

**MINI-SYMPOSIUM: RESPIRATORY CONTROL
IN CHILDREN: NEW TALES, NEW GENES**

Congenital central hypoventilation syndrome: not just another rare disorder

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Summary Congenital central hypoventilation syndrome (CCHS) is a rare syndrome, present from birth, and is defined as the failure of automatic control of breathing. Patients have absent or negligible ventilatory sensitivity to hypercapnia and hypoxaemia during sleep and wakefulness. Therefore, especially while asleep, children with CCHS experience progressive hypercapnia and hypoxaemia. They lack arousal responses and sensations of dyspnoea to the endogenous challenges of isolated hypercapnia and hypoxaemia and to the combined stimulus of hypercapnia and hypoxaemia. Patients with CCHS do not exhibit signs of respiratory distress when challenged with hypercarbia or hypoxia. The diagnosis is one of exclusion, ruling out any primary pulmonary, cardiac, metabolic or neurologic cause for central hypoventilation. CCHS is associated with other manifestations of autonomic nervous system dysfunction, including Hirschsprung's disease. All patients with CCHS require lifelong ventilatory support during sleep but some will be able to maintain adequate ventilation without assistance while awake once past infancy. However, some CCHS patients require ventilatory support for 24 h/day. Modalities of home mechanical-assisted ventilation include positive pressure ventilation via tracheostomy, non-invasive positive pressure ventilation (bi-level ventilation), negative pressure ventilation and diaphragmatic pacers. Supplemental oxygen alone is inadequate treatment. With early diagnosis and adequate ventilatory support, these children can have good outcomes and lead productive lives.

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Once upon a time, there was a mermaid named Ondine. Ondine fell in love and married a mortal knight named Hans, losing her immortality. As time passed, Hans left Ondine for another woman. Poseidon, God of the Sea and Ondine's father, was infuriated by Hans and placed a curse upon him that none of his automatic bodily functions would occur unless he consciously willed them. The story ends as Hans is about to fall asleep, knowing that he will die because he will 'forget to breathe'.

'Ondine's curse' or, more preferably, congenital central hypoventilation syndrome (CCHS) is a rare disorder where patients appear to breathe reasonably well while awake but severely hypoventilate and/or become apnoeic during

sleep. The incidence of CCHS is unknown but it is generally considered to be rare.¹

PATHOPHYSIOLOGY

CCHS is a failure of automatic control of breathing.^{1–7} Since breathing during quiet sleep is controlled almost entirely by the automatic system, ventilation is most severely affected during quiet sleep. Ventilation is better in active, or rapid eye movement (REM) sleep, when cortical input is at its greatest although still not normal.⁸ Hypoventilation is produced by a pattern of decreased tidal volume, with variation in minute ventilation mostly due to variation in respiratory rate. While asleep, children with CCHS experience progressive hypercapnia and hypoxaemia. They have absent or

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negligible ventilatory sensitivity to hypercapnia and hypoxaemia during sleep and wakefulness.⁹ In addition, they lack arousal responses and sensations of dyspnoea to the endogenous challenges of isolated hypercapnia and hypoxaemia and to the combined stimulus of hypercapnia and hypoxaemia, although they may arouse to hypercapnia under controlled circumstances.^{10,11}

Paton *et al.* found that children with CCHS have absent chemoreceptor responses to *both* hypercapnia (central chemoreceptors) and hypoxia (peripheral chemoreceptors), using rebreathing ventilatory response testing, even while awake.⁹ Along with ventilatory responses, humans also have an arousal response to CO₂ and hypoxia. Marcus *et al.* performed hypoxic and hypercapnic arousal responses in CCHS children and showed that most children with CCHS arouse to hypercapnia, under very controlled circumstances, indicating intact central chemoreceptor input.¹¹ Gozal *et al.* hypothesised that the ability of CCHS patients to maintain waking ventilation was due to intact peripheral chemoreceptor function that could stimulate the abnormal brainstem centres if the signal was strong enough.¹² They found that peripheral chemoreceptor function, when assessed by acute hypoxia, hyperoxia or hypercapnia, was present and intact in CCHS children who were able to sustain adequate ventilation during wakefulness. Thus, CCHS appears to represent a primary physiological abnormality of integration of chemoreceptor input to central ventilatory controllers, rather than abnormalities in the chemoreceptors themselves.¹³

