RESEARCH LETTER

Pseudodiastrophic Dysplasia: Two Cases Delineating and Expanding the Pre and Postnatal Phenotype.

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Pseudodiastrophic dysplasia was described and named in 1974 by Burgio *et al.*, characterized by short-limbed short stature at birth, facial dysmorphism (hypertelorism, flat

nose, prominent cheeks, micrognathia), cleft palate, and distinctive skeletal phenotype including narrow thorax, scoliosis, rhizomelia, ulnar deviation of the wrist, proximal interphalangeal (PIP) joint dislocation, dislocation of large joints in particularly of the elbow and talipes equinovarus. [Burgio et al., 1974; Eteson et al., 1986] The clinical presentation is similar to diastrophic dysplasia (DTD) but the radiographic and chondro-osseous features are distinct. The main radiographic features of pseudodiastrophic dysplasia include short ribs, mild to moderate platyspondyly, broad ilia with iliac flaring, increased acetabular angle, metaphyseal widening of the long bones, elongation of proximal and middle phalanges, and PIP joint dislocation. [Burgio et al., 1974; Eteson et al., 1986; Canki-Klain et al., 1990; Bertrand et al., 1991; Fischetto et al., 1997] The distinction from DTD was confirmed by the demonstration of normal sulfate uptake in fibroblasts and normal screening of the *SLC26A2* gene in one patient with pseudodiastrophic dysplasia [Cetta et al., 1997]. The gene responsible for pseudodiastrophic dysplasia has not been identified.

Eleven cases of pseudodiastrophic dysplasia have been reported in the literature [Burgio et al., 1974; Canki et al., 1979; Eteson et al., 1986; Canki-Klain et al., 1990; Bertrand et al., 1991; Fischetto et al., 1997]. These reports broadened the phenotypic spectrum to include joint contractures and C1-C2 instability, [Eteson et al., 1986] as well as omphalocele and ventricular septal defect. [Fischetto et al., 1997] Autosomal recessive inheritance has been proposed because of sibling recurrences affecting both females and males in families with unaffected parents.

Here we report two fetuses with pseudodiastrophic dysplasia and delineate the fetal phenotype of this condition. The fetuses were the products of a healthy, non-consanguineous Caucasian couple with an unremarkable family history and two healthy sons.

Fetus 1 was the product of the couple's third pregnancy, at maternal and paternal age of 31 and 34 years, respectively. The pregnancy was uneventful until fetal demise at 16 weeks' gestation. Post-mortem examination revealed a 14-week gestational size, severely macerated, edematous, and dysmorphic fetus of indeterminate gender. All four limbs were short and bowed and there was marked nuchal edema, a cleft hard palate, and hypoplastic nares. The abdomen was distended with anorectal agenesis and absence of external genitalia. Internal anomalies comprised small and large intestinal malrotation, blind ending large bowel attached to the dome of an enlarged bladder with no outlet, absent left kidney, and normal right kidney with tortuous ureter. Gonads were confirmed by histology to be testes. There were no anomalies of the cardiac, endocrine, respiratory system, placenta or cord. The brain was autolysed. Histologic examination of all organs was normal except for the right kidney which showed normal corticomedullary arrangement but marked reduction of glomeruli, tubules and collecting ducts.

Fetogram findings are described in Figure 1. Histologic examination of a femur showed irregular primary bony trabeculae, and in the growth plates the cartilage columns were well-organized with chondrocytes of normal size and shape. The basal zone was also unremarkable. No cystic changes or other degenerative features were evident in the growth plates. 7-dehydrocholesterol level was normal. G-banded karyotype from cultured fibroblasts showed a normal 46, XY. SNP microarray (Illumina Infinium CytoSNP-850K, <0.1Mb) did not detect any clinically significant genomic imbalances.

Fetus 2 (also known as patient 2) was the product of the couple's next pregnancy 12 months later. Ultrasound scan at 13 weeks' gestation showed a nuchal translucency measurement of 4.7mm (3.1 MoM), with septated subcutaneous edema extending circumferentially around the neck, chest, and abdomen. Bone morphology appeared

normal on transvaginal scanning, however the femur length of 9 mm was short for gestational age, consistent with 11 weeks. The couple declined invasive prenatal testing. Ultrasound scans at 15 and 17 weeks' gestation showed persistent subcutaneous edema of neck and chest, with all long bones measuring <5th centile for gestation. Bowing was most marked in humeri and distal long bones. Wrists were held in a semi-flexed position with normal finger extension and there was bilateral talipes equinovarus. Thoracic circumference measured on the 10th centile with apparent kinking of the lower thoracic spine. A single echogenic focus was seen in the left ventricle. No internal organ anomalies were identified.

Serial ultrasound scans between 22 and 35 weeks' gestation showed persistent severe subcutaneous edema of neck and thorax. Long bones were <2nd centile with distal bones more severely shortened. Bowing had ameliorated by 22 weeks' gestation. (Figure 3) The facial profile showed flat midface and protuberant eyes. Polyhydramnios developed at this stage with AFI (amniotic fluid index) of 24-25cm.

