

Prenatal findings in chondrodysplasia punctata, tibia–metacarpal type

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ABSTRACT

Chondrodysplasia punctata, a skeletal dysplasia with craniofacial dysmorphism and joint contractures can occur with rhizomelia, mesomelia or both. The rhizomelic form is generally lethal, whereas one form of mesomelic chondrodysplasia punctata has been described that is associated with a presumably normal lifespan and intelligence. We describe a case of a fetus suspected prenatally of having rhizomelic chondrodysplasia punctata, who was subsequently diagnosed at 1.5 years of age to have the tibia–metacarpal form of chondrodysplasia punctata. The prenatal sonographic findings of second-trimester micromelic bone shortening and third-trimester proximal femoral stippling may be present in the rhizomelic form but are not specific to this condition.

INTRODUCTION

Chondrodysplasia punctata represents a group of skeletal dysplasias characterized by short-limbed dwarfism, craniofacial abnormalities and joint contractures. The condition may occur prenatally in both a rhizomelic and mesomelic form^{1–3}. Rhizomelia is shortness of the proximal long bones (humerus, femur) and mesomelia is shortness of the distal long bones (radius, ulna, tibia, fibula). When both proximal (rhizomelic) and distal (mesomelic) portions of the bone are affected, the term micromelia may be used. Genetic counselling is important, as affected infants and children with mesomelic chondrodysplasia punctata usually survive with normal intelligence and function, unlike those with rhizomelic form, in which death usually occurs within the 1st year of life^{4,5}.

The prenatal diagnosis of rhizomelic chondrodysplasia punctata has been made by cultured chorionic villus sampling, amniocyte examination⁶ and prenatal ultrasound scanning^{7–12}. Sonographic findings include severe limb shortening with proximal shortening of the humeri and

femora and stippling and/or deformation (flaring or dumb-bell appearance) of the humeral and/or femoral cartilage/heads. The earliest sonographic observation of femoral stippling in a fetus with rhizomelic chondrodysplasia punctata occurred at 19.0 weeks of gestation¹². The humero-metacarpal form of rhizomelia has been described prenatally¹³ with rhizomelic shortening of the humeri.

Chondrodysplasia punctata of the tibia–metacarpal form has previously been described only in the neonate or young child^{2,3}. This mesomelic form of chondrodysplasia punctata should be considered when upper and lower limb shortening is found in association with stippling or deformation of the proximal humerus or femur. It may be impossible to differentiate between the rhizomelic and mesomelic forms prenatally, as both rhizomelic and mesomelic bone shortening (micromelia) has been reported with both types. For example, Sastrowijoto and colleagues¹² described a fetus with rhizomelic chondrodysplasia punctata in which micromelia was present (all long bones below the 5th centile). Some patients with the tibia–metacarpal form also have rhizomelia².

We describe a fetus with the tibia–metacarpal form of chondrodysplasia who presented antenatally with shortening of the proximal and distal long bones (micromelia), excessive second-trimester placental and intra-abdominal calcifications and third-trimester proximal femoral stippling.

CASE REPORT

A 33-year-old woman (gravida 3, para 1, spontaneous abortion 2) presented at 21.0 weeks' gestation for ultrasound findings of shortened femur lengths (23 mm consistent with 16.7 weeks' gestation), polyhydramnios and absent stomach bubble. The family history was negative for congenital anomalies and genetic conditions. The medical

and surgical history was unremarkable. The patient was a non-smoker.

Measurements of femoral, humeral, tibial and ulnar lengths were significantly greater than 2 SD below the mean¹⁴ (Table 1). Noteworthy findings were radial length at the 5th centile and one fibula measuring within normal ranges, whereas the other was plotted at the 5th centile. There was suggestion of bowing or fracture of the right proximal femur. The head and abdominal circumferences were normal for gestational age. Generalized punctate calcifications were observed within the placenta (Figure 1) and near the stomach, kidneys, bladder and pelvis (Figures 2 and 3). There was no evidence of intracranial calcification. A single umbilical artery, a small stomach and right mild hydronephrosis were observed. The amniotic fluid volume was normal. There was no evidence of cloverleaf skull deformity or abnormal ossification of the cranium or other bony structures. A genetic amniocentesis was performed; fluid was obtained that indicated a normal 46,XY karyotype, normal level of α -fetoprotein, and negative acetylcholinesterase and cytomegalovirus cultures. Based on the combination of punctate calcifications and limb shortness, rhizomelic chondrodysplasia punctata was suspected.

