Congenital central hypoventilation syndrome in children: a Hong Kong perspective

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Hong Kong Med J 2023;29:342–8
https://doi.org/10.12809/hkmj219260

Introduction

Congenital central hypoventilation syndrome (CCHS), also known as Ondine's curse, is a central nervous system disorder involving failed autonomic control of breathing. Affected patients generally require tracheostomy and lifetime mechanical ventilator support.[1-4] As a sleep-related breathing disorder, CCHS causes ineffective breathing, apnoea, or respiratory arrest during sleep and—rarely—wakefulness. The condition can be fatal if untreated. An infant with 'Ondine's curse' (a name based on a Greek myth about a curse that prevented breathing during sleep) was described in 1970.[5] The term CCHS was first used in 1962 to describe symptoms in adults,[6] then later to describe symptoms in neonates.[7] The current definition of CCHS includes diverse clinical manifestations. Paired-like homeobox 2B (*PHOX2B*) gene variants are the main causes of the syndrome; other causative variants are rare.[7] Early diagnosis can prevent life-threatening events and long-term sequelae. Better knowledge of CCHS and advances in genetics research will help affected patients to consistently receive early treatment, thereby improving survival and long-term outcomes. This article summarises current management of CCHS in children.

Literature search

A literature search was performed in Ovid MEDLINE, PubMed, and Embase using the key words 'congenital central hypoventilation syndrome', 'alveolar hypoventilation', 'CCHS', 'Ondine's curse', 'autonomic dysregulation', and 'PHOX2B'. Retrieved articles were carefully screened; relevant articles (eg, reviews, randomised controlled trials, case control studies, cohort studies, case reports, and case series) were fully reviewed by the authors. Clinical guideline databases, trials registries, and reference lists of retrieved articles were also reviewed.

Epidemiology

The global incidence of CCHS ranges from 1/50 000 to 1/200 000 live births, with a prevalence of around 1/500 000.[8-10] The demographics of CCHS among children in Hong Kong are unknown. There have been three reports of patients with CCHS in Hong Kong.[4,11,12]

Aetiology

Central hypoventilation syndrome may be congenital or the result of trauma/injury and neurodegeneration.[13] For example, abnormal brainstem auditory evoked responses were observed in a woman with alcoholism who recovered from CCHS.[13] Most congenital cases are identified in neonates.

Genetics

Genetic variants associated with congenital central hypoventilation syndrome

Most cases of CCHS are caused by *PHOX2B* gene variants.[8,14-17] The *PHOX2B* gene contains a repeated sequence of 20 alanines in exon 3, denoted as 20/20. Variants in *PHOX2B* gene result in increased polyalanine repeat expansion mutations (PARMs) and decreased transcription of *PHOX2B*.[18,19] Most patients with CCHS have a heterozygous in-frame PARM that encodes 24 to 33 alanines, producing genotypes 20/24 to 20/33; genotypes 20/26, 20/27, and 20/28 are predominant.[7,18,19] Lower numbers of PARMs are associated with night-time ventilatory support; higher numbers of PARMs are associated with continuous ventilatory support. Late-onset CCHS often involves milder symptoms. Non–polyalanine repeat expansion mutations (NPARMs) usually occur *de novo* and cause 10% of CCHS cases; they are associated with severe respiratory symptoms and multisystem involvement.[18,19] A *PHOX2B* gene variant is not required; some patients with CCHS have no identifiable genetic variant. *MYO1H* and *LBX1* gene variants have been linked to CCHS[20,21]; *ASCL1*, *BDNF*, *BMP2*, *EDN3*, and *RET* variants have also been linked to CCHS, but causal relationships are unclear.[22-25] In Hong Kong, genetic testing for *PHOX2B* variants is available, where assessment by a geneticist is recommended prior to testing for other

variants. All patients with CCHS in Hong Kong exhibited *PHOX2B* variants (Table).[4,11,12]

Relationship between genotype and phenotype

Higher numbers of PARMs (genotypes 20/27 to 20/33) and NPARMs are associated with severe respiratory manifestations requiring continuous ventilatory support,[7,19] worse neurocognitive outcomes, and higher incidences of neural crest tumours.[7,10,19,26]

Clinical features

Autonomic dysfunction may involve multiple systems, as detailed in the online supplementary Table.

