Congenital central hypoventilation syndrome with Hirschsprung’s disease due to PHOX2B gene mutation in a Turkish infant

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The association of congenital central hypoventilation syndrome (also known as Ondine’s curse) and Hirschsprung’s disease is termed Haddad syndrome, which is an extremely rare disorder. Recent studies have described that the PHOX2B gene mutation was responsible for congenital central hypoventilation syndrome. We report a term newborn male infant with clinical manifestations of recurrent hypoventilation with hypercapnia and bowel obstructions. These clinical manifestations were compatible with congenital central hypoventilation syndrome and Hirschsprung’s disease. PHOX2B direct sequencing showed a heterozygous in-frame duplication of 21 bp leading to an expansion of +7 alanines within the 20 alanine stretch of the PHOX2B gene and confirmed our diagnosis. In addition to a high index of clinical suspicion, testing for PHOX2B mutation can assist in the diagnosis of congenital central hypoventilation syndrome and in the prediction of disease progression. Infants presenting with congenital central hypoventilation syndrome should also be screened for Hirschsprung’s disease.

Key words: Haddad syndrome, congenital central hypoventilation, Hirschsprung’s disease.

Case Report

Congenital central hypoventilation syndrome (CCHS, MIM 209880) is characterized by marked reduction in ventilatory sensitivity to hypercapnia and hypoxemia in the absence of other abnormalities of the cardiorespiratory system and of neuromuscular disease. Hypoventilation can be demonstrated during both sleep and wakefulness¹⁻³. Hirschsprung’s disease (HD, MIM 142623) is a congenital malformation defined as the absence of ganglion cells in the myenteric and submucosal plexuses of the terminal rectum ± more proximal bowel. An association of HD with CCHS (Haddad syndrome) was first reported by Haddad in 1978⁴. It has been extremely rare, with approximately 61 cases reported in the worldwide literature⁵⁻⁷. Recent studies described that de novo mutation of the PHOX2B gene was involved in the CCHS pathogenesis⁸.

We report Haddad syndrome with the PHOX2B gene mutation in a Turkish infant.

This 41-week-gestation male was born to a 28-year-old, gravida 2, para 1 mother by vaginal delivery. His birth weight was 3280 g. The baby had Apgar scores of 7 and 9 at 1 and 5 minutes. At the 10th minute of life, the baby presented with shallow breathing, apnea and bradycardia requiring cardiopulmonary resuscitation and immediate endotracheal intubation. The rest of the physical exam was normal. For the next day, several attempts at extubation failed secondary to apnea and hypercarbia and respiratory acidosis (especially during sleep), leading to the clinical suspicion of CCHS. Chest and abdominal X-ray were normal except for nonspecific dilated intestinal loops. Cranial magnetic resonance, echocardiography and renal ultrasound were normal. Over the first three days of life, the baby had increasing abdominal distension, passed only smears of meconium and developed greenish gastric drainage. Meconium extraction was accomplished by rectal stimulation. Intermittent rectal irrigations were done due to ongoing
constipation. Full-thickness rectal biopsy was taken from 2 cm proximal to the dentate line on day 20. Biopsy revealed the absence of ganglion cells and increase in nonmyelinated nerve fibers (Figs. 1, 2). After the diagnosis of HD, the infant underwent an open laparotomy on day 30. Frozen biopsy taken from the proximal bowel to the rectum revealed the presence of ganglion cells, and a sigmoid loop colostomy was done. Intestinal functions were normal during the postoperative follow-ups.

In the genetic study, PHOX2B direct sequencing revealed a heterozygous in-frame duplication of 21 bp leading to an expansion of +7 alanines within the 20 alanine stretch of the PHOX2B gene. This result confirmed the diagnosis of CCHS in this patient. Neither parent had a duplication. Continuous ventilator support was necessary and tracheostomy was ultimately performed at the age of three months due to ventilator dependence. He was fed by feeding tube with minimal oral feeding because of swallowing difficulty. He progressed well in growth and development during the hospital stay. The infant was placed on a home ventilator and prepared for discharge. The infant was discharged with home ventilator support at the age of six months. Unfortunately, we learned that he died from lung infection and respiratory failure one month after discharge.

