigational Therapies

An international CCHS Registry has become clinically available for all patients with the clinical and PHOX2B mutation-confirmed diagnosis of CCHS, as well as unaffected parents carrying the PHOX2B mutation. The purpose of the Registry is to collect data about the clinical development of CCHS in relation to each patient's PHOX2B mutation. Participating families will be asked to fill out an on-line registry questionnaire initially, and will simply be asked for updates annually. This is achieved with a secure questionnaire via REDCap (Research Electronic Data Capture). The aim is to consent and enroll ALL CCHS patients worldwide in order to have a central repository to advance understanding of this rare disease and improve early diagnosis, offer anticipatory management, and decrease disease burden.

If physicians or parents are interested in enrolling in the International CCHS REDCap Registry, they should contact the authors of this NORD entry:
SAGordon@LurieChildrens.org
CRand@LurieChildrens.org
DWeese-Mayer@LurieChildrens.org

For more information on Congenital Central Hypoventilation Syndrome and/or PHOX2B Testing, please contact:

Debra E. Weese-Mayer, M.D.
Professor of Pediatrics at Northwestern University Feinberg School of Medicine
Chief, Center for Autonomic Medicine in Pediatrics (C.A.M.P.)
Ann & Robert H. Lurie Children's Hospital of Chicago
250 East Chicago Avenue--Mailstop #165
Chicago, IL 60611
phone: 312-227-3300
fax: 312-227-9606
e-mail: DWeese-Mayer@LurieChildrens.org
Web address: http://www.luriechildrens.org/en-us/care-services/conditions-treatments/autonomic-medicine/Pages/basics/basics.aspx

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov . All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email: prpl@cc.nih.gov

For information about clinical trials sponsored by private sources, contact: www.centerwatch.com

For information about clinical trials conducted in Europe, contact: https://www.clinicaltrialsregister.eu/

Organizations related to Congenital Central Hypoventilation Syndrome

- CCHS Family Network (Congenital Central Hypoventilation Syndrome)

  71 Maple Street
  Oneonta, NY 13820 USA
  Phone #: 607-432-8872
  800 #: --
  e-mail: vanderlaanm@hartwick.edu
  Home page: http://www.CCHSNetwork.org

- Genetic and Rare Diseases (GARD) Information Center

  PO Box 8126
  Gaithersburg, MD 20898-8126
  Phone #: 301-251-4925
  800 #: 888-205-2311
  e-mail: N/A
  Home page: http://rarediseases.info.nih.gov/GARD/

- International Foundation for Functional Gastrointestinal Disorders

  700 W. Virginia St., 201
  Milwaukee, WI 53217 USA
  Phone #: 414-964-1799
  800 #: 888-964-2001
  e-mail: iffgd@iffgd.org
  Home page: http://www.iffgd.org

- NIH/National Institute of Neurological Disorders and Stroke

  P.O. Box 5801
  Bethesda, MD 20824
  Phone #: 301-496-5751
  800 #: 800-352-9424
  e-mail: N/A
  Home page: http://www.ninds.nih.gov/

References

JOURNAL ARTICLES and CHAPTERS
Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, Keens TG, and Trang H: American Thoracic Society Statement. Congenital central hypoventilation syndrome: Genetic basis, diagnosis, and management. Am J Respir Crit Care Med 181:626-644, 2010.

Carroll MS, Pallavi PP, and Weese-Mayer DE: Carbon dioxide chemoreception and hypoventilation syndromes with autonomic dysregulation. J Appl Physiol 108: 979 - 988, 2010.

Rand CM, Patwari PP, Carroll MS, and Weese-Mayer DE: Congenital central hypoventilation syndrome & sudden infant death syndrome: Disorders of autonomic regulation. Seminars in Pediatric Neurology 20:44-55, 2013.

Weese-Mayer DE, Patwari PP, Rand CM, Diedrich AM, Kuntz NL, and Berry-Kravis EM: Congenital Central Hypoventilation Syndrome (CCHS) and PHOX2B Mutations. In: Primer on the Autonomic Nervous System (Robertson D, Biaggioni I, Burnstock G, Low PA, and Paton, JFR, editors), Academic Press, Oxford, UK, pp. 445 – 450, 2012.

Amiel J, Laudier B, Attie-Bitach, T et al. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 33:459-61, 2003.

