A Triple Threat: Down Syndrome, Congenital Central Hypoventilation Syndrome, and Hirschsprung Disease

abstract

Down syndrome (DS) is recognized by characteristic facial features, intellectual disability, and an increased risk for cardiac malformations and duodenal atresia. Recently, Hirschsprung disease (HSCR), or congenital aganglionic megacolon, has been seen more often among patients with DS. Given the systemic nature of DS-related features, it is natural to attribute neonatal complications to the chromosomal aberration. We describe a biracial male infant with DS who had significantly delayed defecation and required continuous ventilator support, but had no primary cardiac or lung disease. Subsequent evaluations confirmed total colonic aganglionosis. Because we were unable to safely extubate the infant, a diagnosis of congenital central hypoventilation syndrome (CCHS) was considered and confirmed by molecular analysis of the PHOX2B gene, revealing a heterozygous polyalanine repeat-expansion mutation containing 27 repeats (normal gene contains 20 repeats). HSCR coexisting with CCHS is known as Haddad syndrome. This is the first reported case with co-occurrence of DS, CCHS, and HSCR. Pediatrics 2012;130:e1–e3
Down syndrome (DS) is a combination of characteristic facial features and intellectual and physical disabilities. Down syndrome most commonly is due to trisomy 21 chromosomal complement. Patients with DS are at increased risk for cardiac malformations and duodenal atresia. Hirschsprung disease (HSCR) is the congenital absence of intrinsic ganglion cells in the distal rectum, which results in failure to pass meconium within the first 48 hours of life. Approximately 12% of patients with HSCR have an associated chromosomal abnormality, of which DS is the most common. Congenital central hypoventilation syndrome (CCHS) is characterized by failure of the automatic control of breathing during sleep. Patients with CCHS typically present in the newborn period with alveolar hypoventilation and symptoms of autonomic nervous system dysregulation in the absence of primary pulmonary, cardiac, neuro-muscular, or brainstem lesions. In 2003, the CCHS phenotype was determined to be the result of mutations in the paired homeobox PHOX2B gene. A highly conserved transcription factor located on chromosome 4p12, PHOX2B is required for the development of the sympathetic, parasympathetic, and enteric nervous systems. CCHS and HSCR occur as the result of aberrations in early migration, growth, and differentiation of neural crest cells. Haddad syndrome refers to the neurocristopathy with co-occurrence of HSCR and CCHS.

**CLINICAL REPORT**

The patient was a biracial male born at 35 weeks gestational age to a 41-year-old African American gravida 2, para 2 mother and a 57-year-old white father. The mother did not take any medications during the pregnancy and had no prenatal care. Shortly after delivery, the patient was intubated because of minimal respiratory drive and transferred to the NICU. Physical features were consistent with DS, which was confirmed by a karyotype: 47,XY+21. In the NICU, the patient did not pass meconium for >24 hours and developed abdominal distention and copious orogastric drainage. An initial rectal biopsy revealed absence of ganglion cells. A follow-up segmental intestinal biopsy showed absence of ganglion cells up to the ligament of Treitz, confirming total HSCR. Cardiac evaluation revealed a patent foramen ovale and moderate pulmonary hypertension on day 23 of life. The constellation of findings raised suspicion for Haddad syndrome. Because we were unable to extubate the infant, a diagnosis of CCHS was entertained. Molecular analysis with polymerase chain reaction amplification of exon 3 of PHOX2B revealed a heterozygous expansion mutation coding for 27 polyalanine repeats, confirming the diagnosis of CCHS. The patient remained on continuous ventilator support throughout the hospital course. In addition, he remained on total parenteral nutrition because of the functional intestinal obstruction. Because of the poor prognosis in view of CCHS, extensive HSCR and DS, the parents chose to withdraw ventilator support on day 67 of life. Analysis of the PHOX2B testing from parental blood samples revealed homozygosity for the normal 20-repeat allele in both parents.

**DISCUSSION**

We describe an infant with DS, who had a severe case of total HSCR disease and central hypoventilation, prompting the consideration of Haddad syndrome. Genetic testing confirmed trisomy 21 and a polyalanine repeat expansion mutation of PHOX2B. This is the first report of a patient with all 3 conditions occurring simultaneously. In ~90% of individuals with CCHS, de novo mutations in PHOX2B have been discovered. More than 90% of the CCHS-related mutations of PHOX2B are heterozygous in-frame expansions of a polyalanine repeat-encoding tract in exon 3. The exact location and sequence of the mutation requires sequencing of exon 3, which was not done in this case. However, we do know that the mutation is a 721_781insGCXGCXGCXGCXGCXGCX, indicating that 7 alanines were inserted somewhere between 721 and 780 (the 60-bp alanine repeat region). The normal allele has 20 alanines, and the expanded allele has 24 to 33 alanines. As the number of repeats increases, so does the severity of the clinical phenotype. The other 8% to 10% of the CCHS cases have nonpolyalanine repeat expansion mutations in PHOX2B typically resulting in the most severe phenotypes, virtually always including HSCR in addition to CCHS but with a range of effects that also includes mild and partially penetrant mutations. Because of the variability of effects of PHOX2B mutations on PHOX2B protein length and function, in combination with other yet undetermined factors, there is extensive phenotypic variability among individuals with a PHOX2B mutation. Hirschsprung disease is classified according to the length of aganglionosis. In ~80% of individuals, the aganglionosis is limited to the rectosigmoid colon, whereas it extends to the sigmoid colon in 15% to 20% of individuals. Total colonic aganglionosis only occurs in ~5% of individuals. Croaker et al demonstrated that 1.5% of all individuals with HSCR also have CCHS. They also delineated a difference in the amount of bowel involvement in HSCR depending on the presence of CCHS as well as DS. Most patients with HSCR and CCHS had total colonic aganglionosis (46%), whereas 70% of patients with HSCR and DS had HSCR to the sigmoid colon. The total colonic aganglionosis in our patient was not typical for DS and prompted investigation into an exacerbating factor, which was determined to be Haddad syndrome.
Given the severity of the HSCR and CCHS in our patient, we anticipated seeing further phenotypic effects, especially with regard to the cardiovascular and neurologic systems and craniofacial formation. Patients with CCHS may have QTC intervals >450 seconds and prolonged R-R intervals, decreased heart rate variability, and altered blood pressure homeostasis. However, our patient only had moderate pulmonary hypertension and atrial enlargement, which is consistent with DS and hypoxia. Alternatively, the infant’s young age at death precluded development of other aspects of the CCHS phenotype that might have occurred with advancing age.

In 2006, Todd et al observed that PHOX2B has a role in neural crest expression in the rhombencephalon, affecting facial structure development. This results in a characteristic boxlike facies. These patients with CCHS have a generally shorter and flatter facies with a decreased upper facial height and decreased upper lip height. The facial index and decreased upper facial index are decreased, indicating the face is short relative to its width. However, our patient’s facial features were only consistent for midface hypoplasia and upslanting palpebral fissures, all consistent with DS as well as CCHS. The potential CCHS features may have been obscured by the more pronounced DS phenotype.

Although our patient’s DS phenotype was evident upon admission to the NICU, his unusually severe HSCR and central hypventilation prompted further investigation. Molecular analysis revealed a 20/27 polyalanine repeat expansion mutation of PHOX2B consistent with Haddad syndrome. The underlying aneuploidy in our patient might have resulted in a more severe presentation. This case reminds one to consider the co-occurrence of Haddad syndrome with other genetic conditions.

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REFERENCES

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