Discussion

Congenital central hypoventilation syndrome (CCHS) (called Ondine’s curse in older literature), characterized by failure of automatic control of ventilation, was usually most marked during quiet sleep. Severe infants demonstrate hypoventilation even while awake. Apgar scores have been variable and our patient had good scores. Typical presentation occurs in the neonatal period. Cyanosis and other symptoms of respiratory failure with slow, shallow, irregular respirations and long respiratory pauses are often seen in the first day of life. Insensitivity to hypercapnia is the most constant finding, with a variable response to hypoxemia that may result in progressive pulmonary hypertension, cor pulmonale, and central nervous system hypoxic damage. pCO2 levels may rise up to 80-90 mmHg during quiet sleep, when respiration is maximally under chemical control. In our case, the pCO2 levels were rising to 80-90 mmHg during both wakefulness and sleep if not mechanically ventilated. Before making a diagnosis of CCHS, other serious intracranial malformations have to be ruled out, and there should be no significant primary neuromuscular, pulmonary, cardiac, or metabolic disease or identifiable brainstem lesion. In our case, there was no intracranial, lung, cardiac, or metabolic pathology.

The co-occurrence of CCHS and HD (Haddad syndrome) suggests a common etiology involving a failure of neural crest development. The CCHS and HD combination comprises nearly 16-50% of the CCHS population, making HD the most common neurocristopathy associated
with CCHS. CCHS cases have commonly short- (rectosigmoid) or usually long-segment (proximal to splenic flexure) aganglionosis. In HD, generally the first stage of operation is opening of colostomy according to the level of the aganglionic segment, and the second stage is definitive operation at approximately one year of age. Our case was short-segment aganglionic, and a sigmoid loop colostomy was performed.

Approximately 20% of CCHS/HD cases will also have tumors of neural crest origin. We did not detect neuroblastoma or ganglioneuroma in our case. Consistent with a neurocristopathy pathogenesis, patients with CCHS may demonstrate a wide variety of autonomic nervous system abnormalities, including those associated with control of heart rate, impaired swallowing, gastroesophageal dysmotility and reflux, pupillary abnormalities, hypotonia, profuse sweating, and absence of fever with infection. Impaired swallowing was found in our case.

Amiel and colleagues implicated mutations in the PHOX2B gene (on the chromosome region 4p12) as responsible for CCHS in 2003, and its rate was over 90% among CCHS patients. In our case, his parents showed no PHOX2B gene mutation, suggesting de novo mutation of the PHOX2B gene in Haddad syndrome. Polyalanine expansions are the most common mutation in patients with CCHS, although rare mutations have been described including missense and frameshift mutations. Genotype-phenotype correlation has been described. Increasing polyalanine repeat mutation size is associated with a more severe clinical phenotype. Trochet et al. described that Haddad syndrome showed usually expansions of +6 and +7 alanines, and frameshift or missense PHOX2B mutations may predispose to neuroblastoma. In our case, PHOX2B direct sequencing showed a heterozygous in-frame duplication of 21 bp leading to an expansion of +7 alanines within the 20 alanine stretch of the PHOX2B gene. The molecular result confirmed the clinical diagnosis. Our case had severe respiratory phenotype and was associated with HD. He had no neural crest tumor. These results were compatible with the hypothesis of Trochet et al.

To the best of our knowledge, this is the first case of Haddad syndrome reported from Turkey. This report emphasize that pediatricians should have a high index of suspicion for such diagnosis in infants who are difficult to wean from mechanical ventilation. Testing for the PHOX2B mutation can assist in the diagnosis of central hypoventilation syndrome and in the prediction of the disease prognosis. Among children who present with CCHS, due to the high incidence of HD, rectal biopsy should be performed if there is any concern about gut function.

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REFERENCES