Chemoreceptors are thought to be important controllers of ventilation during exercise. In fact, Silvestri *et al.* showed severe gas-exchange abnormalities in full-time ventilatory dependent CCHS patients during moderate exercise.¹⁴ However, Paton *et al.*¹⁵ and Shea *et al.*¹⁶ showed that exercise-induced hyperpnoea can occur in CCHS patients who only require ventilatory assistance during sleep. Paton *et al.* found that these CCHS patients increased minute ventilation and tidal volume with increasing exercise but not as much as normal subjects. Gozal *et al.* showed that *passive* leg motion also increased alveolar ventilation in awake and asleep CCHS children.^{17,18} They speculated that rhythmic entrainment of respiration plays a significant role in the modulation of breathing in CCHS children. This finding also suggests that CCHS patients may be at higher risk for hypoventilation when they are still. Shea *et al.* documented that CCHS patients do increase ventilation with mental activity such as reading, solving arithmetic problems or playing video games,¹⁹ much as normal controls do. Some CCHS children ask to be put back on their ventilators when they perceive the need and can sense dyspnoea due to exercise. Thus, there may be some neural pathways that transmit a feeling of dyspnoea that are independent of brainstem respiratory function.^{20,21}

Most children with CCHS have no pathological lesions in the brainstem, on autopsy and magnetic resonance imaging (MRI), that are thought to be causal.^{22,23} However, children with CCHS have decreased neuronal signal in areas including

the cerebellar vermis when challenged with hypercapnia, hypoxia and cold pressors on functional MRI when compared with controls.^{24–26} Deep cerebellar nuclei in this area integrate sympathetic and parasympathetic responses; dysfunction here may explain both the dysregulation of respiratory responses and other dysautonomias in children with CCHS but much research is needed to prove this further. In addition, reports of neuropathological findings support autonomic nervous system (ANS) dysfunction in CCHS. One infant with CCHS had neuronal loss of the reticular nuclei and nearby cranial nerve nuclei.²⁷ Cutz *et al.* reported small carotid bodies (<50% of control size) with fewer glomus cells in two CCHS patients, suggesting a structural defect in hypoxia responsivity.²³ He also found that neuroepithelial bodies in the airways were relatively hypertrophied, possibly in compensation for the small peripheral chemoreceptors. These remain isolated reports that are not observed in all CCHS patients.

PRESENTATION

In the newborn period, many affected infants will not have the classically described sleep–wakefulness differences; thus, they may appear to have chronic intermittent duskiness, cyanosis and measurable hypercapnia. As their oxygen saturations fall and their carbon dioxide levels rise, affected infants demonstrate no increase in respiratory rate or effort and usually do not arouse or appear distressed. These children, if undetected or misdiagnosed, will present again at a later age with signs of right heart failure and pulmonary hypertension from prolonged periods of hypoxia and hypercapnia.

Some infants with CCHS may present more obviously with frank apnoea and respiratory arrest upon falling asleep. Unlike those infants who have apnoea due to perinatal asphyxia, CCHS patients do not have associated signs of profound neurological damage.

The primitive responses to hypoxia and hypercapnia that ordinarily stimulate respiratory drive in normal breathing are also responsible for increasing the drive in times of stress and illness. Without these responses, patients with CCHS often do not display signs of respiratory distress, such as tachypnoea, nasal flaring or retractions. Without the aid of objective monitoring, their hypoxia/hypercapnia is only detected at a late stage, after the onset of severe cyanosis and central nervous system depression.¹

AETIOLOGY

Interestingly, the legend predicts that this disorder would also include other ANS dysfunctions, which patients with CCHS clearly have. Most commonly, approximately 15–20% of patients with CCHS also have Hirschsprung's disease,^{1,28} aganglionosis of the bowel, that is thought to be caused by neural crest migration abnormalities.²⁹ Other associated manifestations of ANS dysfunction are:³⁰

decreased heart rate variability; decreased breath-to-breath variability; baseline bradycardia or transient asystole; vasovagal syncope; pupillary abnormalities; poor heat tolerance; lack of producing a fever; oesophageal dysmotility³¹ leading to reflux and feeding difficulties and altered sweat patterns. Tumours of neural crest origin (i.e. ganglioneuromas, neuroblastomas) have also been described in patients with CCHS with and without Hirschsprung's disease.¹

The cause of CCHS is unknown but it is likely that this is a generalised disorder of the ANS, perhaps part of a larger neurocristopathy. There are reports of women with CCHS who have given birth to children with CCHS, although there are also CCHS women who have had non-affected children.^{32,33} It has been reported in monozygotic twins, siblings³¹ and half-siblings who have CCHS or CCHS and Hirschsprung's disease. There is an increased incidence of sudden infant death syndrome and other ANS dysfunctions in CCHS relatives. Much research is ongoing to identify genetic links and markers and extent of dysautonomia; however, the details are beyond the scope of this article and are addressed elsewhere in this journal.³⁴

DIAGNOSIS

The diagnosis of CCHS depends on the documentation of hypoventilation during sleep in the absence of primary neuromuscular, lung, cardiac or metabolic disease, or an identifiable brainstem lesion.¹ Confounding variables, including asphyxia, infection, trauma, tumour and infarction, must be delineated from CCHS.

