Kyphomelic dysplasia in two sib fetuses

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Abstract

We present the in utero appearances and postmortem radiographic findings of two sib fetuses, a male and a female, with features suggestive of kyphomelic dysplasia. The fetuses had severe bowing of the long bones, short, flared ribs, platyspondyly, metaphyseal flaring, skin dimpling, with normal external genitalia and karyotypes and a normal pregnancy. They were born to a mother with features of brachydactyly type E. Prenatal ultrasonography of each case showed a normal amount of amniotic fluid, a normal brain, a normal biparietal diameter, symmetrical bowing and shortening of the long bones, and a narrow thorax. Our cases provide support for a familial mode of inheritance for both sexes in kyphomelic dysplasia. Prenatal ultrasound examination can be offered in subsequent pregnancies.

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Keywords: kyphomelic dysplasia; prenatal diagnosis; ultrasound; familial inheritance

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Kyphomelic dysplasia is a rare, congenital, skeletal disorder characterised by a short trunk, micrognathia, midfacial hypoplasia, a long philtrum, a normal occipitofrontal circumference, severe rhizomelic/mesomelic limb shortening, platyspondyly, irregular, flared metaphyses, bowing of the limbs, skin dimpling over bowing, short, angulated femora, a narrow chest, and joint restriction.¹ Khajavi *et al*² first reported two male cases in 1976 as a variant normocephalic type of short limbed campomelic syndrome. In 1979, Hall and Spranger³ further described one pair of affected brothers with congenital bowing and short, broad bones. In 1983, Maclean *et al*⁴ proposed the nomenclature "kyphomelic dysplasia" to describe the skeletal dysplasia in a male infant with short, angulated femora and bowing of other long bones and the cases reported by Khajavi *et al*² and Hall and Spranger.³ Since then, 13 cases of kyphomelic dysplasia have been reported.²⁻¹¹ None of these reports included the appearance in utero. We report two sib fetuses, a female and a male, with kyphomelic dysplasia and distinctive prenatal findings.

Case reports

CASE 1

During her first pregnancy, a 25 year old primigravida came to our hospital for antenatal care from 17 weeks' gestation. Her height was 150 cm. She had acromelic shortening of the fingers and toes, especially the thumbs, little fingers, and big toes, hypoplastic nails, isolated,

and short 4th metatarsals with the 4th toes inserting into the feet, which were consistent with the diagnosis of brachydactyly type E. She and her spouse were Chinese and non-consanguineous. She had neither prenatal exposure to teratogenic drugs nor a family history of malformations. Maternal urine throughout the pregnancy did not contain glucose. Radiographic examination showed shortened metacarpals and phalanges of the hands, shortened metatarsals and phalanges of the feet, 12 pairs of ribs, and normal scapulae, clavicles, humeri, femora, ischial bones, and tibiae. She had a normal karyotype, 46,XX.

Prenatal ultrasonography at 26 weeks' gestation showed a normal amount of amniotic fluid, a biparietal diameter of 67 mm, equal to 26 weeks' gestation, symmetrical angulation and shortening of the long bones, normal cerebral ventricles, and a narrow chest. The long bone lengths measured below the 5th centile, with the femur measuring 36 mm, humerus 32 mm, and tibia 30 mm (fig 1). Amniocentesis showed a 46,XX karyotype. The mother decided to terminate the pregnancy at 31 weeks' gestation. The dead infant measured 34.5 cm in length and weighed 1000 g. Physical examination showed short limbs, joint restriction, a normal occipitofrontal circumference, a normal palate, a flat nasal bridge, hypertelorism, a long philtrum, low set ears, a narrow thorax, pretibial skin dimpling, normal hands and feet, and normal female external genitalia (fig 2). Postmortem radiographic examination (fig 3) showed symmetrical, short long bones with bowed femora, humeri, tibiae, fibulae, ulnae, and radii, 12 pairs of short, flared ribs, normal clavicles and scapulae, a narrow thorax, platyspondyly, metaphyseal flaring, and ossification of the tali. The dysmorphic features and radiological findings (fig 1) of the bowed long bones removed from the proband were consistent with the diagnosis of kyphomelic dysplasia. The internal organs were normal at necropsy.

