Congenital central hypoventilation syndrome and intestinal aganglionosis: A case report

T Ramdin, MB BCh, DCH (SA), FCPaed (SA); **V Davies**, MB BCh, DCH (SA), FCPaed (SA)

Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: *T Ramdin (tanusharamdin@yahoo.com)*

Congenital central hypoventilation syndrome (CCHS), also called 'Ondine's curse', is characterised by an abnormal ventilatory response to progressive hypercapnia and sustained hypoxaemia. Neonates with this condition experience hypoventilation or apnoea while asleep. Patients may also have congenital intestinal aganglionosis (CIA), aganglionic megacolon or Hirschsprung's disease, suggesting an aberrant phenotype arising from a defect of migration or differentiation of neural crest cells. Some patients also have tumours of neural crest cell origin, including neuroblastoma, ganglioneuroma and ganglioneuroblastoma. The association of CCHS and CIA is called Ondine-Hirschsprung disease (Haddad syndrome). A few cases have been diagnosed in South Africa, but none has been reported. We report a case of CCHS and CIA with a *PHOX2B* gene mutation.

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Congenital central hypoventilation syndrome (CCHS) or 'Ondine's curse' is characterised by an abnormal ventilatory response to progressive hypercapnia and sustained hypoxaemia. During the neonatal period, most patients with this condition present with hypoventilation or apnoea while asleep.

Patients with CCHS may also suffer from congenital intestinal aganglionosis (CIA), aganglionic megacolon or Hirschsprung's disease, suggesting an aberrant phenotype arising from a defect of migration or differentiation of neural crest cells.[1] Some patients also have tumours of neural crest cell origin, including neuroblastoma, ganglioneuroma and ganglioneuroblastoma.

The association of CCHS and CIA is referred to as Ondine-Hirschprung disease (Haddad syndrome).[2] In the South African population, a few cases have been diagnosed but none has been reported. A case of CCHS and CIA with a *PHOX2B* gene mutation is reported here.

Case report

A full-term male infant of Chinese descent was delivered at a private clinic in Johannesburg via caesarean section performed for a prolonged second stage of labour and poor maternal effort. His birth weight was 3 480 g and the Apgar scores were 5 and 7 at 1 and 5 minutes, respectively. Cyanosis and poor respiratory effort were

noted shortly after birth. Resuscitation was immediately commenced with bag-mask ventilation, and the baby was transferred to the neonatal intensive care unit (NICU). On arrival in the NICU, he was intubated and positive-pressure ventilation was commenced. The results of blood tests were as follows: pH 7.05, carbon dioxide partial pressure (PCO_2) 10 kPa, oxygen partial pressure (PO_2) 5.9 kPa, base excess -14.5 mEq/l, bicarbonate 13.3 mmol/l and haemoglobin 19.3 g/dl. The arterial blood gas results suggested a mixed metabolic/respiratory acidosis and also raised concerns of perinatal asphyxia.

Physical examination revealed a cephalhaematoma over the right temporal region. No obvious dysmorphic features were found. On cardiovascular examination, all pulses were palpable and of normal volume. The blood pressure was normal. There was a 2/6 ejection systolic murmur at the left parasternal border in the second intercostal space, and the first and second heart sounds were normal. The capillary refill time was >5 seconds and there was no evidence of congestive cardiac failure. The rest of the examination and laboratory findings were unremarkable. The chest radiograph showed minimal cardiomegaly.

The baby was very active and alert on minimal ventilation and was soon extubated to nasal continuous positive airway pressure (NCPAP). However, he developed respiratory failure and had to be re-intubated, and positive-pressure ventilation was recommenced. Enteral feeds were commenced on day 2 after birth.

A cranial ultrasound scan was normal. An echocardiogram showed prolapse of the anterior mitral valve leaflet with mild regurgitation. The mitral valve leaflets had good mobility and did not appear dysplastic. A small patent ductus arteriosus of 1.5 mm was present. There was good left ventricular function with an ejection fraction of 74%.

On day 4 the baby's abdomen became markedly distended with bile-stained aspirates. An abdominal radiograph showed large, dilated bowel loops with air-fluid levels. The baby only passed meconium after rectal stimulation. Gastrograffin studies were then performed, which were suggestive of CIA. Small feeds were continued and the baby passed meconium over the next few days. Extubation to NCPAP was re-attempted a few times over the next few days and repeatedly failed owing to recurrent apnoeic episodes and hypercarbia.

