CASE REPORT

"Where the Body Forgets to Breathe" Congenital Central Hypoventilation Syndrome

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS), also referred to as Ondine's curse, is a rare, life-threatening disorder characterized by autonomic nervous system dysfunction, which mostly manifests as failure to maintain ventilatory homeostasis during sleep.[1,2] Infants with CCHS have inadequate sensitivity to hypoxia and hypercapnia during sleep and in some cases during wakefulness, leading to persistent apnea. Until recently, this has been a diagnosis of exclusion; however recent literature has implicated a genetic etiology.[1-5]

We report a case of CCHS who presented on day D4 of life with persistent apnea. Diagnosis of primary pulmonary, cardiac, metabolic, neurologic disease, or injury was excluded before the diagnosis of CCHS was made. The diagnosis could be confirmed by a PHOX2B sequence analysis.

CASE REPORT

A 3 kg male baby born at term gestation to G3P2L2 by spontaneous vaginal delivery. The baby was well at birth, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. He repeatedly had apnea with cyanosis and desaturation, noticed from the 15 mts after birth, for which he was admitted and monitored in the neonatal intensive care unit. He developed profound apnea during observation, needing ventilaton. He stabilized readily thereafter on conventional ventilation and blood gases were reasonably normal. Attempts at weaning off ventilator supports were unsuccessful in view of profound apneic episodes and he was referred on D4 of life for further evaluation.

At admission, baby was pink, active with endotracheal tube in situ. Vitals were stable with heart rate of 146/mt, Respiratory rate of 50/mt, saturating 100 %. Capillary filling time was less than 3 secs, non invasive BP 60/40 and all peripheral pulses well felt. There was no obvious dysmorphism or external anomalies. Neurological examination showed a normal anterior fontanelle, pupils bilateral equal and reacting to light, tone and movements were normal. Other systems were also normal. Baby was stabilized on synchronized intermittent mandatory ventilation; however on weaning down to support ventilation, he was noted to have slow irregular

respiratory efforts and occasional apneic episodes especially during sleep. There were no associated abnormalities in tone or movements.

INVESTIGATIONS

Hemogram was normal; septic screening was negative and cultures sterile. No abnormalities were noted on the chest radiograph and echocardiography. Cerebrospinal fluid analysis was also normal. Blood samples send for metabolic screening and was negative. Magnetic resonance imaging of the brain was also normal. Serum lactate was normal and serum lactate to pyruvate ratio within normal limits, thereby reasonably ruling out mitochondrial disorders. Electroencephalogram showed diffuse cerebral dysfunction but no pattern abnormalities.

We too attempted to wean ventilation to CPAP; however had recurrent apneic episodes whilst on CPAP. Baby was given a trial of respiratory stimulants and phrenic nerve stimulation; however this did not yield favourable results. We contemplated use of steroids but family was not willing for same. Following discussions with the family, genetic study was sent which showed polyalaninine repeat expansion mutation (PARM- heterozygous inframe duplication observed in the 20 alanine stretch) of PHOX2B gene of chromosome 4p12. Family was counseled regarding the same and the implications. They opted for supportive care alone and baby succumbed on day 22 of life.

DISCUSSION

Congenital central hypoventilation syndrome (CCHS) is a life-threatening disorder of the respiratory and autonomic regulation manifesting as sleep-associated alveolar hypoventilation.[1,7] It is typically characterized by a classic presentation in newborns and, rarely, a milder later-onset (LO-CCHS) presentation in toddlers, children, and adults. Hypoventilation is accentuated during sleep, particularly in the non-REM phase, in which the autonomic control of breathing predominates.

Central hypoventilation syndrome was first reported in 1962 in 3 adult patients after high cervical and brainstem injury (Severinghaus and Mitchell) and Mellins first reported the disorder in newborns in 1970.[6]

The condition is very rare, seen in 1: 200000live births and is a diagnosis of exclusion.[1,7]

Classic CCHS is diagnosed in a neonate as:

- Epidodic or sustained hypoventilation with attenuated or absent response to hypoxia and hypercarbia during sleep only or at times while awake as well as asleep.[1,2,7]
- Autonomic nervous system dysregulation (ANSD):- Symptoms not limited to severe breath-holding spells; includes lack of physiologic responsiveness to environmental stressors; diminished pupillary light response; esophageal dysmotility; severe constipation; profuse sweating; reduced basal body temperature
- No evidence of primary neuromuscular, lung, or cardiac disease or identifiable brain stem lesion that could account for the full constellation of signs and symptoms including autonomic nervous system dysregulation (ANSD)
- In some, there can be associated altered development of neural crest-derived structures (Hirschsprung disease in 20%)[7,9,10] and/or tumors of neural crest origin in 5-10% (neuroblastoma, ganglioneuroma, and ganglioneuroblastoma).[7,9,10]

The disorder can be autosomal dominant inheritance or in some cases, denovo mutation.[2-4] In 2003, PHOX2B gene mutations were identified as responsible for CCHS. The PHOX2B gene, located on chromosome 4p12, encodes a transcription factor responsible for the regulation of genes involved in the development of the autonomic nervous system.[2,3] The most frequently found mutation is a polyalanine expansion in exon 3. More than 90% of affected individuals are heterozygous for this mutation. This gene is important in the development of the autonomic nervous system, including all derivatives from the autonomic neural crest. Studies show that the length of the PHOX2B polyalanine repeat mutation is associated with number of ANS symptoms and that there is also a significant association between the number of repeats in the mutations and the ventilation support required.[2,3] Other types of mutations (missense, frameshift) may occur and are demonstrated by gene sequencing.[8] Nearly 1000 children worldwide have PHOX2B mutation confirmed CCHS.

Treatment of this rare disorder is difficult. Most of the patients require continuous or intermittent ventilatory support to maintain ventilation. Management includes tracheostomy or Diaphragm pacing by phrenic nerve stimulation. A cardiac pacemaker may be required for prolonged sinus pauses. Hirschsprung disease will need surgical correction. Neuroblastomas are removed surgically; those beyond Stage 1 are treated with chemotherapy. No pharmacaological respiratory stimulants have been shown to be effective in achieving respiratory stability or sustained eucapnea. Genetic counseling is also an integral part of management of this rare entity.

The clinical outcome of CCHS can be variable[1,7] with severity ranging from complete apnea during sleep, severe hypoventilation during wakefulness, to mild hypoventilation during sleep.

All those who survive will need at least yearly (every 6 months until age 3 years) comprehensive physiologic evaluation to optimize ventilatory support awake and asleep and in varied levels of activity and concentration simulating activities of daily living; yearly 72-hour Holter recording to identify any prolonged sinus pauses; yearly echocardiogram to identify right ventricular hypertrophy or cor pulmonale

and yearly neurocognitive testing to evaluate the success of artificial ventilation.

CONCLUSION

Congenital central hypoventilation syndrome is a rare debilitating condition that practicing neonatologists and pediatricians need to be aware of. Though outcome is guarded with most children being ventilator dependent and needing multidisciplinary care, it is heartening that an affordable genetic diagnosis is possible even in developing countries.

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