Antic N, Malow BA, Lange N, McEvoy RD, Olson AL, Turkington P, Windisch W, Samuels M, Stevens CA, Berry-Kravis EM, and Weese-Mayer DE: PHOX2B mutation-confirmed congenital central hypoventilation syndrome: Presentation in adulthood. Am J Respir Crit Care Med 174:923-927, 2006.

Axelrod FB, Chelimsky GG, and Weese-Mayer DE: Pediatric autonomic disorders: State of the Art. Pediatrics 118:309-321, 2006.

Berry-Kravis EM, Zhou L, Rand CM, and Weese-Mayer DE: Congenital central hypoventilation syndrome: PHOX2B mutations and phenotype. Am J Respir Crit Care Med 174:1139-1144, 2006.

Chin AC, Shaul DB, Patwari PP, Keens TG, Kenny AS, and Weese-Mayer DE: Diaphragmatic pacing in infants and children with congenital central hypoventilation syndrome (CCHS). In: Sleep Disordered Breathing in Children: A Clinical Guide (Kheirandish-Gozal L and Gozal D, editors), Springer Press, New York, NY, pp. 553-573, 2012. DOI: 10.1007/978-1-60761-725-729, 2012.

Diedrich A, Malow BA, Antic NA, Sato K, Robertson D, Berry-Kravis EM, and Weese-Mayer DE: Vagal and sympathetic heart rate and blood pressure control in adult-onset PHOX2B mutation-confirmed congenital central hypoventilation syndrome. Clin Auton Med 17(3):177-185, 2007.

Goldberg DS, Ludwig IH. Congenital central hypoventilation syndrome: Ocular findings in 37 children. J Pediatr Ophthalmol Strabismus. 33-176-181, 1996.

Gronli JO, Santucci BA, Leurgans SE, and Weese-Mayer DE: Congenital central hypoventilation syndrome: PHOX2B genotype determines risk for sudden death. Pediatr Pulmonol 43:77-86, 2008.

Ize-Ludlow D, Gray J, Sperling MA, et al. Rapid onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation presenting in childhood. Pediatrics 120:e179-e188, 2007.

Marazita ML, Maher BS, Cooper ME, Silvestri JM, Huffman AD, Smok-Pearsall SM, Kowal MH, and Weese-Mayer DE: Genetic segregation analysis of autonomic nervous system dysfunction in families of probands with congenital central hypoventilation syndrome. Am J Med Genet 100:229-236, 2001.

Matera I, Bachetti T, Puppo F, Di Duca M, Morandi F, Casiraghi GM, Cilio MR, Hennekam R, Hofstra R, Schober JG, Ravazzolo R, Ottonello G, Ceccherini I. PHOX2B mutations and polyalanine expansions correlate with the severity of the respiratory phenotype and associated symptoms in both congenital and late onset central hypoventilation syndrome. J Med Genet 41, 373-380, 2004.

Patwari PP, Carroll MS, Rand CM, Kumar R, Harper R, and Weese-Mayer DE: Congenital central hypoventilation syndrome and the PHOX2B gene: A model of respiratory and autonomic dysregulation. Respir Physiol & Neurobiol 173(3):322-335,

2010.

Patwari PP, Stewart TM, Rand CM, Carroll MS, Kuntz NL, Kenny AS, Brogadir CD, and Weese-Mayer DE: Pupillometry in Congenital Central Hypoventilation Syndrome (CCHS): Quantitative evidence of autonomic nervous system dysregulation. Pediatr Res 71(3):280-285, 2012. PMID: 22278185.

Pine DS, Weese-Mayer DE, Silvestri JM, Davies M, and Klein DF: Anxiety and congenital central hypoventilation syndrome. Am J Psychiatry 151:864-870, 1994.

Repetto GM, Corrales RJ, Abara SG, Zhou L, Berry-Kravis EM, Rand CM, and Weese-Mayer DE: Later-onset Congenital Central Hypoventilation Syndrome due to a heterozygous 24-polyalanine repeat expansion mutation in the PHOX2B gene. Acta Paediatr, published on-line October 2008; 98:190-192-195, 2009.

Silvestri JM, Hanna BD, Volgman AS, Jones JP, Barnes SD, and Weese-Mayer DE: Cardiac rhythm disturbances among children with idiopathic congenital central hypoventilation syndrome. Pediatr Pulmonol 29:351-358, 2000.