The initial evaluation may include a detailed neurological evaluation that may require a muscle biopsy, chest x ray, fluoroscopy of the diaphragm, bronchoscopy, electrocardiogram, Holter recording, echocardiogram and MRI imaging of the brain and brainstem. Serum and urinary organic acids, amino acids and carnitine levels should be obtained to rule out inborn errors of metabolism. A rectal biopsy should be considered in the event of abdominal distension and constipation due to the association with Hirschsprung's disease.

Ultimately, each child with suspected CCHS should have a detailed recording in a respiratory physiology laboratory to evaluate spontaneous breathing during REM sleep, non-REM sleep and wakefulness. The recording montage should include (at a minimum) movement of the chest and abdomen (respiratory inductance plethysmography), flow at the nose and mouth, SpO₂, end-tidal pCO₂ and electrocardiogram. Non-invasive monitoring of oxygenation and ventilation are preferred, as intermittent blood gas sampling, capillary or otherwise, would cause arousal and therefore not be an accurate 'sleep state' measurement.

Careful observation should be made of the infant's tidal volume and respiratory frequency response to endogenous hypoxaemia and hypercarbia both awake and asleep. While asleep, an arousal response, or more importantly, a lack

thereof, should also be recorded. Such endogenous challenges during spontaneous breathing may be diagnostic without the need for exogenous challenge testing. Infants receiving supplemental oxygen during the study will have falsely elevated oxygen. While there has not been an established diagnostic value, in general, those with CCHS have end-tidal pCO₂ readings persistently above 60 torr while asleep.

While genetic testing for CCHS is not readily available at present, sending blood work for confirmation of the CCHS genetic profile may play a role in future diagnosis.

MANAGEMENT

Trying to compensate for a young child who functionally 'forgets to breathe' when asleep is challenging. The treatment of CCHS is to ensure adequate ventilation for the patients who are unable to achieve adequate gas exchange during spontaneous breathing, or simply put, to 'breathe' for them. This requires mechanical-assisted ventilation^{1,2,5-7} as no pharmacological respiratory stimulants have shown to be effective³⁵⁻³⁸ and they certainly do not prevent the need for ventilatory support. Children with chronically elevated P_{ET}-CO₂ greater than 55-60 torr, due to decreased central respiratory drive, will develop progressive pulmonary hypertension.^{39,40} Supplemental oxygen alone is not sufficient treatment for hypoventilation and will not prevent pulmonary hypertension. Thus, CCHS children require home mechanical ventilation. As children with CCHS do not usually have severe lung disease, they have many options for different techniques to provide mechanical-assisted ventilatory support at home.

We believe infants are best ventilated with positive pressure ventilation (PPV) via tracheostomy and should have one placed soon after diagnosis. It is usually preferable to ventilate infants for 24 h/day for some period of time, assuring that oxygenation and ventilation remain adequate to minimise possible damage to a developing brain. Passy-Muir one-way speaking valves and tracheostomy capping can be done while awake when patients are older to allow for vocalisation and use of the upper airway.

CCHS patients are not like other children on home mechanical ventilation. They must be managed with extreme vigilance due to their lack of objective or subjective responsiveness to hypoxaemia and hypercapnia. Responses to respiratory infections in children with CCHS differ from non-CCHS ventilator-dependent children. Children with CCHS do not typically develop a fever, increase their respiratory rate or have dyspnoea in response to pneumonia,^{1,20} or exhibit symptoms of severe hypoxia and/or hypercapnia. These limitations emphasise the importance of both objective pulse oximetry and end-tidal Pco₂ monitoring, as well as highly skilled and consistent caretakers in the home.⁴¹

Transition to a home portable ventilator should be made in the hospital and discharge planning for home is extensive.

Arrangements for the home ventilator, a backup ventilator, 16–24 h/day of in-home nursing, supplemental oxygen, a pulse oximeter and end-tidal CO₂ monitor are all things that need to be set up prior to discharge. The latter two help to provide objective measures of physiological compromise and adequate ventilator settings.

PHILOSOPHY OF CHRONIC VENTILATORY SUPPORT

All CCHS patients require assisted ventilation during sleep; thus, weaning these patients off mechanical ventilation totally is not a realistic goal. For these children, ventilators are adjusted to provide P_{ETCO₂} consistently between 30–35 torr and S_{pO₂} greater than 95%.⁴² Optimal ventilation avoids atelectasis and the development of co-existing lung disease. Children who are hyperventilated at night have better spontaneous ventilation while awake than those who are ventilated to higher P_{CO₂} levels.⁴³ It has also been our experience that children with CCHS have fewer complications and generally do better clinically with hyperventilation during assisted ventilation. Allowing these children to be borderline or frankly hypercapnic and/or hypoxic defeats the purpose of chronic ventilatory support.

