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Congenital central hypoventilation syndrome and Hirschsprung’s disease in half sibs

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SUMMARY We report two infants with congenital central hypoventilation syndrome and Hirschsprung’s disease who have the same father but different mothers. The genetic implications of these cases are discussed.

Hirschsprung’s disease was first described 100 years ago and is a familiar disease in the newborn. In contrast, congenital central hypoventilation syndrome (CCHS) was first reported in 1970 by Mellins et al.1 In 1978, Haddad et al2 reported three infants who had both Hirschsprung’s disease and CCHS; two of these infants were sisters. Subsequently, we have found five additional published reports of infants with Hirschsprung’s disease and CCHS and none has been in sibs.3–6 We report two half sibs with Hirschsprung’s disease and CCHS and discuss the genetic implications of these cases.

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CASE 1
This 2440 g black female was born at term to a 22 year old, G6P3A2 mother whose other three children by different fathers are healthy. The pregnancy had been uneventful with no history of maternal drug abuse, medication, fever, or illness. There was no consanguinity. Delivery was by repeat caesarean section. Within the first six hours of life, she was noted to have several apnoeic spells with carbon dioxide retention. Chest x ray was normal. She remained dependent on a ventilator while asleep and failed pharmacological trials with aminophylline, caffeine, and naloxone. Tracheostomy was performed on day 34 of life. Signs and symptoms of cor pulmonale were present by four months of age. This has been managed successfully with ventilator manipulations and intermittent diuretics.

Abdominal distension was noted in the first 36 hours of life. Suction biopsy of the rectum on day 7 showed no ganglion cells and a sigmoid colostomy was performed. Pathological examination showed no ganglia in the rectum but the sigmoid colon did have ganglion cells. Her colostomy was subsequently closed at 20 months of age.

She has had esotropia with surgical correction and multiple ear infections, but only two episodes of pneumonia. She continues to be ventilated at night in the hospital at four and a half years of age. Her physical examination is otherwise normal; she has brown eyes and no pigmented or vascular abnormalities. Development is normal with delayed speech and attention seeking behaviour.

CASE 2
This 3030 g black male was the half sib of case 1; they have the same father, but the mothers are not related. He was born at term to a 26 year old, G4P3 mother whose other three children by different fathers are healthy. The pregnancy was uneventful with no drug exposure, medication, illness, or fever. There was no consanguinity. Delivery was by primary caesarean section because of late decelerations and a prolonged episode of fetal bradycardia. Because of poor spontaneous respiratory effort and hypercapnia, he was intubated. Chest x ray was normal.

He has remained dependent on a ventilator and failed pharmacological trials with aminophylline, naloxone, methylphenidate, and doxapram. Tracheostomy was performed on day 27. At seven months, he first showed signs and symptoms of cor pulmonale. These have been managed with ventilator changes and occasional diuretics.

His abdomen became distended in the first hours of life; suction rectal biopsy on day 4 showed no ganglion cells. Sigmoid colostomy was performed on day 6. Pathological examination showed no ganglia in the rectum, but ganglia were present in the sigmoid colon. The colostomy was successfully closed at 11 months of age.

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He has had two episodes of pneumonia. He is alive in the hospital on a ventilator for about 18 hours daily at two and a half years of age. His physical development is otherwise normal with brown eyes and no pigmented or vascular abnormalities.

Discussion

Congenital central hypoventilation syndrome, also known as congenital Ondine's curse, is a rare disorder characterised by hypoventilation with hypoxia and hypercapnia during sleep, and especially during non-REM sleep. There is no known primary pulmonary, thoracic, cardiac, or neuromuscular pathology. It is thought to be secondary to malfunction of the central chemoreceptors normally found in the ventrolateral area of the medulla. Multiple drugs have been tried unsuccessfully to stimulate adequate ventilation. Current management involves either chronic ventilator dependence or phrenic nerve pacemakers used to induce diaphragmatic muscles to assist in ventilation.

Hirschsprung’s disease has generally been considered to be the result of failure of ganglion cells to migrate from their neural crest origin to the distal colon. Neuroblasts migrate from the neural crest via the vagus nerve to the distal rectum by 10 to 12 weeks of gestation. Other neuroblasts from the neural crest migrate down each side of the developing spinal cord to give rise to the sympathetic ganglia of the sympathetic nervous system as well as the adrenal medulla.