Respiratory aspect

Hypoventilation severity varies among patients with CCHS. Neonates may display recurrent desaturation and/or life-threatening apnoea; infants and children may exhibit severe sleep apnoea, pulmonary hypertension, and cor pulmonale.[19] Late-onset CCHS is occasionally reported,[27-29] usually involving respiratory collapse in adulthood or difficulty in discontinuing ventilation after general anaesthesia.[28-30] Genotype influences hypoventilation severity. Children with high numbers of PARMs (genotypes 20/27 to 20/33) and children with most NPARMs may require 24-hour ventilatory support.[7]

Cardiovascular aspect

Cardiovascular abnormalities include arrhythmias, sinus pause, sinus bradycardia, reduced heart rate variability, and prolonged R-R interval with risk of sudden death.[31] Altered blood pressure can lead to nocturnal hypertension and postural hypotension, characterised by dizziness, fainting, and syncope.

Gastrointestinal aspect

Hirschsprung disease (HD) was first described in 1978[32]; the three affected patients died in infancy. Twenty percent of patients with HD also exhibit CCHS. Hirschsprung disease occurs in most patients with NPARMs but few patients with PARMs (genotypes 20/27 and 20/26).[19] Most patients with CCHS display gastrointestinal motility impairment because enteric nervous system development is impacted by *PHOX2B* variants.[33] In patients with CCHS and HD, long-segment HD is linked to high mortality.[34]

TABLE. Characteristics of patients with congenital central hypoventilation syndrome in Hong Kong

Characteristic	Patient 1[11]	Patient 2[11]	Patient 3[11]	Patient 4[12]	Patient 5[4]
Presentation and brief history	Apnoea at birth requiring ventilatory support	Apnoea at 6 hours after birth requiring ventilatory support	Apnoea at 17 hours after birth requiring ventilatory support	Repeated apnoea at birth requiring ventilatory support	CCHS diagnosed and managed in Canada
Developed pneumonia while travelling to Hong Kong					
Sex	Male	Male	Male	Female	Male
Genetics	Heterozygous c.586_c.590insG mutation in exon 3 (frameshift mutation with translation termination at codon 359)	*PHOX2B* Insertion of 6 alanines into 20 alanine repeats (PARM genotype 20/26)	*PHOX2B* Insertion of 7 alanines into 20 alanine repeats (PARM genotype 20/27)	*PHOX2B* Alleles with 32 alanine repeats (PARM genotype 20/32)	Not applicable Genetic diagnosis in Canada
Other system involvement	Long-segment Hirschsprung disease	Nil	Hirschsprung disease	Hirschsprung disease	Absent
Autonomic system dysfunction	Absent	Strabismus	Strabismus	Absent	Absent
Neural crest tumours	Absent	Absent	Absent	Absent	Absent
Mode of ventilation	Ventilatory support asleep and awake	Ventilatory support asleep and awake	Ventilatory support asleep and awake	Tracheostomy Home ventilation during sleep Ambulatory when awake	Tracheostomy Home ventilation during sleep Ambulatory when awake
Complications	Nil	Nil	Nil	Nil	Developed pneumonia during flight to Hong Kong; received treatment in a tertiary PICU in Hong Kong
Publication year	2006	2006	2006	2014	2015

Abbreviations: CCHS = congenital central hypoventilation syndrome; PARM = polyalanine repeat expansion mutation; PICU = paediatric intensive care unit

Ophthalmological aspect

Ocular disorders affect about 90% of patients with CCHS. Abnormal findings include pupillary defects, poor pupillary responses to various stimuli, irregularly shaped pupils, pupillary hippus, light-near dissociation, and anisocoria.[35] Patients with CCHS display weak sympathetic and parasympathetic pupillary responses[36]; impairment is worse in patients with higher numbers of PARMs and NPARMs. Iris abnormalities and strabismus each occur in ≥54% of cases.[35] Extrinsic ocular abnormalities include convergence insufficiency, isolated ptosis, and third nerve palsy. Microphthalmia, lacrimal duct obstruction, tearing insufficiency, Marcus Gunn jaw-winking, and crocodile tears may also occur.[7]

