

Case Report

Haddad Syndrome

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Key words: **Apnoea, hypoventilation syndrome, Hirschsprung's disease, genetic, sinus arrhythmia.**

Congenital central hypoventilation syndrome (CCHS) causes predominantly sleep apnoea and is one of a growing number of inherited disorders characterised by autonomic nervous system dysfunction/dysregulation (ANS/D). In association with Hirschsprung's disease (HSCR), it presents as Haddad's syndrome. We report a case of Haddad's syndrome complicated by sinus node dysfunction.

Congenital central hypoventilation syndrome (CCHS) is a very rare disorder characterised by inadequate ventilation during sleep.¹ It is an inherited autosomal dominant disease characterised by a PHOX2B mutation.² Recognised as part of the autonomic nervous system dysfunction/dysregulation (ANS/D) group of disorders, CCHS is usually associated with neural crest tumours and/or enteric nervous system abnormalities, such as Hirschsprung's disease (HSCR), the latter known also as Haddad's syndrome.³ Patients with CCHS have a high frequency of arrhythmias and are at increased risk of sudden death.^{1,4}

Case presentation

A 3-year-old boy with a history of recurrent apnoea episodes during his neonatal period is presented. At that time he was hospitalised, intubated and treated in the neonatal ICU. Given the frequency and severity of the episodes and his inability to be extubated he underwent tracheostomy and permanent mobile mechanical ventilation support was instituted. Genetic molecular tests were positive for PHOX2B gene mutation (20/27 genotype) and the diagnosis of CCHS was es-

tablished. The fact that he was also found to have Hirschsprung's disease, for which he underwent a two stage-repair, classifies the patient in the Haddad syndrome group.

During recent hospitalisation for a viral gastrointestinal tract infection the patient suffered an episode of cardiac arrest in the form of asystole, from which he was successfully resuscitated. Holter recordings following this incident revealed repeat episodes of sinus pauses more than 3 s in duration during sleep, with one of them reaching 6 s, while others appeared even when he was awake and during daytime (Figure 1). Consequently, a transvenous permanent VVI pacemaker (Adapta®, Medtronic Inc., Minneapolis, USA) was implanted under general anaesthesia, utilising a 52 cm screw-in type lead (CapSureFix Novus™, Model 5076, Medtronic Minneapolis, USA) via the left subclavian vein, the length of which was calculated according to his height, as previously described (Figure 2).⁵ Measurements were excellent and the pacemaker is set to operate at 60 bpm.

Discussion

CCHS has also been known as Ondine's

Manuscript received:
April 8, 2014;
Accepted:
March 23, 2015.

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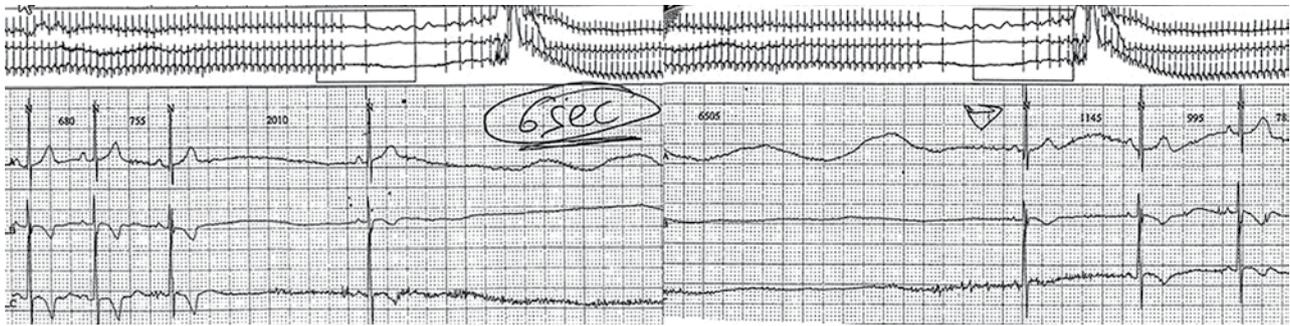


Figure 1. ECG strip showing a 6-s sinus pause.