On day 13 the baby was transferred to Charlotte Maxeke Johannesburg Academic Hospital for further management. On the way to the hospital he had a cardiac arrest requiring resuscitation, which was successful. He failed to pass any meconium after the first week and on day 15 presented with signs of intestinal obstruction. At laparotomy, a narrow rectum and distal sigmoid colon and a dilated proximal sigmoid colon were noted. Rectal biopsy confirmed absence of ganglion cells in the distal colon and rectum. Ganglion cells were found in the proximal sigmoid colon.

At this stage, a provisional diagnosis of CCHS was made because of the recurrent apnoea and associated CIA. Cytogenetic blood samples were sent to the Bristol Genetics Laboratory (Southmead Hospital, UK), as studies for the *PHOX2B* gene are not available in South Africa, and presence of the *PHOX2B* gene with a normal allele (20- residue polyalanine tract) and an expansion mutation was confirmed. Sequence analysis of the polyalanine tract confirmed the expansion mutation and sized it as an 11 al-alanine expansion. No testing was done on the parents.

The baby remained ventilated for a further month while the diagnosis was being confirmed. The parents were counselled regarding the nature and poor long-term prognosis of the condition. Active life support was discontinued and the baby died at 45 days of age.

Discussion

A male neonate of Chinese descent with CCHS presented with apnoea and hypoventilation both when awake and asleep, and was ventilator-dependent for maintenance of normal respiratory function. The diagnosis was confirmed by the presence of the *PHOX2B* gene mutation. Associated CIA resulted in intestinal obstruction in the first week of life and was confirmed on rectal biopsy.

The reported prevalence of CIA in cases of CCHS ranges from 16% to 50%.[1,3,4] Additional associations are ophthalmic abnormalities, oesophageal dysmotility, sensorineural hearing loss, and neural crest tumours (gangliomas, neuroblastomas).[5-7]

The *PHOX2B* found in our patient was identified as the disease-defining gene for CCHS in 2003.[1,5] *PHOX2B* encodes for a transcription factor known to play a key role in the development of autonomic nervous system (ANS) reflex circuits in mice.[3] CCHS is most often caused by a mutation in the *PHOX2B* gene located on chromosome band 4 p 12 (1, 3 and 4). This gene encodes a 314-amino acid transcription factor that is expressed in the developing hindbrain and peripheral nervous system, as well as in all non-adrenergic centres and visceral motor and branchiomotor neurons of the cranial nerves.

Our patient had a polyalanine expansion repeat mutation (PARM) in the *PHOX2B* gene. More than 90% of CCHS cases reported have been heterozygous for an in-frame PARM, and our patient confirmed this statistic. The remaining 10% have been heterozygous for a non-polyalanine expansion repeat mutation (NPARM) in the *PHOX2B* gene. The 20/25, 20/26 and 20/27 genotypes are most common, although increasing numbers of even the less common mutations are being identified monthly.[5]

Although the genotype for a PARM was not tested for in our patient, a relationship exists between the genotype for PARM and continuous ventilatory dependence.[1,6] The mildest cases of hypoventilation are those of late onset, usually presenting after exposure to respiratory depressants or severe respiratory infection and managed with nocturnal ventilatory support only. However, in contrast to PARMs, most individuals with NPARMs require continuous ventilatory support.[5,8]

CIA, also present in our patient, occurs in 20% of cases of CCHS, more often among those with NPARMs (87 - 100%) than PARMs (13 - 20%).[8]

The RET gene may also have an important role as a modifier gene for Hirschsprung's disease phenotypes in patients with CCHS.

Individuals with NPARMs are more likely to have tumours of neural crest origin (50%) than those with PARMs (1%).[8] These tumours are all neuroblastomas. We did not do a chest and abdominal computed tomography (CT) scan on our patient, and associated neuroblastomas were not excluded.

A recent report identified a correlation between the most common PARMs and the length of the R-R interval on continuous Holter monitoring. An ECG on our patient showed sinus rhythm with a normal R-R interval. The risk of an abnormal R-R interval to individuals with NPARMs is uncertain.[4]

It has been demonstrated that the number of symptoms of ANS dysregulation increases with an increase in the number of polyalanine repeats.[1]

Patients between the ages of 2 years and early adulthood (primarily with PARMs) have characteristic facies.[9] The faces of individuals with CCHS are shorter and flatter, with an inferior inflection of the lateral third of the upper vermilion border (lip trait). A characteristic box-shaped face, short relative to its width, is observed in CCHS.

The *PHOX2B* mutation in CCHS is inherited in an autosomal dominant pattern, hence the importance of testing both of a patient's parents. CCHS is no longer diagnosed exclusively in the newborn period, now also being described in adults and children.

