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Unknown syndrome: Hirschsprung's disease, microcephaly, and iris coloboma: a new syndrome of defective neuronal migration

SUMMARY We describe three children with Hirschsprung's disease and microcephaly, two of whom also have an iris coloboma. Two of the children, one with a coloboma and one without, are from the same consanguineous pedigree. The third case is unrelated and was identified by the matching program of the London Dysmorphology Database.¹ This is the first report of this combination of features which are considered to be secondary to defective neuronal migration. An autosomal recessive mode of inheritance is proposed.

Case reports

CASE 1

This male child was born to a consanguineous couple originally from Pakistan. The pedigree is shown in fig 1. The other affected member is case 2 in this report. Case 1 was the first child of the parents and was born by normal delivery at 39 weeks' gestation. Labour was induced because the ultrasound scan suggested intrauterine growth retardation. At birth, his weight was 2.25 kg (3rd centile) but his head circumference at 30 cm was 3 cm less than the

3rd centile. His forehead was described as sloping. When 48 hours old he developed bilious vomiting and his condition deteriorated. An emergency laparotomy performed on the sixth day showed a perforated sigmoid colon and a temporary colostomy was performed. Histology of a rectal biopsy showed aganglionosis. At nine months of age an endorectal pullthrough operation with closure of the colostomy was successful in restoring large bowel continuity.

His mother became worried over his lack of developmental progress when he was nine months old. He sat at one year, crawled at two years and began to walk with both hands held at the age of two years one month. His head circumference at two years one month was 41 cm (5 cm <3rd centile). His height at two years five months was 87 cm (25th centile) and his weight 12.2 kg (25th centile). Physical examination showed an inferonasal coloboma of the right iris, bulbous nose, prominent ears, a high arched palate, tapering fingers, and the scars of his abdominal surgery. His facial features are shown in fig 2. Neurological examination confirmed the developmental delay but was otherwise normal. EEG showed no focal or paroxysmal features although the rhythmic activities over the occipital lobe were slow for the age of the child. CT brain scan was abnormal (fig 3); the vault was small and thick, the margins of the ventricles were irregular, and the deep white matter was of irregular density. This combination of abnormalities suggests defective neuronal migration. Other investigations, including chromosome analysis, visual evoked responses, and electroretinogram, were normal.

CASE 2

This boy is now five years old and is patient IV.4 in the pedigree (fig 1). He was born by normal delivery at term after an uneventful pregnancy. His birth weight was 3.51 kg (50th centile) with a head circumference of 33.5 cm (10th centile). The Apgar score at five minutes was 8. During the neonatal period he was slow to complete his feeds and his weight gain was less than expected. He was admitted for investigation at the age of five months when his weight was 6.0 kg (0.5 kg <3rd centile) and his head circumference was 39 cm (0.5 cm <3rd centile). A clinical diagnosis of Hirschsprung's disease was made and this was confirmed by a suction rectal biopsy. A right transverse colostomy was performed; subsequently he had an endorectal pullthrough with closure of his colostomy. The aganglionic segment extended just proximal to the recto-sigmoid junction. Mild left vesicoureteric reflux was identified but recent urological investigations are normal.

His mother expressed concern over his development at five months. He sat at around eight months, walked at 18 months, and spoke a few words at 20 months. A Griffiths developmental assessment when he was four years four months put his development quotient at 50. His head circumference has remained below the 3rd centile; it was 41 cm at 11 months (3 cm <3rd centile) and 43 cm at 17 months (2 cm <3rd centile).

FIG 1 Pedigree to show the relationship of case 1 to case 2.

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FIG 2 Facial appearance of case 1. Note hypertelorism, bulbous nose, and prominent ears.

FIG 3 CT brain scan of case 1. The deep white matter is of irregular density. The appearance is of defective neuronal migration.

He was reviewed at six years five months. His head circumference was 45.5 cm (4.5 cm <3rd centile), his height was 1.0 m (6.5 cm <3rd centile), and his weight 14.2 kg (2 kg <3rd centile). He also had a large nose and prominent ears (fig 4). He was ambulant and spoke several words. He attends a school for the severely educationally subnormal. There are no focal neurological signs. His CT brain scan is shown (fig 5).

