Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

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Synonyms of Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation
Disorder Subdivisions

- ROHHADNET

General Discussion

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) is a rare disorder of respiratory control and autonomic nervous system (ANS) regulation, with endocrine system abnormalities. Respiratory control is the automatic function of breathing in response to varied activities of daily living (ex. exercise, 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. The endocrine system is regulated by the hypothalamus, and through hormones it controls growth, energy and water balance, sexual maturation and fertility as well as response to stress.

ROHHAD presents after 1.5 years of age, in otherwise healthy children. The rapid-onset weight gain (often 30 pounds in 6-12 months) is typically the herald of the disease and the harbinger of the later features of the ROHHAD phenotype. The acronym ROHHAD describes the typical sequence of symptoms experienced by most children with ROHHAD, in the order of their appearance. The clinical features of ROHHAD seem to “unfold” with advancing age in each child. ROHHAD was first described in 1965 (albeit under a different name) and since that time at least 100 children have been reported in the literature or identified with this disorder. Because of the high prevalence of cardiorespiratory arrest, early recognition and treatment of the symptoms associated with ROHHAD are essential and may be life-saving.

Symptoms

Children with ROHHAD are seemingly normal before the rapid-onset weight gain, making the diagnosis even more challenging to parents and health care personnel. Between 1.5 and 7 years of age, these children begin to manifest abnormalities that will evolve into the features of ROHHAD. Most commonly, the first sign is dramatic (often 20-30 pounds) and rapid (over 6 to 12 months) weight gain with associated abnormal increase in hunger (hyperphagia). This rapid-onset obesity is considered a sign of hypothalamic dysfunction (abnormality of the endocrine system). Other hypothalamic abnormalities may not be detected at the time of the rapid weight gain,
but will be identified any time from months to years following the rapid-onset obesity. These other hypothalamic/endocrine abnormalities may include inability to maintain normal water balance in the body (leading to abnormally high or low sodium levels), high prolactin levels, low thyroid hormone, early or late puberty, and low cortisol among other abnormalities. Children with ROHHAD can have variable timing and number of these symptoms of hypothalamic dysfunction, but all will have some abnormalities. After the rapid weight gain, children with ROHHAD will begin to show breathing abnormalities. Some children will have obstructive sleep apnea which means that airflow is intermittently blocked during sleep; they may have snoring and they may have pauses in breathing related to the airflow blockage (obstructive apnea). Because obstructive sleep apnea is not unusual in young obese children, health care personnel may not be alarmed at this stage, and a connection to the ROHHAD phenotype might be delayed. All children with ROHHAD develop alveolar hypoventilation with very shallow breathing during sleep (nap and night). In more severely affected patients with ROHHAD, the hypoventilation is apparent awake and asleep. In patients with ROHHAD, 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. This hypoventilation/control of breathing deficit is the most life-threatening feature of ROHHAD, yet it is often unnoticed until after a dramatic event such as a cardiorespiratory arrest. Therefore, all children with ROHHAD will require help with their breathing, relying on a ventilator to prevent low oxygen or increased carbon dioxide. Approximately half of the children with ROHHAD require ventilator support during sleep only and the other half require ventilator support awake and asleep (24-hours per day), though the ventilatory needs of a child with ROHHAD may vary with advancing age (and unfolding of the clinical features of ROHHAD). This ventilator support can be provided with bi-level positive airway pressure through a mask that fits tightly at the nose or with nasal pillows (but with an actual ventilator), with a mechanical ventilator through a surgically made hole in the airway called a tracheostomy, and potentially with diaphragm pacing (still requiring a tracheostomy).

Also after the rapid weight gain, the symptoms of ANS dysregulation (ANSD) become more apparent. As described above, ANSD means that there are abnormalities with the "automatic" regulation of different organ systems of the body. At some point, all patients with ROHHAD have signs of ANSD. These include eye abnormalities such as altered pupil response to light, “lazy eye” (strabismus), intestinal abnormalities such as altered motility which causes chronic constipation or diarrhea, temperature dysregulation with episodes of very high body temperature (hyperthermia) or more typically very low body temperatures (hypothermia), decreased sensation of pain, low heart rhythm that may be so slow that a cardiac pacemaker is required, altered sweating, icy cold hands and feet, and many other symptoms reflecting dysregulation
of automatic functions.

