Waardenburg's syndrome associated with total aganglionosis

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SUMMARY A Pakistani child of consanguineous parents had signs of Waardenburg's syndrome and total intestinal aganglionosis. This association seems to be a distinct clinical entity with an autosomal recessive mode of inheritance.

Clinical details

A boy, the fourth child of Pakistani parents, was born at 38 weeks' gestation after a normal pregnancy and delivery. His mother had been taking propranolol throughout pregnancy because of mitral valve disease. The child had a white forelock, medial eyebrow flaring, a broad nasal root, and unusually pale blue eyes. The inner and outer canthal distances, 2.6 cm and 6 cm respectively, confirmed hypertelorism. Subsequent observations of failure to respond to sound suggested a hearing defect, but formal audiological assessment could not be undertaken. A Bishop-Koop anastomosis was performed at mid small bowel level on the first day of life because of abdominal distension and bile stained vomiting. Biopsy specimens from this site confirmed aganglionosis, the transition zone being 32 cm from the duodenojejunal flexure. A Bianchi lengthening procedure¹ was therefore performed to increase the mucosal absorptive surface and gave a total ganglionic bowel length of 60 cm.

Diatrizoic acid was later used to confirm patency of the lengthened bowel, with spontaneous clearance of contrast within 30 minutes, but the child died from fulminating *Escherichia coli* pneumonia on day 115 of life. Consent for necropsy was not given.

Family details

The parents and paternal grandparents were first cousins. Neither parent had signs of Waardenburg's syndrome. Their eye measurements were all within normal limits. They had had four children—the first was stillborn, their second, a daughter, has no signs of the syndrome, but the third, a son aged 2 years, has hypertelorism (his inner canthal and interpupillary measurements were greater than the 97th centile, although his head circumference was on the 50th centile). His parents recalled that he had extremely light hair at birth, but when this grew

again after a ritual shaving at the age of a few weeks, it was black. His hearing is apparently normal, his eyes are brown, and he has no bowel symptoms.

Discussion

Our patient had the typical clinical features of Waardenburg's syndrome type 1,² which is usually inherited as an autosomal dominant condition with highly variable expressivity and incomplete penetrance. He also had Hirschsprung's disease, which is usually considered to be a multifactorial condition. There is evidence, however, that intestinal aganglionosis extending high into the small bowel is a separate genetic entity, inherited in an autosomal recessive manner.³

A recent report from India⁴ has drawn attention to the association of total intestinal aganglionosis and Waardenburg's syndrome, and has suggested that the association is inherited as an autosomal recessive trait. The association may not be fortuitous, but due to a common pathophysiological cause.⁵ Cells from the neural crest migrate during early embryogenesis to produce melanocytes, innervate the developing bowel, form the sensory components of the spinal and cranial nerves, and form the membranous bones of the face and palate. A defect of the derivatives of the neural crest cells in mice has been shown to give rise to piebaldism and Hirschsprung's disease,⁶ and follows an autosomal recessive mode of inheritance. If this is the underlying pathophysiology, it is possible that the range in expression of physical signs noted in siblings of index patients in the study from India, and in the brother of the child reported here, may be caused by differences in the rate of migration of the neural crest cells.

In our patient, neither parent had clinical features of Waardenburg's syndrome, but another sibling had hypertelorism and pigmentary disturbance of the hair. In addition, the parents were first cousins, which is also suggestive of autosomal recessive inheritance, although not conclusive as cousin marriage is common among Moslems. Considering, however, the available genetic information we believe an autosomal recessive inheritance to be the most likely.

Evidence of intestinal obstruction in a child

showing features of Waardenburg's syndrome should raise the possibility of long segment Hirschprung's disease. The parents should be examined for signs of Waardenburg's syndrome, but it seems most likely that the association is a separate clinical entity inherited in an autosomal recessive manner.

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