A new recessive syndrome of unusual facies and multiple structural abnormalities

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Abstract

Two sibs with a similar pattern of dysmorphic facial features and multiple structural abnormalities are reported. Both had a normal karyotype. The parents are first cousins and neither shows any stigmata of the disorder. In view of the consanguinity and pattern of malformations, autosomal recessive inheritance seems likely.

In communities where consanguinity is common there is an increased incidence of autosomal recessive disorders, some of which are provisionally 'private syndromes'. We describe a Pakistani family where two offspring had a similar pattern of unusual facies and multiple structural abnormalities which have not been reported previously. The parents, who are first cousins, did not have any of the stigmata of the disorder and chromosome analysis on both the offspring was normal.

Case reports

The couple had five pregnancies in all; the mother was 22 years old and father 23 years in the first pregnancy. The first and fourth pregnancies resulted in the birth of normal healthy girls who are the only surviving children. In their second pregnancy they had a male infant with clinical features of Werdnig-Hoffmann disease and an incidental finding of 47,XXY on karyotyping. He did not have any of the facial features or structural abnormalities seen in the reported sibs. He lived for five months. A postmortem muscle biopsy showed features of

neurogenic muscle atrophy compatible with a diagnosis of Werdnig-Hoffmann disease, but the anterior horn degeneration could not be verified as permission had been granted only for a limited necropsy.

Their third pregnancy was terminated at 26 weeks and the fetus is case 1. The fifth pregnancy resulted in the birth of a female infant who is case 2.

CASE 1

This female fetus was delivered at 26 weeks' gestation after a therapeutic termination for multiple structural abnormalities identified on ultrasound scanning.

During this pregnancy a second trimester scan had shown marked shortening of the cervical spine. An amniocentesis was performed and normal alpha-fetoprotein level and a 46,XX karyotype were found. By 25 weeks the fetus had gross hydrocephalus which involved the lateral ventricles and the posterior fossa. In view of these abnormalities the parents chose to have the pregnancy terminated. On examination the fetus was a female weighing 940 g (50th centile). She had a large head (OFC 28 cm, >97th centile), with bulging fontanelles, an extremely low posterior hair line, and a very short webbed neck. She was noted to have unusual facial features (fig 1) with long, downward slanting, widely spaced palpebral fissures, a broad nasal bridge, a short nose with a bulbous tip, and anteverted nares. The corners of the mouth were downturned. The postmortem examination showed the presence of multiple malformations. There was dilatation of the ventricular system, but no Arnold-Chiari malformation of the brain. There were cervical spinal abnormalities (Klippel-Feil anomaly), transposition of the great vessels with a ventricular septal defect, and an extremely short oesophagus with intrathoracic stomach, small intestine, spleen, and pancreas. The umbilical cord had four vessels. The muscle tissue was not examined histologically; the rest of the fetal tissue appeared normal.

Radiology of the fetus showed the presence of an occult spina bifida of the cervical spine with six normal pairs of ribs below the abnormal pairs which were superimposed on one another. There was wide

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Figure 1 Case 1, a 26 week gestation fetus. Note the long, downward slanting, widely separated palpebral fissures, short, bulbous tipped nose, small mouth with downturned corners, and short webbed neck.

Figure 2 Case 2 at 53 days of age showing similar facial features to case 1.

divergence of the two halves of the vertebral bodies in the cervical region.

CASE 2

Case 2 was a female, the sib of case 1. In view of the previous poor obstetric history an amniocentesis had been performed at 16 weeks' gestation which showed a normal alpha-fetoprotein and 46,XX karyotype. The antenatal scan at 26 weeks identified Fallot's tetralogy. Delivery was at 36 weeks' gestation by an emergency LSCS for intrauterine growth retardation and fetal distress. Her birth weight was 1580 g (3rd centile) and OFC 28.0 cm (3rd centile). She needed resuscitation with oxygen through a face mask.