Taguchi et al suggested that adventitial fibromuscular dysplasia leading to intestinal ischaemia could interrupt the craniocaudal migration of ganglion cells. Tam and Lister hypothesised that neuronal development followed a dual gradient proceeding from both ends to the middle of the gut in the second trimester, on the basis of examinations of 28 nine to 21 week human fetuses. Recent experiments with the lethal spotted mouse mutant, which develops a segmental aganglionosis of the terminal portion of the bowel as a result of a recessive mutation on chromosome 2, suggest that this animal aganglionosis results from an inherent abnormality of the gut wall itself. It appears that non-neuronal elements of the wall of the presumptive aganglionic region prevent gut colonisation with viable neural precursors from the neural crest. Thus, alteration of the microenvironment of enteric neurones may offer a better explanation for abnormalities of the intramural ganglia of the human gut, such as Hirschsprung’s disease, than the hypotheses of early fetal insult or abnormal genetic control of the migration and stabilisation of neural crest precursor cells themselves. Such changes may also help explain the association of Hirschsprung’s disease with several other disorders, such as Waardenburg’s syndrome, phaeochromocytoma, rubella embryopathy, and myelomeningocele. Alterations in the environment of the developing neurones or the integration and control of the environment could be the causal link for the association of Hirschsprung’s disease and CCHS.

Generally, Hirschsprung’s disease has been considered to be a heterogenous disorder. Animal models have shown both recessive and dominant modes of inheritance. Dominant neural crest disorders are well known and our pedigree suggests that dominant inheritance may be the genetic mechanism responsible for our two cases.

In reviewing the previous eight cases of Hirschsprung’s disease and CCHS, several similarities are found. All patients were born at term with a birth weight appropriate for gestational age. Apgar scores have been unremarkable and most deliveries have been vaginal. There have been three females and five males. In the four cases where race was mentioned, all were Caucasian. The presenting symptoms for CCHS have been apnoea, irregular or shallow breathing, and cyanosis.

Five of the eight had the more unusual long segment variety of Hirschsprung’s disease with no ganglia distal to the terminal ileum. All previous patients died, except one who was 23 months old at the time his case was reported. Necropsies were performed on six of seven cases. Two patients had multiple thoracic sympathetic chain and adrenal gland neuroblastomas and ganglioneuroblastomas.3 Otherwise, necropsy findings have not shown any consistent central nervous system pathology.

Although sharing many similarities with previously published cases, the half sibs we report are unique in some respects. They are the first half sibs reported. Although race is not mentioned in four of the previous cases, they are the first black infants reported. Both had the more common short segment Hirschsprung’s disease with ganglia found in the sigmoid colon. The other most striking difference in these two is their survival to four and a half and two and a half years of age with reasonable developmental milestones given chronic illness and the hospital environment.

Neither child has evidence of neurocutaneous disease or neural crest tumours. The father has no known gastrointestinal, respiratory, or neurocutaneous findings or a positive history. The absence of known relationship in the mothers raised the question of autosomal dominant inheritance with reduced penetrance. We have been unable to
document any similar environmental exposures or events in either of the mothers' pregnancies. The possibility of a neural crest disorder with low penetrance in the father offers the most likely explanation for the occurrence of half sibs with these disorders.

References

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CASE 1
The first child, a girl, was normocephalic (OFC 33 cm, 50th centile=34 cm) and had shortening of the frontal skull, flattening of the nose, and severe microphthalmia of the right eye with a normal left eye. She was treated for seizures on the first day and she died two days later.

Necropsy showed shortening of the anterior fossa and hypoplasia of the lamina cribrosa. The brain (weight 255 g) showed a monoventricle, a marginal frontal indentation, hypoplasia of the frontal cortex, and aplasia of the corpus callosum and the olfactory bulbs. No other congenital defects were found.

CASE 2
The second child, a boy, died on the first day of life. He was microcephalic (OFC 27 cm, 2nd centile=32 cm) and had a proboscis of 3.5 cm protruding from the glabellar region between two extremely

Holoprosencephaly: variation of expression in face and brain in three sibs

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SUMMARY A family is described containing three sibs with holoprosencephaly. They showed a striking diversity of both cerebral and facial abnormalities. Autosomal recessive inheritance seems most likely. Because of the great variety in expression of this disorder, it is of importance for genetic counselling to examine both sibs and parents.

Holoprosencephaly is a malformation disorder comprising a basic defect in the development of the embryonic forebrain, which is often associated with facial anomalies. The aetiology is heterogeneous. We report a family containing three sibs with holoprosencephaly showing a striking variation in expression of both cerebral and facial abnormalities. No similar published report could be found.

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