CASE 2

During her third pregnancy, the same mother and father as of case 1 came for prenatal care six years after the delivery of their first malformed child. Five years previously, the mother had given birth to her second child, a healthy boy without any skeletal abnormalities. Prenatal ultrasonography at 23 weeks' gestation showed a normal amount of amniotic fluid, a biparietal diameter of 56.3 mm, equal to 23 weeks' gestation, normal cerebral ventricles, a narrow chest, and symmetrical angulation and shortening of the long bones. The long bones measured below the 5th centile, with the femur measuring 25.8 mm, tibia 23.8 mm, fibula 23.6 mm, humerus 29.1 mm, ulna 23.6 mm, and

Figure 1 The clinical and radiographic appearance of the long bones removed from case 1 (order from left to right: fibula, tibia, femur, radius, ulna, and humerus). Prenatal ultrasonography at 26 weeks' gestation showing in utero angulation of the tibia, fibula, and humerus.

radius 23.8 mm (fig 4). Amniocentesis showed a 46,XY karyotype. The same findings as in the earlier case were obvious. The mother opted to terminate the pregnancy at 23 weeks' gestation. The infant at birth weighed 600 g and measured 26 cm in length. Physical examination showed a normal occipitofrontal circumference, a normal palate, a flat nasal bridge, hypertelorism, a long philtrum, low set ears, short limbs, joint restriction, a narrow thorax, pretibial skin dimpling, normal hands and feet, and normal male external genitalia (fig 5). Postmortem radiographic examination (fig 6) showed short long bones with symmetrically bowed femora, humeri, tibiae, fibulae, radii, and ulnae, 12 pairs of short, flared ribs, normal clavicles and scapulae, platyspondyly, metaphyseal flaring, and ossification of the tali.

Samples of DNA were obtained from parental whole blood, umbilical cord, and muscle of case 2. Polymerase chain reaction methods using primers flanking the SOX9 gene were applied according to previously published methods.^{12 13} The amplification was carried out

Figure 2 Case 1 at birth.

Figure 3 Whole body radiograph of case 1.

in an "OmniGene" module (HYBAID, UK) with 30-35 cycles at 94°C for 60 seconds, 55-64°C for 60 seconds, and 72°C for two minutes. Sequencing reactions were performed with the ABI PRISM dye terminator cycle sequencing kit (Perkin Elmer, USA) and then analysed on an ABI 377 automated DNA sequencer. Both strands were sequenced using either the forward or reverse primer. Paternity was confirmed by a DNA fingerprint of the family. Analysis of the SOX9 gene in case 2 showed no mutation in either of the SOX9 alleles. The internal organs were normal at necropsy.

Figure 4 Prenatal ultrasonography of case 2 at 23 weeks' gestation showing in utero angulation of (A) the humerus, radius, and ulna, (B) the femur, tibia, and fibula.

Figure 5 Case 2 at birth.

Discussion

A comparison of our probands with the 13 previously reported cases of kyphomelic dysplasia is shown in table 1. Differential diagnosis of kyphomelic dysplasia should include short stature/short limb skeletal dysplasia (SLSD) with severe combined immunodeficiency (SCID), campomelic dysplasia, congenital bowing of the long bones, Antley-Bixler syndrome, Larsen syndrome, diastrophic dysplasia, Stüve-Wiedemann dysplasia, Fuhrmann syndrome, and asymmetrical (symmetrical) long bone bowing with craniosynostosis.¹ Short stature/SLSD with SCID is characterised by autosomal recessive inheritance, bowing of the long bones, metaphyseal chondrodysplasia, flaring of the rib ends, decrease in the vertical height of vertebral bodies, lymphopenia, reduced immunoglobulin levels, recurrent respiratory infection, diarrhoea and moniliasis.¹⁻¹⁴ The classical form of campomelic dysplasia is characterised by autosomal dominant inheritance, sex reversed XY females, dwarfism, respiratory distress, macrocephaly, micrognathia, malformed ears, cleft palate, bowing of the lower limbs, central nervous system anomalies, neonatal death, polyhydramnios, associated abnormalities such as hydronephrosis and congenital heart defects, an enlarged and elongated skull, hypoplasia of the cervical vertebrae, a bell shaped thorax with