If a diagnosis of CCHS is suspected, blood should be sent for a *PHOX2B* screening test. If the test is negative and the patient's phenotype supports the diagnosis of CCHS, or the family or the doctor want to rule out CCHS completely, the sequel *PHOX2B*

sequencing test should be performed.[5] While awaiting results of *PHOX2B* testing (high sensitivity and specificity), other causes of hypoventilation should be ruled out to expedite proper intervention and facilitate treatment and strategies for home care.[5] Primary lung disease, ventilatory muscle weakness and cardiac disease should be ruled out with a chest radiograph, a CT scan of the chest, comprehensive neurological evaluation, a muscle biopsy, an ECG, magnetic resonance imaging or a CT scan of the brain to exclude brain or brainstem pathology,[10] and a metabolic screen to exclude inborn errors of metabolism.

Independent of respiratory control abnormalities, children with CCHS have other evidence of diffuse autonomic dysregulation. A barium enema examination or manometry and a full-thickness rectal biopsy should be performed on patients presenting with constipation to diagnose CIA. Serial chest and abdominal imaging is essential in children with the NPARMs to exclude a neural crest tumour, specifically neuroblastoma in NPARMs and ganglioneuroblastoma or ganglioneuroma in PARMs.[7]

Cardiac rhythm abnormalities, including decreased beat-to-beat variability, reduced respiratory sinus arrhythmia and transient abrupt asystoles, have been described.[11,12] Annually performed 72-hour Holter monitoring may determine aberrant cardiac rhythms and sinus pauses that will necessitate bipolar cardiac pacemaker implantation. Bipolar cardiac pacemaker implantation decreases the frequency of short pauses that may have physiological and neurocognitive impacts.

As a result of recurrent hypoxaemia, children with CCHS are at risk of progressive pulmonary hypertension and cor pulmonale due to inadequate ventilator settings or tracheostomy calibre, unrecognised hypoventilation during spontaneous breathing while awake, excessive exercise with resultant physiological compromise, or suboptimal compliance with artificial ventilation. Annually performed echocardiograms, haematocrits and reticulocyte counts will provide valuable information regarding potential cor pulmonale or polycythaemia, with more frequent testing if clinically indicated.

Children with CCHS frequently have ophthalmological abnormalities, reflecting the effect of *PHOX2B* on the cranial nerves controlling pupillary function.[6] Comprehensive ophthalmological testing will determine the nature of the involvement and allow for intervention strategies to avoid interference with learning. An ophthalmological examination was not done on our patient. Comprehensive autonomic testing, which may include tilt testing, deep breathing, Valsalva maneouvre, thermal stressors and pupillometry, is indicated to assess syncope and assess ANS function.

CCHS is usually identified in the newborn period, and as management of these vulnerable children with their complex disorder becomes more standardised, improved neurocognitive performance is anticipated, with distinction between sequelae of hypoxaemia (due to hypoventilation or asystole) and innate disease specific to CCHS. In a controlled setting, comprehensive neurocognitive testing should be performed annually. This will assess the child's progress relative to intervention, management and compliance and may identify the need for further intervention.

Aggressive educational intervention, coupled with careful ventilatory and cardiovascular management, is essential.[5,13] The primary goals are to secure the airway and ensure optimal ventilation and oxygenation. As CCHS does not resolve spontaneously, appear to respond to pharmacotherapy[5] or improve with advancing age, long-term ventilatory support is needed at home.[5] Options include positive-pressure ventilation via tracheostomy,[14] bi-level positive airway pressure,[15] negative-pressure ventilation or diaphragm pacing.[16] Although oxygen administration without ventilation improves the partial pressure of oxygen in the arterial blood (PaO_2) and relieves cyanosis, this treatment is inadequate, as hypoventilation persists and pulmonary hypertension follows.

In the ideal situation, centres with extensive expertise in CCHS should provide care for these individuals, working together with regional paediatric pulmonologists and paediatricians.