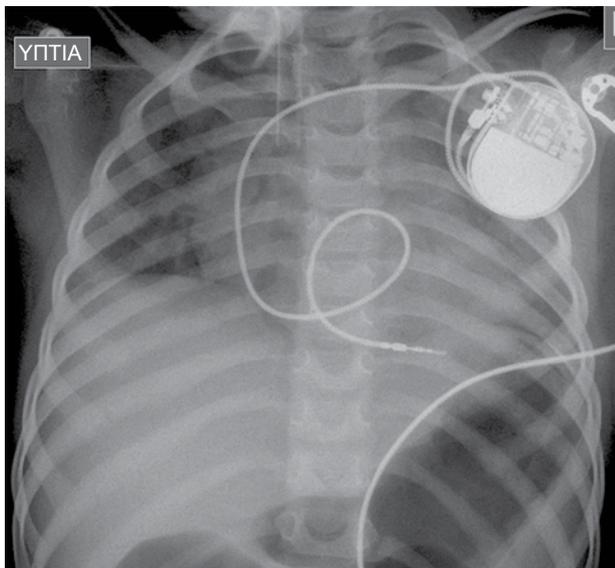


Figure 2. Chest X-ray showing pacemaker implantation. The long pacing lead allows for the child's growth.

course. Ondine (or “Undine”), a mythological figure, was a water nymph or sprite with an unfaithful mortal lover who swore to her that his “every waking breath would be a testimony of his love”. Upon witnessing his adultery, she cursed that if he should fall asleep, he would forget to breathe.⁶

CCHS is inherited in an autosomal dominant manner and a PHOX2B mutation is required to confirm the diagnosis. The syndrome is present at birth, yet diagnosis may be delayed because of the diversity in the severity of its manifestations. Identification of the gene related to this disease has been followed by an increasing interest in genotype–phenotype correlation for its different manifestations, including cardiovascular abnormalities.^{7,8} CCHS is associated with neural crest tumours (neuroblastomas) and/or enteric nervous system abnormalities owing to defective migration of neural crest cells.^{3,9,10} Currently, nearly 1000 individuals worldwide have PHOX2B muta-

tion-confirmed CCHS, although some feel that this number is most likely underestimated.^{2,7} About 15–20% of patients with CCHS are known also to have Hirschsprung’s disease (aganglionic megacolon), an extremely rare combination (less than 1 in 1,000,000 live births) termed Haddad syndrome by some.^{3,7,11} Interestingly, inconclusive current evidence points to PHOX2B gene involvement in Hirschsprung’s disease.¹² In addition, Haddad syndrome has been reported in association with other genetic disorders such as Down syndrome.¹³

CCHS is characterised in general by adequate ventilation while the patient is alert and hypoventilation, with typically normal respiratory rates and diminished tidal volume, during sleep. More severely affected children hypoventilate both awake and asleep. In particular while asleep, children with CCHS experience progressive hypercapnea and hypoxaemia, due to absent or negligible ventilatory sensitivity to these factors.^{2,4,14} Nevertheless, their ventilation is more “normal” in rapid eye movement sleep.¹⁵ During exercise these children may be at risk for hypercarbia and hypoxaemia, because although they maintain conscious control of breathing they lack perception of dyspnoea.^{4,16} In general, patients exhibit sustained abnormalities in control of breathing and continue to require long-term ventilatory support, with several of them, however, entering early adulthood. On occasion, these patients will demonstrate apnoeic pauses after discontinuation of mechanical ventilation and before initiation of spontaneous breathing.¹⁷

Children with CCHS exhibit an increased frequency of arrhythmia, primarily sinus bradycardia and transient asystole.⁴ It has been postulated that inadequate central control of ventilation with decreased sensitivity to hypoxia and hypercapnia may be associated with the cardiac rhythm disturbances observed.¹⁴ Patients with CCHS display several as-

sociated cardiovascular symptoms reflecting ANSD, and the cardiovascular profile suggests vagal dysfunction.¹⁸ Moreover, recent research has revealed evidence of PHOX2B gene involvement in sudden infant death syndrome.¹⁹ Nevertheless, studies confirm a disturbance of cardiac autonomic regulation in CCHS, indicate that PHOX2B genotype is related to the severity of dysregulation, and predict the need for a cardiac pacemaker, thus offering the potential to avert sudden death.¹