Neurological and neurodevelopmental aspect

Acute neurological events may be precipitated by cardiovascular, respiratory or endocrine factors.[7] Concerning long-term neurodevelopmental outcomes, magnetic resonance imaging of children with CCHS revealed significantly reduced grey matter volumes in autonomic, respiratory, and cognitive areas; gradual increases in grey matter were limited, consistent with age-related functional deterioration.[37] Children with CCHS exhibit diverse impairments (eg, cognition, vision, language, abstract reasoning, and memory),[38-40] along with learning disabilities and attention deficits.[41] For example, preschool-age children with more severe symptoms display significantly lower motor and mental development scores on the Bayley Scales of Infant Development, indicating early onset of developmental problems[42]; higher numbers of PARMs are associated with lower Bayley scores. Neurodevelopmental delays are suspected to arise from neonatal hypoxia or intrinsic developmental abnormalities.

Endocrine aspect

Abnormal glucose homeostasis in CCHS may constitute asymptomatic to profound hypoglycaemia, which usually arises from hyperinsulinaemia; dopamine-beta-hydroxylase function may be impaired.[43] In neonates with CCHS, hypoglycaemia treatment involves high glucose and diazoxide. Hyperglycaemia and abnormal oral glucose tolerance are present in many children with CCHS.[44] Growth hormone deficiency and hyperthyroidism may also be present.[7]

Tumours aspect

Neural crest tumours occur in approximately 5% of children with CCHS. Incidences are the highest among children with NPARMs and children with PARM genotypes 20/28 and 20/33.[8,15,45]

Diagnosis

Congenital central hypoventilation syndrome constitutes hypoventilation related to deficient central control of breathing and global autonomic dysfunction. Medical examinations should exclude brain, heart, and lung lesions; they should demonstrate impaired responses to hypercapnia and hypoxia.[7] Alveolar hypoventilation should be diagnosed via continuous polysomnography or cardiorespiratory polygraphy.[7,19] Partial pressure of carbon dioxide (PCO_2) should be monitored during multiple sleep cycles and while awake, using end-tidal CO_2 or transcutaneous CO_2 measurements plus blood gas analysis. Diagnostic criteria for nocturnal hypoventilation include a PCO_2 level of >6.7 kPa (50 mm Hg) for >25% of total sleep time.[7,19] Hypoventilation when awake is defined as a PCO_2 level of ≥6.0 kPa (45 mm Hg). Hypoventilation typically is the most severe during non–rapid eye movement sleep; mild hypoventilation may occur during rapid eye movement sleep and wakefulness.[7,19,46] The diagnosis of CCHS is based on fulfilment of criteria for nocturnal hypoventilation.[19] Patients with suspected CCHS should undergo cardiac assessments including ambulatory electrocardiography, ambulatory sphygmomanometry, exercise/treadmill test, and echocardiography.[7,19] An implantable electrocardiography monitor may be needed to capture prolonged sinus pauses.[47] Patients with suspected CCHS should undergo a complete ophthalmological assessment at the time of diagnosis, then annually throughout childhood.

Manifestations of CCHS are influenced by age, hypoventilation severity, co-existing conditions, and causative gene variant.[7,19] Diagnosis may be delayed because of inconsistent manifestation severity or lack of clinician awareness. Genetic testing is recommended for patients with unexplained central hypoventilation; it is also recommended for patients with central hypoventilation in the first month of life, after general anaesthesia or sedation, with HD, with neural crest tumours, with hyperinsulinaemia, with parental history of CCHS, and/or with rapid-onset obesity and hormonal disturbance.[7] Parents of children with confirmed CCHS should consider genetic testing.

Differential diagnosis of CCHS includes causes of primary central hypoventilation and central nervous system–induced secondary hypoventilation.

Management of congenital central hypoventilation syndrome

There are two international guidelines for CCHS diagnosis and management.[7,19,48] Principles of diagnosis and management are similar; differences include genotypes and phenotypes, ventilation

devices, use of non-invasive ventilation, transition from tracheostomy to other ventilatory support, and phrenic nerve pacing (PNP).