Labour was induced at 37+5 weeks' gestation for maternal discomfort related to polyhydramnios. A live female was delivered in good condition by normal vaginal delivery. No resuscitation was required. Clinical examination revealed a dysmorphic female infant with generalised micromelia. Length was 40.2cm (<1st centile). Head circumference and weight were 33.5cm and 2550 grams, respectively (both on 10th centile, but probably inflated secondary to edema). Facies was distinctive with midface hypoplasia, flat profile, protuberant eyes with blue sclera and small anteverted nose. Subcutaneous edema of head, neck and thoracic wall was evident, with short neck. Micrognathia and cleft palate were present, and the mouth was small with restricted opening. Naevus flammeus was present over the glabella and eyelids. The earlobes were large and fleshy with no cystic abnormality. The wrists were held in fixed flexion and ulnar deviation. Contractures were

present at the elbows, shoulders, knees and hips. There was severe talipes equinovarus and camptodactyly in association with hyperextensible and subluxable fingers. “Hitchhiker” thumbs were not present. Thoracic kyphosis and normal female genitalia were noted. Ophthalmological examination identified several bilateral anterior polar cataracts.

Skeletal survey showed mild platyspondyly and thoracolumbar kyphosis. The ilia were broad and flared. All long bones were short with broadened distal metaphyses. There were proximal radial head dislocation and bilateral talipes equinovarus. The metacarpals and phalanges appeared broad and short, with subluxation of PIP joints. There was marked ulnar deviation at the radiocarpal joint (Figure 2). Lymphocyte karyotype showed a normal female (46, XX). Serum 7-dehydrocholesterol and urine metabolic screen including mucopolysaccharides and oligosaccharides were normal. *SLC26A2* sequencing did not detect any pathogenic variants. Cranial and renal ultrasound scans, echocardiogram and audiology screen were normal. Hip ultrasound scan confirmed bilateral dislocation. Flexible endoscopy of the upper airway identified a normal epiglottis, edematous arytenoids and thickened vocal cords. She developed respiratory distress requiring prolonged intensive care and invasive ventilation. She developed severe pulmonary hypertension and care was withdrawn at 6 months of age.

The prenatal phenotype of significant bowing and shortening of long bones in fetus 1 prompted consideration of a primary skeletal dysplasia in the “campomelic dysplasia and related disorders” category of the latest nosology, [Bonafe et al.,2015] a category that comprises campomelic dysplasia, Stüve-Wiedemann dysplasia, and the various kyphomelic dysplasias. None of these entities reconcile with the clinical and radiographic features. Some of the clinical and radiographic features present in our sibs overlap with the sibs reported by

Reardon and colleagues [Reardon et al.,1993]; however their cases had more pronounced mesomelia and neither had internal organ anomalies.

The typical clinical and radiographic features of pseudodiastrophic dysplasia in patient 2 allowed retrospective diagnosis of the previous pregnancy, and unmasked the unrecognized prenatal phenotype of pseudodiastrophic dysplasia. It is notable that the significant bowed long bones in early gestation had resolved almost completely by term, leaving straight but short bones (Figure 3) with the typical joint dislocations.

Murali *et al.* highlighted the similarity between the skeletal phenotype of pseudodiastrophic dysplasia and congenital disorder of glycosylation type Ig (CDG-Ig). [Murali et al.,2014] No pathogenic variants were detected in *ALG12* sequencing in fetus 1.

This is the first report in the English literature delineating the early prenatal features of pseudodiastrophic dysplasia, which are quite distinct from the classic postnatal phenotype. This report highlights bowed and short long bones as manifestation of pseudodiastrophic dysplasia in prenatal setting, as well as adding a variety of genitourinary anomalies and anterior cataracts to the list of associated features. This diagnosis must be considered when the finding of bowed and short long bones is observed antenatally with or without other malformations.

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Legends

Figure 1: Fetogram of fetus 1 at 16 weeks' gestation.

Figure 2: Skeletal survey of patient 2 on day 2 of life.

Figure 3: Antenatal ultrasound scans at 15, 17, 22 and 35 weeks gestation, depicting the amelioration of the bowing of long bones as the pregnancy progressed.

Table 1. Pre- and postnatal phenotype of pseudodiastrophic dysplasia in this report.

Table 1: Pre and postnatal phenotype of Pseudodiastrophic dysplasia in this report.

Prenatal	Postnatal
Flat facial profile Short and bowed long bones Joint contractures Talipes equinovarus Nuchal edema Polyhydramnios	Facial dysmorphism: flattened profile, midface hypoplasia, protuberant eyes with blue sclerae, small anteverted nose, microstomia Cleft palate and micrognathia Platyspondyly and thoracolumbar kyphosis Micromelia Radial head dislocation Proximal interphalangeal joint dislocation Joint contractures Talipes equinovarus
Expanding the spectrum: <ol style="list-style-type: none"> 1. Genitourinary anomalies 2. Anterior cataracts

Fig1 .

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Fig2 .

Fig3 .

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