References

1. Weese-Mayer DE, Berry-Kravis EM, Zhou L, et al. Idiopathic congenital central hypoventilation syndrome: Analysis of genes pertinent to early autonomic nervous system embryology development and identification of mutations in PHOX2B. Am J Med Genet A 2003;123A(3):267-278. [http://dx.doi.org/10.1002/ajmg.a.20527]
2. Lee CW, Lee JH, Jung EY, et al. Haddad syndrome with PHOX2B gene mutation in a Korean infant. J Korean Med Sci 2011;26(2):312-315. [http://dx.doi.org/10.3346/jkms.2011.26.2.312]
3. Matera I, Bachetti T, Puppo F, et al. PHOX2B mutations and polyalanine expansions correlate with severity of the respiratory phenotype and associated symptoms in both congenital and late onset central hypoventilation syndrome. J Med Genet 2004;41(5):373-380. [http://dx.doi.org/10.1136/jmg.2003.015412]
4. Gronli JO, Santucci BA, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital hypoventilation syndrome: PHOX2b genotype determines risk for sudden death. Pediatr Pulmonol 2008;43(1):77-86. [http://dx.doi.org/10.1002/ppul.20744]
5. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome. Am J Respir Crit Care Med 2010;181(6):626 -644. [http://dx.doi.org/10.1164/rccm.200807-1069ST]
6. Goldberg DS, Ludwig IH. Congenital central hypoventilation: Ocular findings in 37 children. J Pediatr Ophthalmol Strabismus 1996;33(3):175-180.
7. Maris JM, Hogarty MD, Bageatell R, Cohn SL. Neuroblastoma. Lancet 2007;369(9579):2106-2120. [http://dx.doi.org/10.1016/S0140-6736(07)60983-0]
8. Loghmanee DA, Rand CM, Zhou L, et al. Paired-liked homeobox gene 2b (PHOX2B) and congenital central hypoventilation syndrome (CCHS): Genotype/phenotype correlation in cohort of 347 cases. Am J Respir Crit Care Med 2009;179:A6341. [http://dx.doi.org/10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A6341]
9. Todd ES, Weinberg SM, Berry-Kravis EM, et al. Facial phenotype in children and young adults with PHOX2B-determined congenital central hypoventilation syndrome: Quantitative pattern of dysmorphology. Pediatr Res 2006;59(1):39-45. [http://dx.doi.org/10.1203/01.pdr.0000191814.73340.1d]
10. Weese-Mayer DE, Brouillette RT, Naidich TP, McLone DG, Hunt CE. Magnetic resonance imaging and computerized tomography in central hypoventilation. Am Rev Respir Dis 1988;137(2):393-398. [http://dx.doi.org/10.1164/ajrccm/137.2.393]
11. Woo MS, Woo MA, Gozal D, Jansen MT, Keens TG, Harper RM. Heart rate variability in congenital central hypoventilation syndrome. Pediatr Res 1992;31(3):291-296. [http://dx.doi.org/10.1203/00006450-199203000-00020]
12. Silvestri JM, Hanna BD, Volgman AS, Jones PJ, Barnes SD, Weese-Mayer DE. Cardiac rhythm disturbances among children with idiopathic congenital central hypoventilation syndrome. Pediatr Pulmonol 2000;29(5):351-358. [http://dx.doi.org/10.1002/(SICI)1099-0496(200005)29:5<351::AID-PPUL3>3.0.CO;2-Z]
13. Oren J, Kelly DH, Shannon DC. Long-term follow-up of children with congenital central hypoventilation syndrome. Pediatrics 1987;80(3):375-380.
14. Beckerman RC. Home positive pressure ventilation in congenital central hypoventilation syndrome: More than twenty years of experience. Pediatr Pulmonol 1997;23(2):154-155. [http://dx.doi.org/10.1002/(SICI)1099-0496(199702)23:2<133::AID-PPUL13>3.0.CO;2-9]
15. Villa MP, Dotta A, Castello D, et al. Bi-level positive airway pressure (BIPAP) ventilation in an infant with central hypoventilation syndrome. Pediatr Pulmonol 1997;24(1):66-69. [http://dx.doi.org/10.1002/(SICI)1099-0496(199707)24:1<66::AID-PPUL12>3.3.CO;2-0]
16. Weese-Mayer DE, Hunt CE, Bouillette RT, Silvestri JM. Diaphragm pacing in infants and children. J Pediatr 1992;120(1):1-8. [http://dx.doi.org/10.1016/S0022-3476(05)80588-8]
17. Kwon MJ, Lee GH, Lee MK, Kim JY, et al. PHOX2B mutations in patients with Ondine-Hirschsprung disease and a review of the literature. Eur J Pediatr 2011;170(10):1267-1271. [http://dx.doi.org/10.1007/s00431-011-1434-5]
18. Zelko FA, Nelson MN, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital central hypoventilation syndrome: neurocognitive functioning in school age children. Pediatr Pulmonol 2010;45(1):92-98. [http://dx.doi.org/10.1002/ppul.21170]
19. Mellins RB, Balfour HH Jr, Turino GM, Winters RW. Failure of autonomic control of ventilation (Ondine's curse): Report of an infant born with this syndrome and review of the literature. Medicine (Baltimore) 1970;49(6):487-504.
20. 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(3):381-387. [http://dx.doi.org/10.1016/S0022-3476(05)80901-1]