At 28.0 weeks' gestation, polyhydramnios was observed with an amniotic fluid index of 245 mm. The stomach size was normal. Punctate liver calcifications were observed, whereas the renal and pelvic calcifications were less prominent. Limb lengths were significantly shortened (Table 1). Radial lengths were only slightly above the 5th centile. Left femoral bowing was observed. Symmetric growth retardation was evident, with an estimated fetal weight of 677 g; this was plotted at the 8th centile.

At 35.0 weeks' gestation, the radial and fibular lengths were 2 SD below the mean. Femoral head stippling was apparent (Figure 4). Renal calcifications and growth retardation were observed.

At 37.6 weeks' gestation, a spontaneous labor occurred and a low transverse Cesarean section was performed, due to breech presentation. A male infant was delivered with Apgar scores of 6 and 8 at 1 and 5 min, respectively. The birth weight was 2085 g, length 38 cm and head circumference 31 cm; these were all below the 3rd centile.

Neonatal examination demonstrated depressed nasal bridge, flat mid-face (Figure 5), depressed nasal tip, thin upper lip, flat philtrum, short proximal limbs and short, tapered digits with hypoplastic nails. The infant fed poorly and experienced transient tachypnea and bradycardia.

Table 1 Measurements of limb length (mm) in chondrodysplasia punctata of the tibia-metacarpal type

	21.0 weeks		28.0 weeks		35.0 weeks	
	Patient	Normal range	Patient	Normal range	Patient	Normal range
Humerus	24	28–38	33	43–53	NM	54–64
Radius	23	24–33	34	33–48	39	41–54
Ulna	23	26–36	35	41–51	39	52–62
Femur	21	29–38	28, 32	47–56	39	52–62
Tibia	22	25–35	30, 33	41–51	46	53–64
Fibula	26	24–37	35	38–53	40	51–62

NM, not measured

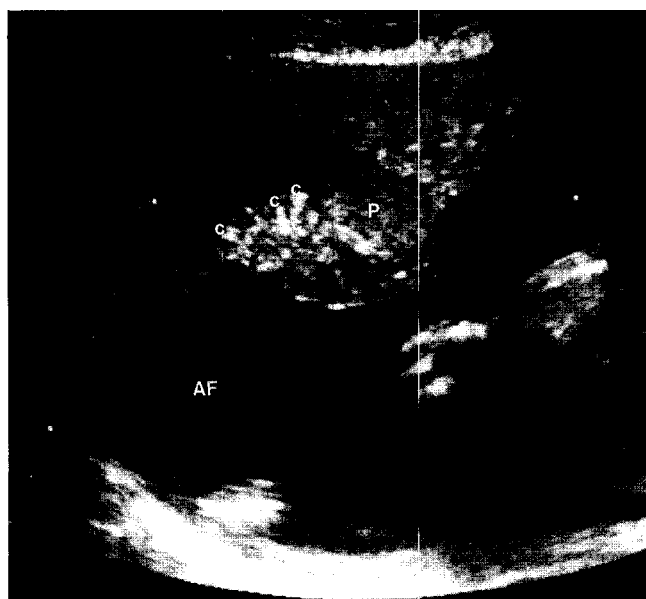


Figure 1 Generalized placental calcifications (c) at 21.0 weeks of gestation in a fetus with tibia-metacarpal chondrodysplasia punctata. P, placenta; AF, amniotic fluid

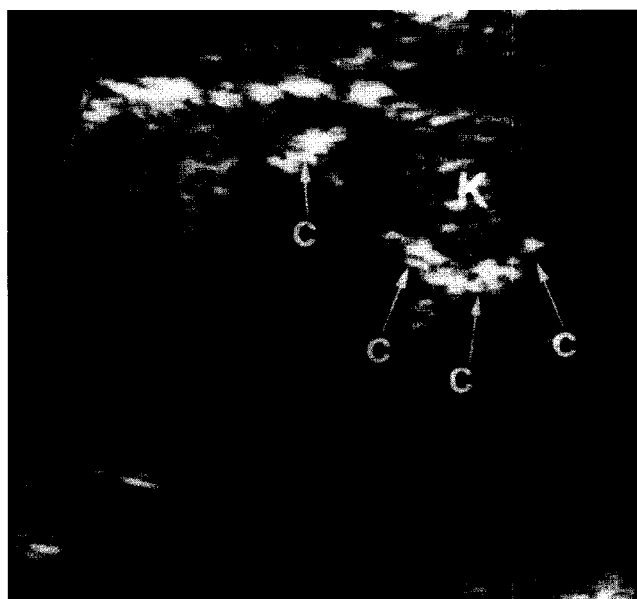


Figure 2 Sagittal scan demonstrating intra-abdominal and renal calcifications (c) at 21.0 weeks of gestation in a fetus with tibia-metacarpal chondrodysplasia punctata. K, kidney