CASE 3

This girl was born to a non-consanguineous British couple. Her mother had had two previous pregnancies, a normal girl born two years earlier and, more recently, a spontaneous abortion at six weeks' gestation. The third pregnancy was complicated by hyperemesis for which her mother took Debendox between the sixth and 20th week of pregnancy. The mother is hypothyroid and has thyroxine replacement. Labour was spontaneous at term and the delivery was normal; the child had Apgar scores of 9 at one minute and 10 at five minutes. Her birth weight was 3.3 kg (50th centile) and head circumference 33.5 cm (10th centile). She was noticed to have rather large bat ears, a pointed chin, and a depressed nasal bridge with mild hypertelorism.

Bilious vomiting developed at 24 hours of age and she had a laparotomy and temporary colostomy when four days old. Biopsies taken during the operation confirmed aganglionosis in the rectum and descending colon, but the left transverse colon was ganglionic. She later had a pullthrough procedure followed by closure of her colostomy and now has a normal bowel habit. Development was delayed at her one year assessment but this was initially attributed to her prolonged stay in hospital. A

formal assessment at 20 months showed that she was thriving and her weight was on the 50th centile. Her head circumference (45 cm) was on the 3rd centile. Hypertelorism and a beaked nose were noted. All aspects of her development were retarded and equivalent to a chronological age of 10 to 11 months. Neurological examination

FIG 4 Facial appearance of case 2. Note similar features to case 1.

FIG 5 CT brain scan of case 2. Asymmetrical ventricular dilatation, cerebral atrophy.

(a)

(b)

FIG 6 (a) Facial appearance of case 3. (b) Lateral view of case 3. She also has hypertelorism, a broad nasal bridge, and prominent ears.

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showed increased tone in all four limbs with brisk deep tendon reflexes.

Her subsequent developmental progress has been slow. The head circumference has progressed below the 3rd centile and was 47.6 cm at six years. Additional dysmorphic features were recorded when she was six years old and included a coloboma of the left iris, long tapering fingers, and a high arched palate. Her facial features are shown in fig 6. Normal investigations included metabolic screen, congenital infection screen, CT brain scan, and chromosome analysis. Spike discharges over the left temporal area were recorded on EEG.

Discussion

Normal development of the central and peripheral nervous system depends on neuronal proliferation and migration. The central nervous system (CNS) is derived from neural tube elements whereas the peripheral nervous system (PNS) originates from the neural crest. The spinal and autonomic ganglia and the glial cells of the PNS are neural crest derivatives. Neural crest also gives rise to non-neural tissue including the membranous bones of the face and palate, melanocytes, chromaffin cells of the adrenal medulla, and the connective tissue covering the CNS. The composition of the tissues through which the neural crest cells migrate has been extensively studied in order to find a substance which is controlling the process, but none has been positively identified. The migration of the cells of the CNS appears to be different. The neurones are derived from around the ventricular area of the brain and migrate to more superficial areas of the cortex. The signal which controls this process is not known, but at a tissue level it could be the same as that in the PNS.

Hirschsprung's disease is defined histologically by the absence of ganglia in the submucosal and intermuscular layers of the rectum. The lesion may affect a varying length of bowel but is continuous and spreads upwards from the rectum. Many congenital malformations have been described in association with Hirschsprung's disease or congenital intestinal aganglionosis. In particular, the incidence of the condition is higher in infants with Down's syndrome. There are reports of Hirschsprung's disease occurring with abnormalities in organs of neural crest origin: the Waardenburg-Hirschsprung association²⁻⁴ and bilateral bicoloured irides and Hirschsprung's disease.⁵ The ganglion cells of the gut are derived from neural crest tissue. They migrate to the large bowel along the vagus and are found in the duodenum at six weeks' gestation before progressing caudally until the whole of the large bowel is innervated at 12 weeks. Thus, the features of the above two variants of Hirschsprung's disease were thought to be secondary to a more generalised problem of neural crest

development and migration. The inheritance of both these syndromes is thought to be autosomal recessive.

We believe that we are describing a defect of neuronal migration affecting cells of neural crest and neural tube origin. The occurrence of two affected children in the same consanguineous pedigree suggests autosomal recessive inheritance of this syndrome. These two cases also illustrate the variability of the migrational defect and a spectrum in the severity of the neuronal migrational defect is to be expected. We therefore propose that these three infants have an inherited defect in the migration of nervous tissue and that this defect has led to microcephaly, mental retardation, Hirschsprung's disease, and iris colobomata.

Addendum

Since writing this report JAH and EMB have seen another child with Hirschsprung's disease, microcephaly, and mental retardation. The CT brain scan showed a neuronal migration defect with an associated agenesis of the corpus callosum.

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