Upon diagnosis with CCHS, children should undergo cardiac, respiratory, and sleep assessments.[7,19] Ventilatory support modality and duration depend on age, hypoventilation severity, facilities, and available resources. The main approaches are invasive ventilation with tracheostomy and diverse non-invasive modalities. Respiratory pacing may be effective.[49-52]

Respiratory management

Tracheostomy ventilation

Tracheostomy-based positive pressure ventilation is a common and stable ventilatory support modality for CCHS; it prevents hypoxic brain damage in young infants. Tracheostomy provides a secure airway with effective ventilation, which is appropriate for management of severe CCHS and instances of infection; it minimises dead space and facilitates secretion suctioning. Portable battery-operated ventilators enhance patient mobility. Tracheostomy plus PNP can improve mobility in children and adolescents. Tracheostomy complications include respiratory infections, tube obstruction, granulomas, feeding/phonation problems, and speech delays.[7,39] Multidisciplinary management should incorporate input from paediatric respiratory specialists. Some older children may undergo decannulation,[53,54] particularly after tracheostomy capping.[53] Phrenic nerve pacing can facilitate decannulation.

Non-invasive mask ventilation

Non-invasive ventilation is recommended for cooperative children requiring only night-time ventilation. For older children requiring 24-hour ventilation, management can comprise daytime PNP and night-time mask ventilation. Mask ventilation minimises invasiveness while improving swallowing, phonation, and speech development. Leakage, poor fit, and asynchrony can hinder effective ventilation. Careful monitoring and close surveillance are necessary to prevent aspiration. Infants and young children may experience pressure sores and mid-face deformation after prolonged mask use.[7]

Phrenic nerve pacing

In PNP, bilateral electrodes are surgically placed under the phrenic nerves; the electrodes are connected by lead wires to subcutaneous radio receivers. Radio waves are sent from a battery-powered external transmitter to the receiver implants, which are then converted into stimulating pulses that travel along the electrodes to the phrenic nerves. Phrenic nerve stimulation leads to diaphragmatic contraction and subsequent inspiration.[49-52] Older children and adults with mild CCHS may require respiratory pacing, occasionally with decannulation. This approach enhances independence and mobility, while avoiding complications from tracheostomy or face mask ventilation. Tracheostomised patients may be decannulated within approximately 12 months after PNP.[55] However, tracheostomy stabilises tidal volume, PCO_2, and oxygen saturation; both it and pacing are recommended for children aged <6 years.[7] Phrenic nerve pacing involves multiple implantation procedures, along with medical centre–based technical support. Pacing alone does not secure the airway; system malfunction can allow severe hypoventilation. Additional ventilatory support may be needed during respiratory illnesses. In Hong Kong, diaphragmatic pacing (but not PNP) has been used for CCHS management[56]; in other countries, PNP has been used for CCHS management.[7,55] Effective treatment requires experienced clinicians and good support. If PNP is considered in Hong Kong, it should be performed in tertiary centres with multidisciplinary support to allow personalised treatment.

Negative pressure ventilation

Negative pressure ventilation involves a rigid cuirass enclosing the body below the neck. A pump attached to the cuirass produces negative pressure outside the chest and abdomen; subsequent ribcage expansion promotes inspiration.[57,58] This ventilation does not require tracheostomy or prolonged face mask use; it is appropriate for night-time ventilatory support. However, the cuirass is not portable, may cause pain, and does not secure the airway. Additional support may be necessary during respiratory illness.[7] Negative pressure ventilation has not been used for CCHS management in Hong Kong.

Long-term follow-up

Regular multidisciplinary assessment can identify potential complications using the investigations summarised in the online supplementary Table. Careful evaluations and detailed discussions involving the medical team, child, and family should guide long-term treatment. Ventilatory support modalities, decannulation risks and benefits, PNP feasibility, and training/education requirements should be regularly reviewed. Regular imaging investigations can identify potential neural crest tumours.