Atrial pacing has been shown to be beneficial in reducing the number of apnoea episodes. In particular, there is evidence to show that reducing the variations in heart rate, caused in part by changes in autonomic tone, markedly reduces the number of episodes of sleep apnoea. Atrial pacing counteracts sustained increases in vagal tone by maintaining sympathetic activity.²⁰

References

- Gronli JO, Santucci BA, Leurgans SE, Berry-Kravis EM, Weese-Mayer DE. Congenital central hypoventilation syndrome: PHOX2B genotype determines risk for sudden death. *Pediatr Pulmonol.* 2008; 43: 77-86.
- Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. *Am J Respir Crit Care Med.* 2010; 181: 626-644.
- 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.
- 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: 351-358.
- Gheissari A, Hordof AJ, Spotnitz HM. Transvenous pacemakers in children: relation of lead length to anticipated growth. *Ann Thorac Surg.* 1991; 52: 118-121.
- Nannapaneni R, Behari S, Todd NV, Mendelow AD. Retracing "Ondine's curse". *Neurosurgery.* 2005; 57: 354-363.
- Trang H, Dehan M, Beaufilets F, et al. The French Congenital Central Hypoventilation Syndrome Registry: general data, phenotype, and genotype. *Chest.* 2005; 127: 72-79.
- Weese-Mayer DE, Marazita ML, Rand CM, Berry-Kravis EM. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014.
- Axelrod FB, Chelimsky GG, Weese-Mayer DE. Pediatric autonomic disorders. *Pediatrics.* 2006; 118: 309-321.
- van Limpt V, Schramm A, van Lakeman A, et al. The Phox2B homeobox gene is mutated in sporadic neuroblastomas. *Oncogene.* 2004; 23: 9280-9288.
- Amiel J, Lyonnet S. Hirschsprung disease, associated syndromes, and genetics: a review. *J Med Genet.* 2001; 38: 729-739.
- Garcia-Barceló M, Sham MH, Lui VC, Chen BL, Ott J, Tam PK. Association study of PHOX2B as a candidate gene for Hirschsprung's disease. *Gut.* 2003; 52: 563-567.
- Jones KL, Pivnick EK, Hines-Dowell S, et al. A triple threat: Down syndrome, congenital central hypoventilation syndrome, and Hirschsprung disease. *Pediatrics.* 2012; 130: e1382-1384.
- Idiopathic congenital central hypoventilation syndrome: diagnosis and management. American Thoracic Society. *Am J Respir Crit Care Med.* 1999; 160: 368-373.
- Fleming PJ, Cade D, Bryan MH, Bryan AC. Congenital central hypoventilation and sleep state. *Pediatrics.* 1980; 66: 425-428.
- Shea SA, Andres LP, Shannon DC, Banzett RB. Ventilatory responses to exercise in humans lacking ventilatory chemosensitivity. *J Physiol.* 1993; 468: 623-640.
- Weese-Mayer DE, Berry-Kravis EM. Genetics of congenital central hypoventilation syndrome: lessons from a seemingly orphan disease. *Am J Respir Crit Care Med.* 2004; 170: 16-21.
- Trang H, Girard A, Laude D, Elghozi JL. Short-term blood pressure and heart rate variability in congenital central hypoventilation syndrome (Ondine's curse). *Clin Sci (Lond).* 2005; 108: 225-230.
- Rand CM, Weese-Mayer DE, Zhou L, et al. Sudden infant death syndrome: Case-control frequency differences in paired like homeobox (PHOX) 2B gene. *Am J Med Genet A.* 2006; 140: 1687-1691.
- Garroque S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. *N Engl J Med.* 2002; 346: 404-412.