Amelia, dextrocardia, asplenia, and congenital short bowel in deleted ring chromosome 4

J W Hou, T R Wang

Abstract
We report a female baby with multiple congenital anomalies including left upper amelia, congenital short bowel with malrotation and pseudo-obstruction, dextrocardia with situs solitus, patent ductus arteriosus, and a tiny atrophic spleen. Chromosome study showed de novo 46,XX/46,XX,-4,+r(4)(p16→q22.3)/47,XX,4,+r(4) (p16→q22.3),+del(4)(pter→q22.3). The clinical findings in the patient were probably caused by the interaction of partial trisomy 4pter→q22.3 or 4p16→q22.3 and partial monosomy of 4q22.3→q4ter. This karyotype and phenotype have not previously been reported.

Key words: amelia; congenital short bowel; chromosome 4.

Limb deficiency defects are relatively rare, particularly in chromosomal aberrations such as segmental autosomal monosomies or trisomies. The occurrence of ectodactyly or its equivalents in patients with del(4q) and r(4) in several cases' suggested that the genes related to limb deficiency may be assigned to the tips of 4p and 4q. We describe a patient with congenital short bowel with midgut malrotation and pseudo-obstruction, dextrocardia, and dysplastic spleen as well as amelia, as a result of del(4q) mosaicism.

Case report
The female patient was the first child of unrelated, healthy Chinese parents. Birth weight was 3500 g, length 50 cm, and OFC 33.5 cm (all were normal for a term Chinese female baby). The perinatal history was uneventful. Her mother denied any history of smoking, alcohol, drug or radiation exposure, and the procedures of chorionic villus sampling or amniocentesis. Ultrasonography at 25 weeks' gestation showed dilated bowel, but limb anomalies could not be detected. The amount of amniotic fluid was normal and no amniotic bands were visible. The mother was referred to our hospital with the suspicion of gastrointestinal obstruction in the fetus.

After birth, the baby was noted to have good activity. No significant head deformity or facial dysmorphism, except for naevus flammeus over the forehead, was noted. The musculature of the chest was normal but the apical impulse of the heart was located on the right side. No murmur was heard. The liver was palpable 1 cm below the right costal margin at the midclavicular line. The tip of the spleen was not palpable. Absence of the whole left upper extremity was the most significant finding (fig 1).

Abdominal distension with bile stained vomit developed gradually during the first 24 hours of life although normal meconium passage was noted. Radiographs showed suspected triple bubble sign as well as dextrocardia, left aetheiria, and hypoplasia of the left scapula (fig 2A). Laparotomy was performed on the second day because of the progressive course of intestinal obstruction. Haemogram, liver enzymes, acid base, and electrolytes were all normal. The operative findings showed dila-
Radiographs of the patient showing (A) triple bubble bowel sign (note dextrocardia, hypoplastic left scapula, and total absence of the left upper extremity at 1 day), (B) short bowel with segmental dilatation below the duodenum with malrotation by contrast study at 40 days. Gastro-oesophageal reflux was also noted.

Figure 3  Partial karyotype by G banding of the proband's normal and abnormal chromosomes 4 with a deleted ring form.

Histopathology of the resected intestine showed diffuse congestion and oedematous changes with inflammatory cell infiltration. Ganglion cells and nerve bundles were present throughout the whole intestinal segment. The structure of villi was intact.

Dextrocardia with situs solitus, patent ductus arteriosus, and incomplete patent foramen ovale with a left to right shunt were documented by echocardiography. Sonographs of the brain, liver, and kidneys were all negative. Liver scan with Tc-99m phytate showed no spleen uptake shadow postoperatively. Chromosome study from the peripheral lymphocytes stimulated by phytohaemagglutinin of the patient showed 46,XX/46,XX,4,+r (4) (p16→q22.3)/47,XX,−4,+r (4) (p16→q22.3),+ del(4)(pter→q22.3) in a ratio of 84%/12%/4% (fig 3). The karyotypes of both parents were normal.

The postoperative course was smooth and total parenteral nutrition (TPN) was given. Contrast study with urographin showed patency but poor peristalsis of the anastomotic intestine at 9 days of age. Incremental enteral feeding was tried from 12 days. There was often vomiting without bile and large residual gastric volume. Oesophagogram showed moderate gastro-oesophageal reflux. The emptying time from upper oesophagus to rectum was about three hours, which is within normal limits for 44 days of age. The gastric half emptying time following administration of a test meal labelled with 2 mCi of Tc-99m sulphur colloid was 96.15 minutes (normal 66 ± 32 minutes). The patient was discharged at 62 days old. Home TPN was started. Frequent bile stained
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The complex of the chromosome 4 rearrangements in this case could explain the phenotypic spectrum involving multiple organs. The genetic interactions include different aneuploid segments: monosomy 4q22.3→qter, trisomy 4pter→q22.3, and deletion of the tips of 4p in the ring form. The generation of mosaic aneuploid cells during embryogenesis influences the rate of proliferation and differentiation and has a pronounced effect on the organisation of certain structures, especially vascular disruption in the territories of major arteries for left upper limb budding, midgut elongation, spleen formation, and cardiac loop orientation.

Ivemark syndrome, a rare disorder of asplenia-cardiovascular anomalies, has been described as a single gene disorder (autosomal recessive inheritance). The present case indicates that one gene or the gene whose mutation can cause Ivemark syndrome may be on chromosome 4.

Short bowel syndrome encompasses a spectrum of metabolic and physiological disturbances resulting from massive anatomical or functional diminution of the small bowel in this patient. Home parenteral feeding may allow long term survival, but the prognosis in this case will not be good because of the susceptibility to infection because of asplenia.

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