Figure 3 Transverse scan at 21.0 weeks of gestation at the level of the bladder (b), demonstrating calcifications (c) encircling the bladder area



Figure 4 Femoral stippling (S) observed at 35.0 weeks of gestation. f, femur

Radiological studies were performed and interpreted as rhizomelic chondrodysplasia punctata. Humeral shortening and speckled calcifications of the elbow, wrist and metacarpals were observed. Metacarpal shortening was evident. There was shortening of all long bones of the lower extremities, with predominant shortening of the femora (Figure 6). Speckled calcifications were found at the greater trochanter and the proximal portions of both femurs. Extensive irregular calcifications were evident in the soft tissue of the proximal portions of the feet. Coronal clefts of the vertebral bodies in the lower thoracic and lumbar vertebrae were noted along with stippled calcifications anterior to the lower sacrum.

Abdominal ultrasound examination revealed a normal liver, gallbladder, hepatic bile ducts, kidneys and spleen. The cranial ultrasound examination was normal. The infant had no problems in the neonatal period and was discharged on the 3rd day of life. Metabolic studies, including assays of very long-chain fatty acid and plasmalogen levels, were normal. Based on clinical features and normal metabolic studies, at 1.5 years of age, a diagnosis of chondrodysplasia punctata of the tibia-metacarpal form was suggested; review of radiographs by the International Skeletal Dysplasia Registry confirmed the clinical impression. They noted hypoplastic tibia, proximal fibular overgrowth, stippling of the coxal area and cervical vertebrae, hypoplasia and deformation of the proximal phalanges and stippling at the base of the metacarpals, which were characteristic manifestations of chondrodysplasia punctata of the tibia-metacarpal type.

The child was reported as doing well at 3 years of age, which is consistent with the diagnosis.

DISCUSSION

The clinical manifestations of chondrodysplasia punctata of the tibia-metacarpal type include skeletal dysplasia con-



Figure 5 Photograph of child with tibia-metacarpal chondrodysplasia punctata demonstrating a flat facial profile, small nose, thin upper lip and micrognathia

sistent with dwarfism, which is characterized by shortened limbs and an abnormal face (flattened mid-face and nose)². Radiographic findings include shortened and bowed tibia and radii, overgrowth of the fibulae, ulnar hypoplasia, calcific stippling of the proximal bones, punctate calcifications of the trachea and sacrum, clefting (coronal and/or sagittal) of the vertebral bodies, shortened second and third metacarpals and of the radial head, along with patellar dislocation².

Stippled cartilaginous calcifications may be seen in other chondrodysplasia punctata syndromes, CHILD syndrome, GM1 gangliosidosis, mucopolipidosis II, vitamin K reductase deficiency and alcohol, phenacetin and hydantoin syndromes associated with stippled epiphyses.

