British Paediatric Orphan Lung Diseases (BPOLD)

Congenital Central Hypoventilation Syndrome - Dr Colin Wallis

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Definition

Congenital central hypoventilation syndrome (CCHS) – also known as Ondine's curse – is a rare congenital condition in which there is an abnormality of control of respiration in the absence of any identifiable primary central nervous system, neuromuscular, lung or cardiac disease. There is an estimated prevalence of approximately 300 cases worldwide.

Causes

The precise pathophysiological mechanisms underlying CCHS are unclear. Systematic detailed neuroimaging of children with CCHS has not demonstrated any structural defect. Recent genetic studies have identified a heterozygous mutation of the PHOX2B gene in the majority of children with CCHS and consider this a disease defining mutation. Most mutations consist of 5 – 9 alanine expansions within a 20-residue polyalanine tract. Some investigators have claimed an association between the repeat mutation length and the severity of the disease. Mutations of other genes acting as modifiers may explain the heterogeneity of the condition.

Clinical Presentations

Affected children show hypoventilation during sleep, especially non-rapid-eye movement (non-REM) sleep. There is a wide range of phenotypic expression. More severely affected children may also demonstrate hypoventilation whilst awake. Children typically present in the newborn period with cyanosis when falling asleep and no increase in respiratory effort. A clear association of hypoventilation with sleep may only manifest after 2 – 3 months of age. In the most severely affected children, spontaneous ventilation can be troublesome during waking hours as well.
The increase in severity during non-REM sleep helps differentiate CCHS from other causes of hypoventilation which is usually more noticeable during non-REM sleep

If not recognised as a neonate, children with the milder forms may present with cyanosis, oedema, right heart failure or apparent life threatening events.
CCHS is associated with a number of other conditions affecting the autonomic nervous system. These included Hirschprung's disease and neural crest tumours. Other clinical associations include seizures, gastro-oesophageal reflux, cardiac arrhythmias and lack or circadian temperature variation.

Investigations

The diagnosis requires the following criteria:
1. Persistent evidence of hypoventilation during sleep
2. Onset of symptoms usually in the first year of life
3. Absence or primary pulmonary or neuromuscular disease
4. No evidence of primary heart disease

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Initial assessment includes a detailed history, examination, chest imaging. ECG, EEG and MRI of brain and brain stem. Additional assessments may also include metabolic evaluations, exclusion of Hirschprungs disease and additional neuromuscular tests including diaphragmatic function.
The sleep study will require the recording of adequate periods of sleep spent in non-REM and REM states. Full polysomnography is recommended and the measurements or end-tidal and blood gas measurements may be required for objective evidence of hypoxaemia and hypercarbia. CCHS children have an absent or negligible response to hypercarbia. There is now a DNA test for the diagnosis of CCHS. If the test is negative and the physician is confident that the child has the phenotype for CCHS, then sequencing of the PHOX2b gene should be performed. Because of the autosomal dominant inheritance pattern, it would be advisable to perform the test on parents of CCHS probands and on probands with CCHS who are pregnant. Prenatal testing for CCHS can be done on cultured chorionic villus sampled tissue or amniocytes if the PHOX2b mutation in the family is known.

Management
CCHS is a life long condition Respiratory stimulants are ineffective in CCHS. The management requires a multidisciplinary approach to provide long term home ventilatory support tailored to the child's individual needs. The organisation of home ventilation will require the expertise of a team experienced in the discharge and management of home ventilation. Home pulse oximetry monitoring is recommended. There are some children who are able to have ventilation delivered via a non-invasive approach using either mask or negative pressure thoracic devices. The vast majority of young children however require a tracheostomy to deliver ventilatory support reliably.
. Long-term survival is dependent on the optimal maintenance of oxygenation and ventilation. Regular follow up is required with sleep studies to determine that the ventilation remains sufficient. The ventilatory needs can change during childhood and adolescence with some children seemingly appearing to "acquire" awake hypoventilation - especially in the toddler age group. For children with day-time involvement, phrenic nerve pacing has been suggested.

Useful references:

1. Congenital Central Hypoventilation Syndrome: an update.	**Gozal, D.**	**Ped Pulmonology 1998;26:273-282.**
2. Central chemoreceptor function in children.	**Gozal, D.**	**Ped Pulmonology 2001 supplement 23:110 – 113.**
3. Noninvasive ventilator strategies in the management of a newborn infant and three children with congenital central hypoventilation syndrome .	**Tibbals J, Henning RD.**	**Ped Pulmonolgy 2003; 36:544-548.**

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4. Idiopathic congenital central hypoventilation syndrome: diagnosis and management.	**American Thoracic Society**	**Am J Respir Crit Care Med 1999:160;368-373.**
5. Genetics of congenital hypoventilation syndrome: lessons from a seemingly orphan disease.	**Weese-Mayer DE, Berry-Kravis EM.**	**Am J Respir Crit Care Med 2004:170;16.**