While it should be emphasised that children with CCHS are not candidates for weaning off mechanical-assisted ventilation while asleep, mobility and quality of life are maximised if the child can breathe unassisted for periods of time while awake. Some CCHS children gradually develop the ability to breathe adequately during wakefulness. The weaning of daytime assisted ventilation is best accomplished by sprint weaning.⁴² Sprint weaning is performed by removing the child from the ventilator for short periods of time during wakefulness, between two and four times per day. Between sprints, the child remains on full ventilator settings and support. Initially, these sprints may only last a few minutes and supplemental oxygen may be required. The child must be carefully monitored non-invasively during sprints to prevent hypoxia or hypercapnia. Sprints should be stopped if S_{aO₂} is less than 95%, P_{ETCO₂} is greater than 45–50 torr or there are obvious signs of distress. These parameters should be provided as written orders if home or hospital nursing is involved. However, the CCHS child may *not* exhibit these signs of distress, reiterating the importance of objective non-invasive monitoring. The length of each sprint is increased daily or every few days as tolerated. Increasing the sprint length too rapidly often hinders the progress of weaning.

MODALITIES OF HOME MECHANICAL VENTILATION

Portable PPV via tracheostomy

Portable PPV via tracheostomy is the most common method of providing home mechanical ventilation, espe-

cially for infants and younger children.⁴² Commercially available positive pressure ventilators have the capability for battery operation, are relatively portable and thus maximise mobility. However, they are not as powerful, technologically sophisticated or versatile as traditional hospital ventilators that run on compressed air. Consequently, when infants and children acquire an intercurrent illness (which can be often), hospitalisation with additional ventilatory support may be required.⁴² An uncuffed tracheostomy is required for positive pressure ventilator access to the patient; this is a mainstay for providing optimal ventilatory support at home.

To achieve successful mechanical ventilation at home, the F_{iO₂} that maintains S_{pO₂} greater than or equal to 95% should be 40% or less. The requirement for peak inspiratory pressures (PIP) to achieve adequate ventilation should be less than 40 cmH₂O. Some home ventilators are now available that provide continuous flow of gas, therefore positive end-expiratory pressure (PEEP) and pressure support modes of ventilation are available for the home.

Most commercially available portable positive pressure ventilators are volume pre-set ventilators. In traditional hospital practice, a delivered tidal volume of 10–15 ml/kg is used for mechanical-assisted ventilation in infants, children and adults. A significant portion of the ventilator-delivered breath escapes in the leak around the uncuffed tracheostomy. The tracheostomy leak can be compensated for by using the ventilator in a pressure-limited modality, also known as *pressure plateau ventilation*.^{42,44} The pressure limit on the volume pre-set ventilator is adjusted to the desired PIP and a tidal volume setting is chosen that is sufficient to inflate the lungs, compensate for tubing compliance and accommodate the leak. This technique is very successful in home mechanical ventilation of infants and small children. Some CCHS children have acquired lung disease that may require PEEP or pressure support for successful home ventilation. Ventilator settings should be titrated non-invasively (i.e. sleep laboratory) periodically to ensure adequate oxygenation and mild hyperventilation. Home ventilators have been shown to be safe and, in one large study, ventilator failures did not have any adverse patient outcomes.⁴⁵

Bi-level positive airway pressure ventilation

Non-invasive intermittent PPV is delivered via a nasal mask or face mask using a bi-level positive airway pressure ventilator. Bi-level ventilators are smaller, less expensive and generally easier to use than conventional ventilators. Newer models have pressure and apnoea alarms, adjustable rise times and can be battery operated. Bi-level ventilators can provide variable continuous flow through a blower (fan), have a fixed leak preventing CO₂ retention and can compensate for leaks around the mask. Inspiratory positive airway pressure (I-PAP) and expiratory positive airway pressure (E-PAP) can be adjusted independently.

The I-PAP to E-PAP difference is proportional to tidal volume. I-PAPs greater than 20 cmH₂O generally require chin straps, full face masks or newer oral devices that prevent pressure pop-off through an open mouth, especially during REM sleep.⁴⁶ Heated humidification and supplemental oxygen can be added to the circuit. Only the spontaneous/timed and timed modes guarantee breath delivery and should be used in CCHS patients because these patients can not be trusted to generate their own adequate respirations.

Bi-level ventilation has been used successfully in treating children with CCHS as young as 3 months of age.⁴⁶ Bi-level ventilation is not as powerful as PPV via tracheostomy and generally delivers lower pressures. Bi-level ventilation should not be used for 24 h/day because the mask interferes with daily activities and social interaction and may cause some mid-face hypoplasia. However, CCHS patients who only require ventilatory support during sleep are good candidates for bi-level ventilation. Well-fitting mask/prongs are important to achieve efficacy, improve comfort, increase compliance and reduce complications.

