Congenital Central Hypoventilation Syndrome and Hirschsprung’s Disease in an Extremely Preterm Infant

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ABSTRACT. Congenital central hypoventilation syndrome with Hirschsprung’s disease, also known as Haddad syndrome, is a rare disorder with a variable phenotypic severity. The underlying cause is thought to be an abnormality of neural crest development and/or migration. Surviving neonates can have generalized autonomic nervous system dysfunction. Recent reports have identified mutations in the PHOX2B gene in a significant number of patients with this disorder. Diagnosis and management of this disorder in the setting of extreme prematurity is difficult as the manifestations of failure to maintain breathing effort and failure to establish feeds overlap with the complications of prematurity. We describe an infant who had congenital central hypoventilation syndrome with Hirschsprung’s disease and was delivered at 26 weeks’ gestational age and had total aganglionosis of the bowel, failure to wean from ventilation, and a mutation in the PHOX2B gene. Pediatrics 2005;115:e737–e738. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1910; aganglionosis, hypoventilation, preterm infant, congenital central hypoventilation syndrome.

ABBREVIATIONS. CCHS, congenital central hypoventilation syndrome; HD, Hirschsprung’s disease.

C
ongenital central hypoventilation syndrome (CCHS) is a rare condition characterized by impairment of autonomic control of spontaneous respiration in the absence of cardiopulmonary disease, resulting in inadequate ventilation with progressive hypercapnia and hypoxia, particularly during sleep. Hirschsprung’s disease (HD) is the variable congenital absence of ganglion cells from the enteric nervous system resulting in varying degrees of functional bowel obstruction. These 2 conditions were described previously as types of “neurocrisopathy,” as first suggested by Bolande1 in 1974. CCHS with HD was first reported in the same patient by Haddad et al2 in 1978. CCHS has also been described with tumors of neural crest origin and autonomic nervous system dysfunction, again suggesting a common pathogenesis involving neural crest-derived cell lineages. Genetic cause has long been sought, and recent reports3–6 have confirmed PHOX2B as the major gene involved in CCHS pathogenesis. All of the cases described in the literature to date were born at term or near-term gestation.7 We report a case of CCHS with HD in an extremely preterm infant.

CASE REPORT

A male infant was born at 26 weeks’ gestation after spontaneous onset of labor in an otherwise uncomplicated pregnancy. The infant was delivered by emergency caesarean section for abnormal cardiotocogram findings of lack of baseline fetal heart rate variability and late decelerations. He was intubated and mechanically ventilated at birth and required surfactant treatment. Attempts at extubation over the next 3 weeks were unsuccessful as a result of poor spontaneous respiratory efforts with no apparent cause. His spontaneous breathing efforts were least marked during sleep. There was a poor respiratory response to both hypercarbia (challenge test: carbon dioxide reached 120 mm Hg with no spontaneous respirations while asleep) and hypoxia.

Establishment of enteral feeds was complicated by recurrent abdominal distension and bilious gastric aspirates. He was noted to pass a small amount of meconium on day 8 and day 10. Plain and barium contrast study on day 35 revealed dilated small bowel, and an inspissated milk plug was subsequently removed at laparotomy. Postoperatively, he continued to have persistent abdominal distension and bilious aspirates, and plain abdominal radiographs revealed fixed bowel loops. In view of his lack of spontaneous breathing efforts and the bowel pseudo-obstruction, a provisional diagnosis of CCHS with HD was made. Intestinal biopsy subsequently demonstrated total aganglionosis of both small and large intestine. Apart from the initial lack of heart rate variability on cardiotocogram, there was no evidence of autonomic nervous system dysfunction such as abnormalities of pupillary motility, postnatal heart rate variability, body temperature regulation, or hypoglycemia.