Figure 6 (A) Anteroposterior and (B) lateral views of the whole body radiographs of case 2.

11 pairs of ribs, hypoplastic scapulae, some shortness and angulation of the upper extremities, a contracted pelvis, angulation of the proximal femoral shaft, hypoplasia and angulation of the tibia, hypoplasia of the fibula, no ossification of the talus, and talipes equinovarus.¹ The SOX9 gene, an SRY related gene located on chromosome 17q24.3-q25.1, has been considered a candidate gene for sex reversal and campomelic dysplasia.^{12 13 15 16} Campomelic dysplasia is an autosomal dominant disorder with a heterozygous mutation in SOX9.^{12 13 16} The present sister and brother pair was distinguished from the classical form of campomelic dysplasia by the presence of a normal cranium and brain, severely bowed extremities, ossification of the tali, absence of hypoplasia of the fibula, and absence of either sex reversal or SOX9 gene mutations in case 2. Some reported cases of the normocephalic form of campomelic dysplasia or pseudocampomelia have been regarded as actual cases of kyphomelic dysplasia.¹ To date, three sib pairs with kyphomelic dysplasia have been described.¹ Hall and Spranger³ reported two affected brothers, Rezza *et al*¹¹ reported an affected brother and sister pair, and Turnpenny *et al*⁷ reported two affected brothers. We report an additional pair of affected sibs of different sexes which provides further support for autosomal inheritance. The familial mode of inheritance may be either homogeneous or heterogeneous and will require further studies to elucidate this.

Kyphomelic dysplasia has been associated with normal mental development.¹⁷ Other associated reported abnormalities include cleft lip, cleft palate, and apnoea,⁶ pure red cell aplasia,⁷ severe combined immunodeficiency,¹⁰ Perthes disease,⁹ and avascular necrosis of the proximal femoral epiphyses.⁸ Although the

Table 1 Clinical and radiographic findings of the present two cases and the 13 previously reported cases*

	<i>Previous reports† (13 cases)</i>	<i>Present reports</i>	
		<i>Case 1</i>	<i>Case 2</i>
Clinical findings			
Sex	10 M/1 F	F	M
Normal OFC	11/11	Yes	Yes
Small chest	10/10	Yes	Yes
Short limbs	12/12	Yes	Yes
Limited joint movement	5/5	Yes	Yes
Normal hands and feet	5/9	Yes	Yes
Skin dimpling	6/6	Yes	Yes
Cleft lip and palate	2/12	No	No
Midfacial hypoplasia	6/8	Yes	Yes
Micrognathia	5/8	No	No
Radiographic findings			
Bowed femora	13/13	Yes	Yes
Bowed humeri	7/12	Yes	Yes
Bowed tibiae	8/11	Yes	Yes
Bowed radii	10/12	Yes	Yes
Eleven pairs of ribs	2/10	No	No
Short, flared ribs	10/10	Yes	Yes
Platyspondyly	4/9	Yes	Yes
Metaphyseal flaring	11/11	Yes	Yes

*Data compiled from references 2-11.
†Expressed only in those patients with specific findings well described in reports.

prognosis of kyphomelic dysplasia appears to be encouraging, orthopaedic sequelae as well as haematological problems should be advised in genetic counselling. In the absence of molecular and biochemical tests, prenatal ultrasound is the only tool available for prenatal diagnosis.

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