Home and school

Long-term ventilation should be performed at home when possible. Parents and caregivers should receive education regarding ventilation procedures and troubleshooting. Partial pressure of carbon dioxide and oxygen saturation should be monitored.

Many units provide a 24-hour hotline for advice and specific emergency management instructions.[7]

Children should be active and attend school. Portable battery-operated ventilators are useful when away from home. Teachers should receive CCHS-focused guidance. Early developmental assessments facilitate timely training/intervention and special education referral.

Sports

Children with CCHS should participate in normal activities. However, strenuous exercise should be minimised; prolonged immersion when swimming should be avoided.[7]

Anaesthesia

There are no definitive anaesthesia management guidelines for patients with CCHS. The authors of a systematic review[59] concluded that possible intra- and postoperative complications should be thoroughly evaluated; anaesthetic agents should be carefully selected. Complications can occur after neuromuscular block.[60-62] Patients with CCHS are sensitive to sedatives and narcotics. Significant respiratory depression can occur after non-oral opioid administration[60,63,64]; short-acting sedatives are recommended.[60,65] Electrocardiography can detect bradycardia and arrhythmias; glucose monitoring can identify hypoglycaemia or hyperglycaemia.

Patients with CCHS may experience difficulty in discontinuing ventilatory support after surgery. This difficulty may be the first manifestation of late-onset CCHS.[62] Pain relief should consist of non-opioid analgesic agents. Patients may require increased and prolonged ventilatory support after surgery. Management should be conducted in collaboration with anaesthesia and respiratory medicine teams.

Pharmacotherapy

Current pharmacotherapy is mainly supportive. In-vitro studies are examining *PHOX2B* signalling to elucidate CCHS pathophysiology.[66] Respiratory-stimulating medications may improve respiratory outcomes.[66,67] Further research is needed regarding CCHS pharmacotherapies.

Genetic assessment and counselling

Parents of children with confirmed CCHS should receive genetic workup and counselling. *PHOX2B* gene transmission is autosomal dominant with variable penetrance; variant carriers have a 50% risk of transmission to their children.[9] Most patients have a *de novo* mutation; their parents show no genetic abnormalities. Asymptomatic parents may carry a low-penetrance *PHOX2B* variant in some or all cells.[9] Prior to pregnancy, patients with CCHS should receive counselling regarding variant transmission risk. Pre-implantation genetic diagnosis may be beneficial. Pregnancy may require increased ventilatory support; delivery should be planned with input from the family as well as obstetrics, medical, neonatal, and anaesthesia teams.

Hong Kong perspective and future developments

Despite increasing knowledge regarding CCHS pathophysiology, genetics, and management, clinician awareness remains limited. Patient management can be aided by national registry creation and treatment network formation. Evidence from Hong Kong currently consists of isolated case reports (summarised in the Table).[4,11,12] Standardised diagnostic criteria and genetic testing availability may facilitate future diagnoses.[19] A territory-wide central registry would be useful; medical care in a tertiary/quaternary centre with multidisciplinary input would ensure robust management. Collaborations with other international centres could improve knowledge of CCHS. Extensive information about patients with CCHS is available from databases in the United States and Europe, but not Hong Kong. However, these databases do not include infants or children who did not receive ventilator support.[68] Modern management allows children with CCHS to live a relatively normal life and participate in most activities.[4,48,68] Enhanced educational, social, and family support can improve neurodevelopmental outcomes and quality of life.

Conclusion

Congenital central hypoventilation syndrome is a rare autonomic regulation disorder involving hypoventilation primarily during sleep; long-term ventilatory support is often necessary. The syndrome is associated with *PHOX2B* variants. Patients usually require positive pressure ventilation via tracheostomy or through a mask; some may use PNP. There have been few reported cases of CCHS in Hong Kong; a territory-wide registry would facilitate management. Early diagnosis and appropriate management strategies can improve CCHS outcomes.

Author contributions

Concept or design: All authors.
Acquisition of data: KL Hon, GPG Fung.
Analysis or interpretation of data: KL Hon, GPG Fung.
Drafting of the manuscript: KL Hon, GPG Fung.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have no conflicts of interest to disclose.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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