She had identical facial features (fig 2) to her sib (case 1) with long, downward slanting, widely spaced palpebral fissures, a broad nasal bridge, a short nose with a bulbous tip, and anteverted nares. The corners of the mouth were downturned and the ears were long (fig 3). In addition she was noted to have anal atresia. Over the course of her short life (53 days) other structural abnormalities were identified by radiological investigations. These included hemivertebra at the T4/T5 level, bilateral hydro-nephrosis on ultrasound scanning, and agenesis of the corpus callosum on CT scanning. The Fallot's

Figure 3 Lateral view of case 2. Note the large, posteriorly rotated ear.

tetralogy was confirmed by an echocardiogram. The anal atresia was associated with rectovaginal fistula.

Within a few hours of birth, she became cyanosed and required ventilatory support in addition to a prostaglandin infusion to maintain the patency of the ductus arteriosus. She remained ventilator dependent. Palliative treatment with balloon dilatation was attempted but was unsuccessful because of severe infundibular stenosis. A left descending colon/sigmoid colostomy was performed on day 2.

In addition to ventilator dependence and swallowing impairment, she had paucity of movement and hypotonia suggesting a neuromuscular abnormality. The reflexes were preserved and there was no tongue fasciculation.

Regular measurements of the OFC had been made difficult by the need for ventilation. One obtained at 4 weeks showed no growth since birth. Fundoscopy showed pale discs but no lacunae of Aicardi's syndrome.

A number of metabolic investigations were carried out. These included amino acid and organic acid excretion and white cell and plasma lysosomal enzymes which were all normal. Her calcium values were always above 2.05 mmol/l and the cell marker studies showed normal subsets of T3/B1. A repeat chromosomal analysis after birth showed a normal female karyotype.

Intensive support was maintained at the parents' request. On day 53 her condition deteriorated and she died. Necropsy was limited to a muscle biopsy according to the parents' wishes. The tissue sample showed uniform muscle atrophy with some evidence of an inflammatory cell infiltrate. The features, though not characteristic of Werdnig-Hoffmann disease, were compatible with a neurogenic atrophy.

Discussion

The malformations and facial features of the two sibs are summarised in the table. A search using the London Dysmorphology Database did not indicate any condition with a similar pattern of malformations.

Di George syndrome^{1,2} was considered in case 2 in view of the presence of a congenital heart defect, anal atresia, and facial dysmorphism. The normal

Features of the two sibs.

Features	Case 1	Case 2
Sex	F	F
IUGR	—	+
Long, downward slanting palpebral fissures	+	+
Hypertelorism	+	+
Short nose with a bulbous tip	+	+
Small mouth with downturned corners	+	+
Posteriorly rotated ears	+	+
Long ears	—	+
Vertebral anomalies	+	+
Brain malformation	+	+
Cardiac malformation	+	+
Gastrointestinal malformation	+	+
Renal malformation	—	+
Karyotype	46,XX	46,XX

levels of calcium and lymphocyte subsets made this unlikely.

The facial features show some resemblance to those of Lambotte syndrome.³ Comparison of our case 2 and Lambotte's patient 4 shows striking similarity in the shape of the eyes, mouth, nose, ears, and chin. Other features in common with this syndrome include brain malformation, failure to thrive, and early death. The major differences are the presence of polydactyly and abnormalities of the external auditory meatus and pelvis in the Lambotte syndrome. The more extensive structural abnormalities in both our cases add further support to this being a distinct entity.

In addition to the malformation syndrome, case 2 also showed features of the neurogenic atrophy which affected the phenotypically normal brother. In view of the consanguinity, it is not unreasonable to consider two separate autosomal recessive conditions in this family.

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- 1 Conley ME, Beckwith JB, Mancor JFK, Tenckhoff L. The spectrum of Di George syndrome *J Pediatr* 1979;94:883-90.
- 2 Carey JC. The spectrum of Di George syndrome. *J Pediatr* 1980; 96:955.
- 3 Verloes A, Dodinval L, Beco J, Lambotte C. Lambotte syndrome: microcephaly, holoprosencephaly, intrauterine growth retardation, facial anomalies and early lethality - a new sublethal multiple congenital anomaly mental retardation syndrome in four sibs. *Am J Med Genet* 1990;37:119-23.