Some individuals (approximately 40%) with ROHHAD will develop anatomic malformations of the ANS which include tumors of neural crest origin (meaning, they originate from a specific type of cell that is seen very early in development of the body). These neural crest tumors found in children with ROHHAD are ganglioneuromas or ganglioneuroblastomas. These neural crest tumors are found in the chest or abdomen, or anywhere along the sympathetic nervous system chain, and can develop at any age. Thus far, no children with ROHHAD have anatomic/structural malformations of the intestine such as Hirschsprung disease (absent ganglion cells of the distal intestine) (in contrast to children with congenital central hypoventilation syndrome (CCHS) which co-occurs with Hirschsprung disease in 16-20% of individuals with CCHS). Tumors of neural crest origin have been described in patients with CCHS, though rarely with polyalanine repeat expansion PHOX2B mutations (PARMs) (genotypes 20/29 and 20/33; if present typically ganglioneuromas and ganglioneuroblastomas) but more commonly with the non-PARMs (NPARMs) (~40% of cases have a neuroblastoma).

Bougneres, et al. suggested the suffix “NET” be added to the name designated by Ize-Ludlow et al in 2007, “ROHHAD”, because of the findings of associated neural crest tumors in a subset of patients with ROHHAD. Because only a subset of patients (33-39%) with ROHHAD will develop these neuroendocrine tumors, and they may be ganglioneuromas or ganglioneuroblastomas but not typically neuroblastoma, the name ROHHADNET is potentially misleading. Further, the development of neural crest tumors has been reported to occur as late as 7 and even 16 years after the onset of obesity. Consequently, making co-occurrence of tumors of neural crest origin requisite to the diagnosis of ROHHAD would lead to missed diagnosis of many of the children and may subsequently lead to devastating consequences due to the high incidence of cardiorespiratory arrest in this population.

Other features in a subset of individuals with ROHHAD include behavioral, mood, and developmental disorders such that the Intelligence Quotient (IQ) score may be reduced. However, a remarkably high percentage of children with ROHHAD have normal or high IQs, suggesting that IQ in children with ROHHAD likely has many related factors. Preliminarily, those children with the behavioral and mood disorders have more typically had suboptimal ventilatory support. Some children with ROHHAD may develop seizures, though this feature may be related to episodes of low oxygen (hypoxemia) levels due to inadequate ventilator support.

Causes
The diagnosis of ROHHAD is currently based on clinical criteria and though investigation of genetic mutations is underway, no specific cause for ROHHAD has been found to date.

**Affected Populations**

ROHHAD is a very rare disorder with approximately 100 cases reported in the literature and clinically to date. Though first described under a different name in 1965, it was not re-named until 2007 nor shown to be distinct from CCHS (documented absence of CCHS-related PHOX2B mutations). Therefore, as ROHHAD is a relatively "new" disorder without many cases identified thus far, it is not yet clear if any certain population is at greater risk for developing ROHHAD. Because of the explosion of exogenous obesity worldwide, a very high level of vigilance in consideration of ROHHAD is essential.

**Related Disorders**

Congenital central hypoventilation syndrome (CCHS) is a disorder of the ANS caused by a gene mutation in the PHOX2B gene that affects the embryologic development of the ANS. Similar to ROHHAD, the "automatic" control of breathing, heart-beat, digestion, and other features of ANSD are among the affected features. In CCHS, the hallmark is hypoventilation while sleeping and, in severe cases, hypoventilation while awake and asleep - despite anatomically normal heart, lung, and airways. Both CCHS and ROHHAD fall within the rubric of respiratory and autonomic disorders of infancy, childhood, and adulthood (RADICA). CCHS is a rare disorder with approximately 1,000 cases described worldwide. Numbers of reported CCHS cases continue to grow, likely because of increased awareness and introduction of a clinically available genetic test (in 2003) - allowing for early diagnosis and improved treatment. CCHS is often diagnosed in the newborn period because of breathing problems, but milder forms of CCHS may go undiagnosed through infancy, childhood, and even adulthood. A simple blood test can be done to look for a PHOX2B gene mutation (PHOX2B is the disease-defining gene for CCHS). Different types of mutations can occur in this gene which will determine how severely an individual with CCHS is affected. Stepwise testing for PHOX2B mutations should be done with close involvement by a physician and genetic counselor. (For more information about this disease, choose “CCHS” as your search term in the Rare Disease Database.)