Silvestri, JM, Weese-Mayer DE, and Flanagan EA: Congenital central hypoventilation syndrome: Cardiorespiratory responses to moderate exercise, simulating daily activity. Pediatr Pulmonol 20:89-93, 1995.

Todd ES, Weinberg SM, Berry-Kravis EM, Silvestri JM, Kenny AS, Rand CM, Zhou L, Maher BS, Marazita ML, Weese-Mayer DE. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: quantitative pattern of dysmorphology. Pediatr Res 59:39-45, 2006.

Todd, ES, Scott NM, Weese-Mayer DE, Weinberg SM, Berry-Kravis EM, Silvestri JM, Kenny AS, Hauptman SA, Zhou L, Marazita ML. Characterization of dermatoglyphics in PHOX2B-confirmed congenital central hypoventilation syndrome. Pediatrics 118(2):e408-414, 2006.

Trochet D, Hong SJ, Lim JK, Brunet JF, Munnich A, Kim KS, Lyonnet S, Goridis C, Amiel J. Molecular consequences of PHOX2B missense, frameshift and alanine expansion mutations leading to autonomic dysfunction. Hum Mol Genet 14:3697-3708, 2005.

Trochet D, de Pontual L, Keren B, Munnich A, Vekemans M, Lyonnet S, Amiel J. Polyalanine expansions might not result from unequal crossing-over. Hum Mut 10:1043-1044, 2007.

Trochet D, de Pontual L, Straus C, Gozal D, Trang H, Landrieu P, Munnich A, Lyonnet S, Gaultier C, Amiel J. PHOX2B germline and somatic mutations in late-onset central hypoventilation syndrome. Am J Respir Crit Care Med 177:906-911, 2008.

Trochet D, O'Brien LM, Gozal D, Trang H, Nordenskjd A, Laudier B, Svensson P-J, Uhrig S, Cole T, Munnich A, Gaultier C, Lyonnet S, Amiel J. PHOX2B genotype allows for prediction of tumor risk in Congenital Central Hypoventilation Syndrome. Am J Hum Genet 76:421-426, 2005.

Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, and Marazita ML: Idiopathic congenital central hypoventilation syndrome: Analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in PHOX2B. Am J Med Genet, published on-line 24 September 2003, 123A:267-278, 2003.

Weese-Mayer DE, Rand CM, Berry-Kravis EM, Jennings LJ, Patwari PP, and Ceccherini I: Congenital central hypoventilation syndrome from past to future: Model for translational and transitional autonomic medicine. Pediatr Pulmonol 44(6):521-535, 2009.

Weese-Mayer DE, Silvestri JM, Marazita ML, and Hoo JJ: Congenital central hypoventilation syndrome: Inheritance and relation to SIDS. Am J Medical Genet 47(3):360-367, 1993.

Weese-Mayer DE, Silvestri JM, Huffman AD, Smok-Pearsall SM, Kowal MH, Maher BS, Cooper ME, and Marazita ML: Case/Control family study of ANS dysfunction in idiopathic congenital central hypoventilation syndrome. Am J Med Genet 100:237-245, 2001.

Zelko FA, Nelson MN, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE: Congenital central hypoventilation syndrome: Neurocognitive functioning in school age children. Pediatric Pulmonology 45(1):92-98, 2010.

INTERNET

Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: congenital central hypoventilation syndrome, genetic basis, diagnosis, and management. Am J Respir Crit Care Med. 2010;181: 626-644. Available at: http://www.atsjournals.org/doi/pdf/10.1164/rccm.200807-1069ST

Accessed August 5, 2013.

Weese-Mayer DE, Marazita ML, Berry-Kravis EM, and Patwari PP: Congenital central hypoventilation syndrome (November 2011) in: GeneReviews at GeneTests: Medical Genetics Information Resource [database online]. Copyright, University of Washington, Seattle, 1997-2013. Available at http://www.ncbi.nlm.nih.gov/books/NBK1427/ Accessed August 5, 2013.

Kniffin CL, ed. Online Mendelian Inheritance in Man (OMIM). Baltimore, MD: The Johns Hopkins University; Entry No. 209880; Last Update: 11/1/2012. Available at: http://omim.org/entry/209880 Accessed August 5, 2013.