For most CCHS patients, bi-level ventilation allows for tracheostomy decannulation. Therefore, bi-level settings are initially set in a sleep study. As CCHS patients do not usually require high E-PAP to maintain upper airway patency, the E-PAP is usually set low at 4–5 cmH₂O. The I-PAP is then increased to achieve the desired tidal volume, based on $S_{pO_2} \geq 95\%$ and $P_{ETCO_2} \leq 40$ torr. For patients with normal lungs, tidal volume increases as the I-PAP to E-PAP difference increases up to about 15 cmH₂O, after which there is no significant increase in tidal volume.⁴⁶ If successful, tracheal decannulation can be considered.⁴⁷ When anticipating tracheostomy decannulation, we recommend an evaluation of the upper airway size and possible tonsillectomy and adenoidectomy prior to decannulation to optimise upper airway size and minimise upper airway collapse during inspiration. In general, non-invasive ventilation is best started after 5–6 years of age, when the clinical course of CCHS is usually more stable. Many centres now have experience with the successful use of bi-level ventilation in infants and children.

Negative pressure chest shell (cuirass) ventilator, wrap ventilator or Port-a-lung

Negative pressure ventilation (NPV) works by generating a negative inspiratory pressure outside the chest and abdomen to cause an inspiration.⁴⁸ Negative pressure ventilators are not as portable as electronic positive pressure ventilators. The *chest shell (cuirass)* ventilator uses a dome-shaped shell that is fitted over the anterior chest and abdomen. The *negative pressure wrap ventilator* is a 'jump suit' that fits snugly around the neck, wrists and ankles to minimise leaks. A *Port-a-lung* is a portable negative pressure ventilator that an infant or child may fit inside. A negative inspiratory pressure is generated inside the chest shell, wrap or Port-a-lung that expands the chest and upper abdomen.

The ventilator rate and the negative pressure developed inside the chest shell, wrap or Port-a-lung can be selected. The negative pressure is proportional to the tidal volume but may be limited by leaks around the chest shell or wrap. However, airway occlusion can occur when breaths are generated by a negative pressure ventilator during sleep, especially in young children and infants, which may make this a less optimal technique. The effectiveness of NPV depends on the ability to move the chest wall; therefore, those with marked chest wall deformities are poor candidates for NPV. Nevertheless, NPV is used in some children with CCHS, allowing decannulation of the tracheostomy.^{6,42}

Diaphragm pacing

Diaphragm pacing generates breathing using the child's own diaphragm as the respiratory pump and is well suited to infants and children with CCHS.⁴⁹ Commercially available diaphragm pacing systems have a battery-operated external transmitter. An antenna is taped on the skin over subcutaneously implanted receivers. The transmitter generates a train of pulses for each breath that is transmitted through the antenna to the receiver under the skin, similar to radio transmission. The receiver converts this energy to standard electrical current that is directed to a phrenic nerve electrode by lead wires. The electrical stimulation of the phrenic nerve causes a diaphragmatic contraction that generates the breath. The amount of electrical voltage is proportional to the diaphragmatic contraction or tidal volume. In children, simultaneous bilateral diaphragm pacing is generally required to achieve optimal ventilation. As this technique is portable, it is useful for daytime support of ambulatory children requiring full-time ventilatory support, in combination with PPV via tracheostomy or bi-PAP for nocturnal ventilation. In addition, we have successfully transitioned CCHS children from PPV via tracheostomy to diaphragm pacing without the tracheostomy for night-time support. As with all non-invasive ventilation, upper airway obstruction can occur during inspiration and must be properly addressed before tracheostomy decannulation.

Diaphragm pacing requires surgical implantation of bilateral phrenic nerve electrodes, usually intrathoracically. We have recently performed this in nine patients and observed a reduction in the post-operative morbidity from surgery.⁵⁰ Pacing is then gradually initiated 4–6 weeks later, which allows for tissue reaction around the electrodes to stabilise. Initially, diaphragm pacing results in fatigue (decreasing diaphragmatic contraction for the same electrical stimulus) after 60–90 min. Thus, 'aerobic training' of these muscle fibres is required to sustain pacing for the desired 12–16 h/day. We start pacing at 1–2 h/day and gradually increase weekly by 30–60 min/day. Thus, a 'training period' of up to 3–4 months is usually required to achieve full pacing. In general, most children are limited to 12–16 h/day of

diaphragm pacing, although there are a small number of CCHS children who are being paced continuously (24 h/day) without fatigue.