Immunoreactive trypsin levels were normal. MRI of the brain and brainstem structures showed no intracranial abnormality. Echocardiography was normal. There were no dysmorphic facial features apart from a small skin tag on his right ear lobe anteriorly, and karyotype was normal. Mutation testing of the PHOX2B gene showed a de novo heterozygous frameshift mutation resulting in an 8-nucleotide deletion (693–700 del 8 nt) in the PHOX2B gene. In view of the guarded prognosis and his extreme prematurity, life support was withdrawn with parental consent at 9 weeks of age. An autopsy was obtained, and histologic examination confirmed extensive aganglionosis of the bowel involving the entire colon and most of the small intestine, sparing only the duodenum and most proximal jejunum. The ganglion cells within the duodenum were morphologically normal. In addition, small nodules (up to 1.5 mm) that were composed of primitive neuroblastic cells were noted on histologic examination of the adrenal glands bilaterally. Although these lesions were too small to be considered neuroblas-
tomic tumors at this stage, they most likely represent early precursors of this. Histologic examination of the brain and in particular brainstem was normal, and the arcuate nucleus was present.

DISCUSSION

The combination of CCHS with HD (Haddad syndrome) is a rare association that has not been described in preterm infants before. We are uncertain as to whether this is because this condition does not occur in the premature infant or, more likely, that it is not often considered. As premature infants often have problems of recurrent central apneas and feeding intolerance, it is likely to be difficult to diagnose in this setting. A strong clinical suspicion, intestinal biopsy, and genetic mutation detection may help to diagnose this disorder in this age group.

HD when associated with CCHS is different from classical HD. Intestinal aganglionosis is more extensive, and the gender ratio is equal as opposed to 4:1 male preponderance in classical HD. The reported incidence of CCHS is 1.5% in HD cases, which increases to 10% as aganglionosis increases. The incidence of HD in CCHS cases varies between 16% and 50% as reported by various authors. Associated features include ophthalmic abnormalities in 20% of cases (up to 60% in the Weese-Mayer series), esophageal dysmotility in up to 20% of cases, sensorineural hearing loss in 10%, neural crest tumors (ganglioneuromas, neuroblastomas) in ~5% of cases, and signs and symptoms of autonomic nervous system dysfunction. In our case, cardiotocogram performed before delivery had shown lack of fetal heart rate variability, which may have been indicative of autonomic nervous system dysfunction in the fetus. Temperature instability and heart rate abnormalities are common in extreme prematurity, and it is difficult to ascribe these findings to generalized autonomic nervous system dysfunction. Autopsy findings in our case demonstrated nodules in the adrenal glands, which might represent early stages of neural crest tumor. Minutillo et al described facial dysmorphism in their case, but there are no other reports with characteristic facial features that identify this disorder. Apart from a small preauricular skin tag on the right side, no dysmorphic features were identified in this case.

A genetic basis for this disorder has been suggested, with familial cases (sibling recurrence, mother-to-child transmission) reported. Amiel et al first demonstrated that a significant number of individuals with CCHS have mutations in the PHOX2B gene. The mutation detection rate is >90%. The inheritance pattern is autosomal dominant. Most cases are the result of new mutations, and polyalanine expansions are the most common mutation.

Our case had a frame shift mutation, which is relatively uncommon. Genotype-phenotype correlations are becoming apparent; in particular, increasing polyalanine repeat mutation size is associated with a more severe clinical phenotype. Neither parent in this case had the mutation detected in the infant in their peripheral blood lymphocytes. Hence, the recurrence risk would be low and based on the possibility that 1 parent has gonadal mosaicism. Prenatal diagnosis is an option in subsequent pregnancies. Management of this rare disorder when it presents in an extremely premature infant is challenging as a result of the complexities of parenteral feeding and providing ongoing ventilatory support and carries a guarded prognosis. Withdrawal of life support is a reasonable option in the setting of extreme prematurity. Presentation at a later age makes management easier, and, subsequently, the prognosis may be more optimistic.

CONCLUSIONS

CCHS with HD is likely to be more difficult to diagnose when it presents in the premature infant as a result of overlap of symptoms and signs. Strong clinical suspicion, intestinal biopsy to assess for aganglionosis, and testing for PHOX2B mutation can confirm the diagnosis. Mutation testing also assists in estimating recurrence risk, planning future pregnancies, and prenatal diagnosis.

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