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Unknown syndrome in sibs: microcephaly, seizures, mental retardation, congenital heart disease, and skeletal abnormalities

SUMMARY We present two male sibs with a series of malformations including microcephaly, mental retardation,

congenital heart disease, skeletal abnormalities, micropenis, and mild hypothyroidism. Both have had seizures. While the pattern of abnormalities is similar to that previously reported in this journal as an unknown syndrome, the facies is clearly distinct, the hypothyroidism is mild, micropenis is present, and there are additional minor skeletal abnormalities.

History

Prenatal. Sib 1. Vaginal delivery after 39 weeks. Meconium stained and with meconium in trachea. Apgar scores 2 and 7 at one and five minutes. Sib 2. Spontaneous vaginal delivery after 37 weeks. Apgar scores 8 and 9 at one and five minutes.

Family. No other sibs, no stillbirths or abortions. Parents healthy and unrelated. Father aged 30 years, mother 29 years at birth of sib 1, and 32 and 31, respectively, at birth of sib 2. Four maternal cousins with osteogenesis imperfecta.

Clinical examination

SIB 1

At birth. Weight 2700 g (10th centile), length 49.5 cm (25th centile), head circumference 31 cm (less than 3rd centile). Transient nystagmus, hypotonia, atrial septal defect, micropenis, and left undescended testicle. Hypothermia and seizures in neonatal period.

At 30 months. Weight 9 kg (less than 3rd centile), height 81.2 cm (less than 3rd centile), head circumference 42.7 cm (less than 3rd centile) (fig 1). Hypotonia, marked delay in psychomotor development, poorly controlled seizures.

FIG 1 AP and lateral view of sib 1 at 35 months of age. Note depressed nasal bridge.

FIG 2 AP and lateral view of sib 2 at 15 months of age. Note the facial similarity. Both sibs have a prominent antitragus.

Persistent atrial septal defect. Prominent, hairy sacrum without presacral dimple. Rockerbottom foot on right.

SIB 2

At birth. Weight 3500 g (75th centile), length 52 cm (75th centile), head circumference 32.5 cm (3rd centile). Gross nystagmus; facies is similar to brother. Redundant skin of forehead and neck. Rudimentary, supernumerary nipple on left. Postaxial polydactyly of left hand. Hypoplastic segment (1.5 cm) of aortic arch distal to left subclavian with persistent ductus arteriosus, ASD, VSD. Micropenis.

At 10 months. Weight 6.2 kg (less than 3rd centile), length 72 cm (25th centile), head circumference 39.5 cm (less than 3rd centile) (fig 2), hypotonia, left esotropia, right epicanthic fold. Persistent heart murmur. Delayed psychomotor development. Onset of seizures at 21 months.

Investigations

Sib 1. CT of head at birth showed microcephaly. Echocardiogram confirmed presence of large ASD. EEG showed bilateral paroxysmal sharp wave discharges, more pronounced on the right. Chest x ray showed paddle shaped ribs and butterfly ninth thoracic vertebra. Prophase chromosomes (800 bands) were normal. MRI at 30 months of age showed agenesis of posterior corpus callosum. T4 7.2 µg/dl, TSH 8.4 mIU/l. TSH returned to normal and T4 remained in normal range on oral L-thyroxine replacement.

Sib 2. CT of head normal at birth. Echocardiogram at six months of age showed closing VSD, open ASD. Chest x ray showed short, broad ribs with bilateral hypoplastic 13th ribs and hypersegmentation of the sternum. Hypersegmentation of the sacrum. Prophase chromosomes (800 bands) were normal. T4 8.1 µg/dl, TSH 9.2 mIU/l. TSH level returned to normal with replacement.

Discussion

Two male sibs have similar features including microcephaly, congenital heart disease, micropenis, numerous skeletal abnormalities, delayed somatic growth, mental retardation, and seizures. The older sib has more severe central nervous system disability (possibly on the basis of aspiration and hypoxia). Both sibs have mild hypothyroidism as evidenced by the raised serum TSH levels, corrected by L-thyroxine supplementation. The sibs superficially resemble the isolated cases reported by Young and Simpson¹ and by Fryns and Moerman.² However, those infants had a distinctly different facies including bulbous nose, blepharophimosis, carp shaped mouth, and low set ears. The present sibs have a pug nose with depressed nasal bridge, the other facial features being essentially normal. In addition, they have skeletal abnormalities and micropenis, and the hypothyroidism is less severe. On this basis, we feel the syndrome is distinct.

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