Diaphragm pacers work well but they require frequent attention. Thus, successful diaphragm pacing requires proximity to a medical team willing to maintain this system. Adults have shown no diaphragm or phrenic nerve problems after as long as 30 years of diaphragm pacing but longer-term consequences of phrenic nerve stimulation are unknown. Diaphragmatic pacing is truly portable and allows patients to do things such as go on camping trips. Diaphragmatic pacing has also been used in a term pregnancy of a CCHS mother, who ultimately gave birth to a CCHS child, without compromised ventilation. However, frequent monitoring (every 6 weeks) by polysomnography to assess for adequate oxygenation and ventilation is recommended in pregnancy with any ventilatory support system.³³

CLINICAL COURSE AND PROGNOSIS

During the first few years of life, CCHS infants may be very unstable. Even minor respiratory infections may cause complete apnoea during both sleep and wakefulness. As they mature, the neurological condition does not change (i.e. they will not regain the ventilatory responses to hypoxia or hypercarbia at any age) but the other parts of the respiratory system (lungs, ventilatory muscles and chest wall) will mature, allowing these patients to gradually become more stable. All patients with CCHS will need supported ventilation while asleep but about 65% of CCHS patients are able to come off assisted ventilation while awake.⁶

Children with CCHS can have prolonged survival, with several patients now in young adulthood; most have a good quality of life. Long-term follow-up and neurodevelopmental outcome reveal a broad range of results with a great deal of variability, usually correlating with the degree of severity of their CCHS.⁹

Many children demonstrate findings that may be related to sequelae of intermittent hypoxaemia, such as seizures. Most children have adequate growth and nutrition. Many CCHS children have swallowing discoordination requiring temporary gastrostomies. Many children attend regular classes in regular schools; however, overall, children with CCHS are in the slow learner range of mental processing abilities with learning disabilities but some children with mild CCHS test in the above-average range.

No known cure for CCHS exists and the disorder appears to be lifelong. With an increasing awareness of the disease entity, patients will be recognised and treated earlier than in the past. With earlier diagnosis and treatment, vigilant management of ventilation, improved home equipment and monitoring abilities and rigorous efforts to support an age-appropriate and progressively independent lifestyle, the outlook for these CCHS children is encouraging.

PRACTICE POINTS

- CCHS patients will require lifelong mechanical-assisted ventilation while asleep, as they do not outgrow this disorder
- Not all patients with CCHS will have adequate ventilation in wakefulness and thus may require mechanical-assisted ventilation during wakefulness as well as while asleep
- CCHS patients do not subjectively feel or objectively exhibit signs of dyspnoea or respiratory distress with increasing hypercarbia and hypoxia, reiterating the importance of objective non-invasive monitoring and vigilant care in the home or chronic care setting
- Many patients with CCHS will require additional ventilatory support while acutely ill, frequently requiring admission to hospital for increased ventilator support. Those who are non-invasively ventilated may require endotracheal intubation for PPV with acute illnesses
- Supplemental oxygen alone is inadequate treatment for CCHS as it will not prevent pulmonary hypertension and cor pulmonale from chronic hypoventilation
- CCHS is only diagnosed in the absence of primary pulmonary, cardiac, metabolic or neurologic disease
- While some infants with CCHS present with frank apnoea and respiratory arrest upon falling asleep, the diagnosis of CCHS should also be considered in any infant who presents with intermittent cyanosis and hypercarbia (that is not necessarily more pronounced when asleep)

RESEARCH DIRECTIONS

- Phenotypic correlation with genotypic sequencing.
- Further evaluation and definition of dysautonomias in CCHS.

REFERENCES

1. Weese-Mayer DE, Shannon DC, Keens TG, Silvestri JM. Idiopathic congenital central hypoventilation syndrome: diagnosis and management. *Am J Respir Crit Care Med* 1999; **160**: 368–373.
2. Gozal D. Congenital central hypoventilation syndrome: an update. *Pediatr Pulmonol* 1998; **26**: 273–282.
3. Mellins RB, Balfour HH Jr, Turino GM, Winters RW. Failure of automatic control of ventilation (Ondine's curse). *Medicine* 1970; **49**: 487–504.
4. Guilleminault C, McQuitty J, Ariagno RL, Challamel MJ, Korobkin R, McClead RE. Congenital central alveolar hypoventilation syndrome in six infants. *Pediatrics* 1982; **70**: 684–694.