**Standard Therapies**

Diagnosis
The criteria for diagnosis of ROHHAD include the following: 1) Rapid-onset obesity
and alveolar hypoventilation during sleep starting after the age of 1.5 years, 2) Evidence of hypothalamic dysfunction, as defined by at least 1 of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failed growth hormone stimulation test, corticotrophin deficiency, or altered onset of puberty (delayed or precocious), and 3) Absence of a CCHS-related 
PHOX2B mutation (to genetically distinguish ROHHAD from CCHS). At present there is no genetic testing available to diagnose ROHHAD, so the diagnosis is based on the clinical presentation and clinical course which should include cooperative consultation by experts in the fields of respiratory, endocrine, autonomic medicine, oncology, psychiatry, surgery, ENT, cardiology, psychology, and nutrition.

Clinical Testing
As the symptoms of ROHHAD can have variable presentation in severity and timing, it is essential that an initial comprehensive evaluation be performed to identify the nature of the ANSD and to address appropriate intervention—especially regarding the child’s breathing. Initial evaluation can include overnight polysomnography to evaluate for any signs of obstructive sleep apnea and, more importantly, evidence of central hypoventilation, imaging of chest and abdomen to screen for evidence of neural crest tumors, and comprehensive cardiac evaluation. As the prevalence of cardiorespiratory arrest is relatively high (up to 60% as reported in the literature), it is essential that a comprehensive respiratory, cardiac, endocrine, and oncology evaluation be performed as soon as the diagnosis of ROHHAD is considered.

Sequential comprehensive evaluation is recommended, ideally at a Center with expertise in respiratory and autonomic medicine—including expertise specifically with ROHHAD. This evaluation includes detailed respiratory physiologic evaluation while awake and while asleep, comprehensive cardiac evaluation including 72-hour Holter, cycle ergometry (exercise test), and echocardiogram, neurocognitive testing for tracking intellectual function as a marker for neurologic stability vs. decline, endocrine evaluation for development of new symptoms of hypothalamic dysfunction, and age-appropriate evaluation of ANSD. The frequency of these comprehensive evaluations is dependent upon each patient’s clinical condition and may be as frequent as 3 months and as extended as 12 months.

Children with ROHHAD are typically evaluated in keeping with the current recommendations in the 2010 ATS Statement on CCHS, as there is not an ATS Statement on ROHHAD at present. For children with ROHHAD, the physiologic evaluation should include annual comprehensive physiologic 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 ROHHAD (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 bradycardia 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 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 ROHHAD. 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 ROHHAD (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.

A complete evaluation of endocrine function should be performed with particular attention to water balance regulation, obesity, and other signs of pituitary dysfunction. If hypernatremic dehydration is found, formal testing of antidiuretic hormone secretion should be done before assuming the patient has diabetes insipidus. Patients with ROHHAD can become dehydrated due to lack of thirst with normal or partial antidiuretic hormone function. Obesity can alter growth hormone secretion and levels of insulin-like growth factor-1 (IGF-1) which should be taken into account when assessing growth hormone function.

Complications of obesity including fatty liver, elevated lipids, or diabetes mellitus should be considered. A high suspicion should be maintained for tumors of neural crest origin, with imaging performed upon recognition of scoliosis or an unidentified shadow on chest x-ray.

Treatment
The treatment of ROHHAD at present is based on the clinical features and their relative severity. The obesity is exceedingly difficult to control with diet and exercise. More effective is special emphasis to avoid further weight gain as the child grows vertically (with or without growth hormone supplement to treat growth hormone deficiency), but intervention requires consultation with a nutritionist and
endocrinologist. Since patients with ROHHAD do not increase their breathing adequately during physical exertion, it is important to recommend only modest exertion until safe parameters have been established by a physician based on end tidal carbon dioxide and pulse oximetry monitoring during exercise.