5. Oren J, Kelly DH, Shannon DC. Long-term follow-up of children with congenital central hypoventilation syndrome. *Pediatrics* 1987; **80**: 375–380.
6. Marcus CL, Jansen MT, Poulsen MK *et al*. Medical and psychosocial outcome of children with congenital central hypoventilation syndrome. *J Pediatr* 1991; **119**: 888–895.
7. Weese-Mayer DE, Silvestri JM, Menzies LJ, Morrow-Kenny AS, Hunt CE, Hauptman SA. Congenital central hypoventilation syndrome: diagnosis, management, and long-term outcome in thirty-two children. *J Pediatr* 1992; **120**: 381–387.
8. Gaultier C, Trang-Pham H, Praud JP, Gallego J. Cardiorespiratory control during sleep in the congenital central hypoventilation syndrome. *Pediatr Pulmonol* 1997; **23**: 140–142.
9. Paton JY, Swaminathan S, Sargent CW, Keens TG. Hypoxic and hypercapnic ventilatory responses in awake children with congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1989; **140**: 368–372.
10. Shea SA, Andres LP, Shannon DC, Guz A, Banzett RB. Respiratory sensations in subjects who lack a ventilatory response to CO₂. *Respir Physiol* 1993; **93**: 203–219.
11. Marcus CL, Bautista DB, Amihya A, Davidson Ward SL, Keens TG. Hypercapnic arousal responses in children with congenital central hypoventilation syndrome. *Pediatrics* 1991; **88**: 993–998.
12. Gozal D, Marcus CL, Shoseyov D, Keens TG. Peripheral chemoreceptor function in children with congenital central hypoventilation syndrome. *J Appl Physiol* 1993; **74**: 379–387.
13. Spengler CM, Gozal D, Shea SA. Chemoreceptive mechanisms elucidated by studies of congenital central hypoventilation syndrome. *Respir Physiol* 2001; **129**: 247–255.
14. Silvestri JM, Weese-Mayer DE, Flanagan EA. Congenital central hypoventilation syndrome: cardiorespiratory responses to moderate exercise simulating daily activity. *Pediatr Pulmonol* 1995; **20**: 89–93.
15. Paton JY, Swaminathan S, Sargent CW, Hawksworth A, Keens TG. Ventilatory response to exercise in children with congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1993; **147**: 1185–1191.
16. Shea SA, Andres LP, Shannon DC, Banzett RB. Ventilatory responses to exercise in humans lacking ventilatory chemosensitivity. *J Appl Physiol* 1993; **68**: 623–640.
17. Gozal D, Marcus CL, Davidson Ward SL, Keens TG. Ventilatory responses to passive leg motion in children with congenital central hypoventilation syndrome. *Am J Respir Crit Care Med* 1996; **153**: 761–768.
18. Gozal D, Simnakajomboon N. Passive motion of the extremities modifies alveolar ventilation during sleep in patients with congenital central hypoventilation syndrome. *Am J Respir Crit Care Med* 2000; **162**: 1747–1751.
19. Shea SA, Andres LP, Paydarfar D, Banzett RB, Shannon DC. Effect of mental activity on breathing in congenital central hypoventilation syndrome. *Respir Physiol* 1993; **94**: 251–263.
20. Shea SA, Andres LP, Shannon DC, Guz A, Banzett RB. Respiratory sensations in subjects who lack a ventilatory response to CO₂. *Respir Physiol* 1993; **93**: 203–219.
21. Spengler CM, Banzett RB, Systrom DM, Shannon DC, Shea SA. Respiratory sensations during heavy exercise in subjects without respiratory chemosensitivity. *Respir Physiol* 1998; **114**: 65–74.
22. Weese-Mayer DE, Brouillette RT, Naidich TP, McClone DG, Hunt CE. Magnetic resonance imaging and computerized tomography in central hypoventilation. *Am Rev Respir Dis* 1998; **137**: 393–398.
23. Cutz E, Ma F, Perrin DG, Moore AM, Becker LE. Peripheral chemoreceptors in congenital central hypoventilation syndrome. *Am J Respir Crit Care Med* 1997; **155**: 358–363.
24. Gozal D, Harper RM. Novel insights into congenital central hypoventilation syndrome. *Curr Opin Pulm Med* 1999; **5**: 335–338.
25. Spriggs D, Saeed MM, Alger JR *et al*. Neural responses to hypoxia in congenital central hypoventilation syndrome (CCHS) visualized by functional magnetic resonance imaging. American Thoracic Society International Conference, San Diego, CA, USA, 23–28 April 1999.
26. Yu PL, Kim AH, Kuo L *et al*. Functional magnetic resonance imaging during cold pressor challenges in congenital central hypoventilation syndrome. Society for Neuroscience Abstracts 26, 2000.
27. Liu HM, Loew JM, Hunt CE. Congenital central hypoventilation syndrome: a pathological study of the neuromuscular system. *Neurology* 1978; **28**: 1013–1019.