The hypothalamic dysfunction seen in these patients must be evaluated and treated by a pediatric endocrinologist. Since patients with ROHHAD have variable hypothalamic abnormalities, it is important that their care be individualized to meet their particular needs. These treatments may include hormone replacement, a strict fluid intake regimen, and other measures designed to make up for a dysfunctional hypothalamus. Growth hormone administration on the basis of failed stimulation testing has not been shown to improve body composition and use of dopamine agonist to normalize prolactin levels has not been shown to modify the clinical course.

One of the main challenges in ROHHAD is the control of breathing deficit that is typically unapparent at the time of the rapid-onset weight gain, but seems to worsen with advancing age in many children. Some children may initially need artifical ventilation during sleep only, then progress to need for continuous support (awake and asleep). From the beginning, the key goal is optimization of oxygenation and ventilation. Many patients with ROHHAD can be managed with mask ventilation and bi-level positive airway pressure at night only (but provided with an actual mechanical ventilator); those children requiring 24 hour/day mechanical ventilation will need a tracheostomy (surgically creating a temporary opening in the throat into which a small tracheostomy tube is inserted), through which the patient is then mechanically ventilated. These children require a mechanical ventilator at home (with a back-up ventilator, pulse oximeter, end tidal carbon dioxide monitor, and power generator) as well as experienced registered nursing care ideally 24 hours/day. Other assistive breathing techniques such as diaphragm pacing may have limited success due to the obesity associated with ROHHAD, but should be considered in select patients.

In terms of ANSD, individuals with ROHHAD are at risk for severely low heart rates (bradycardia). Their lack of temperature control requires careful regulation of ambient temperature and attention to reduced body temperatures. Ophthalmologic findings including pupillary or other ocular abnormalities (such as “lazy eye”) should be evaluated by a pediatric ophthalmologist. Often, chronic constipation due to gastrointestinal motility dysfunction can be symptomatically treated with stool softeners. Lastly, tumors of neural crest origin, thought to be a form of anatomic (as opposed to physiologic) ANSD, require surgical removal and should be treated in consultation with a pediatric oncologist. To date, surgical removal of the neural crest tumors have not interrupted the unfolding of the ROHHAD phenotype nor induced recovery from the ROHHAD phenotype.
Multidisciplinary care with input from a Center with expertise in ROHHAD is crucial to the successful management of these patients. This team may include primary care physicians, pulmonologists, endocrinologists, cardiologists, intensivists, otolaryngologists, surgeons, gastroenterologists, neurologists, ophthalmologists, psychologists, psychiatrists, respiratory therapists, nurses, social workers, speech and language therapists, special education teachers, and more, all working together with the child and the family to optimize care and quality of life.

A high index of suspicion, early detection, and aggressive conservative intervention are critical to optimizing neurocognitive outcome. If the diagnosis of ROHHAD is delayed and/or if the clinical symptoms are not anticipated and adequately treated, the affected child will likely suffer neurocognitive compromise and be at heightened risk for sudden death. If treated conservatively and followed comprehensively, individuals with ROHHAD can have a good quality of life. It remains unknown if optimally managed children with ROHHAD will have a normal life span, but the anecdotal observation of improved breathing while awake with advancing age is remarkably heartening.

**Investigational Therapies**

An International ROHHAD Registry has become clinically available for all patients with the clinical diagnosis of ROHHAD. The purpose of the Registry is to collect data about the clinical development of ROHHAD with advancing age as the disease process unfolds (and ideally recedes). The Registry is achieved through a secure questionnaire via REDCap (Research Electronic Data Capture). The aim is to consent and enroll ALL patients worldwide with ROHHAD 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 ROHHAD REDCap Registry, they should contact the authors of this NORD entry at the following e-mail addresses:
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For more information on Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) and clinical trials please
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 Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation**

- Genetic and Rare Diseases (GARD) Information Center
  
  PO Box 8126
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  e-mail: N/A

- NIH/National Institute of Neurological Disorders and Stroke
References

JOURNAL ARTICLES


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