28. Haddad GG, Mazza NM, Defendini R *et al*. Congenital failure of automatic control of ventilation, gastrointestinal motility and heart rate. *Medicine Baltimore* 1978; **57**: 517–526.
29. Bolande RP. The neurocristopathies a unifying concept of disease arising in neural crest maldevelopment. *Human Pathol* 1974; **5**: 409–429.
30. Weese-Mayer DE, Silvestri JM, Huffman AD *et al*. Case/control family study of autonomic nervous system dysfunction in idiopathic congenital central hypoventilation syndrome. *Am J Med Genet* 2001; **100**: 237–245.
31. Faure C, Viarme F, Cargill G, Navarero J, Gaultier C, Trang H. Abnormal esophageal motility in children with congenital central hypoventilation syndrome. *Gastroenterology* 2002; **122**: 1258–1263.
32. Silvestri JM, Chen ML, Weese-Mayer DE *et al*. Idiopathic congenital hypoventilation syndrome: the next generation. *Am J Med Genet* 2002; **112**: 46–50.
33. Sritippayawan S, Hamutcu R, Kun SS, Ner Z, Ponce M, Keens TG. Mother-daughter transmission of congenital central hypoventilation syndrome. *Am J Respir Crit Care Med* 2002; **166**: 367–369.
34. Weese-Mayer DE, Berry-Kravis EM, Zouh L *et al*. 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* 2003; **123A**: 267–278.
35. Swaminathan S, Paton JY, Davidson Ward SL, Sargent CW, Keens TG. Theophylline does not increase ventilatory responses to hypercapnia or hypoxia. *Am Rev Respir Dis* 1992; **146**: 1398–1401.
36. Lugliani R, Whipp BJ, Wasserman K. Doxapram hydrochloride: a respiratory stimulant for patients with primary alveolar hypoventilation. *Chest* 1979; **76**: 414–419.
37. Oren J, Newth CJL, Hunt CE, Brouillette RT, Bachand RT, Shannon DC. Ventilatory effects of almitrine bismesylate in congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1986; **134**: 917–919.
38. Hunt CE, Inwood RJ, Shannon DC. Respiratory and nonrespiratory effects of doxapram in congenital central hypoventilation syndrome. *Am Rev Respir Dis* 1979; **119**: 263–269.
39. Barlow PB, Bartlett D Jr, Hauri P *et al*. Idiopathic hypoventilation syndrome: importance of preventing nocturnal hypoxemia and hypercapnia. *Am Rev Respir Dis* 1980; **121**: 141–145.
40. Trowitzsch E, Schluter B. Reversible cor pulmonale in central disorder of respiratory regulation. *Monatsschr Kinderheilkd* 1989; **137**: 733–736.
41. Schafer C, Schafer T, Wolfle GL, Schlafke ME. Continuous ambulatory monitoring in quality control of home therapy for congenital central hypoventilation syndrome (CCHS). *Wien Med Wochenschr* 1996; **146**: 323–324.
42. Keens TG, Davidson Ward SL. Ventilatory treatment at home. In: Beckerman RC, Brouillette RT, Hunt CE (eds). *Respiratory Control Disorders in Infants and Children*. Baltimore: Williams and Wilkins, 1992; 371–385.
43. Gozal D, Keens TG. Passive nighttime hypocapnic hyperventilation improves daytime eucapnia in mechanically ventilated children. *Am J Respir Crit Care Med* 1998; **157**: A779.
44. Gilgoff IS, Peng RC, Keens TG. Hypoventilation and apnea in children during mechanical assisted ventilation. *Chest* 1992; **101**: 1500–1506.
45. Srinivasan S, Doty SM, White TR *et al*. Frequency, causes, and outcome of home ventilator failure. *Chest* 1998; **114**: 1363–1367.
46. Marcus CL. Ventilator management of abnormal breathing during sleep: continuous positive airway pressure and nocturnal noninvasive positive pressure ventilation. In: Loughlin GM, Marcus CL, Carroll JL (eds). *Sleep and Breathing in Children*. Lung Biology in Health and Disease series. New York: Marcel Dekker, 2000; 797–811.

47. Schafer T, Schafer C, Schlafke ME. From tracheostomy to non-invasive mask ventilation: a study in children with congenital central hypoventilation syndrome. *Med Klin* 1999; **94**: 66–69.
48. Hartmann H, Samuels MP, Noyes JP, Southall DP. Negative extrathoracic pressure ventilation in infants and young children with central hypoventilation syndrome. *Pediatr Pulmonol* 1997; **23**: 155–157.
49. Weese-Mayer DE. Diaphragm pacing in infancy and childhood. In: Loughlin GM, Marcus CL, Carroll JL (eds). *Sleep and Breathing in Children*. Lung Biology in Health and Disease series. New York: Marcel Dekker, 2000; 813–824.
50. Shaul DB, Danielson PD, McComb JG, Keens TG. Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing in children. *J Pediatr Surg* 2002; **37**: 974–978.