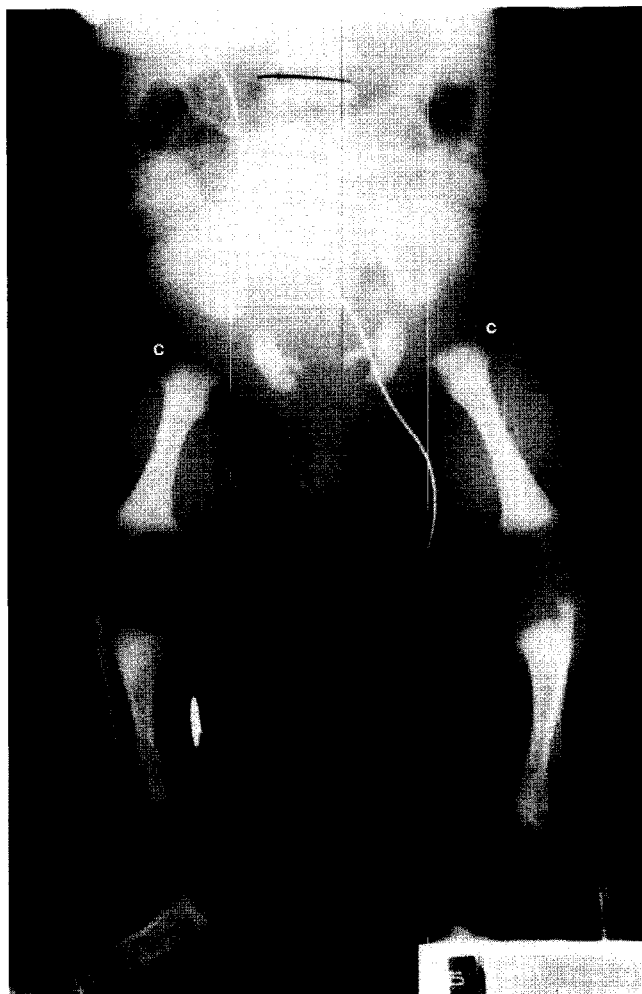


Figure 6 Radiograph of affected child demonstrating shortening of all long bones of the lower extremities, with predominant shortening of the femora. Speckled calcifications are observed at the greater trochanter (c) and proximal portions of both femora

The prenatal diagnosis of rhizomelic chondrodysplasia punctata has been reported by several investigators⁷⁻¹². Connor and associates⁷ reported on one prenatal observation of rhizomelic chondrodysplasia punctata in a family with a previous affected infant. Rhizomelic shortening was observed at 22.0 weeks' gestation. Specific limb involvement and other markers were not described.

In the report of Duff and colleagues⁸, evidence of rhizomelic chondrodysplasia punctata was shown by femoral and humeral shortening with mild tibial shortening (20th centile) at 28.0 weeks' gestation. In this case, femoral and humeral stippling with deformation were observed in later pregnancy.

Gendall and associates⁹ reported the antenatal observation of rhizomelic chondrodysplasia punctata in a twin gestation. Retrospective review of ultrasound findings at 15.0 weeks' gestation demonstrated a short humerus, with flared and dumb-bell shaped humeral ends, which were hyperechoic. There was no evidence of femoral shortening/epiphyseal stippling. At 25.0 weeks' gestation, femoral shortening, along with humeral and femoral stippling, were observed. Intrauterine growth retardation was

evident in later pregnancy. Rhizomelic chondrodysplasia punctata was confirmed by radiological and post-mortem studies, which revealed absent alkyl-dihydroxyacetone phosphate synthase activity from cultured skin fibroblasts. The co-twin was unaffected.

Fetal abdominal ascites has been reported in a fetus with the Conradi-Hunermann type of chondrodysplasia punctata¹².

A unique form of chondrodysplasia punctata was detected prenatally in a fetus at 27.0 weeks' gestation³. The humerus was short (20-week size) and the femora were of normal length. Later in pregnancy, other long bones were described as abnormally shortened (radii, ulnae, tibiae and fibulae were reported as normal in length). Postnatally, symmetrically shortened and abnormally shaped humeri and short hands were reported. The child was reported as doing well at 2.5 years of age.

In our case of chondrodysplasia punctata of the tibia-metacarpal type, micromelia of the femora, humeri, tibiae, ulnae and radii were observed by 21.0 weeks' gestation. Femoral bowing was observed, without early evidence of humeral or femoral proximal stippling. The fibular length was normal in early gestation, with shortening of the right fibula by the 28th week of gestation. In the early second trimester, excessive placental calcifications were evident, along with punctate intra-abdominal calcifications, which appeared to be present near the bladder and kidneys, liver and lower pelvic regions. By 28.0 weeks' gestation, the right fibular length was abnormally shortened. Intrauterine growth retardation and polyhydramnios were apparent. Femoral head stippling and deformation were not appreciated until 35.0 weeks' gestation.

In cases of prenatal micromelia and stippling/deformation of the femoral or humeral heads, investigators should consider other forms of chondrodysplasia punctata besides the rhizomelic form. Care must be taken not to assume that the child has a lethal or poor prognosis as documented in the rhizomelic form of chondrodysplasia punctata. Distinguishing the rhizomelic from the mesomelic type using ultrasound findings alone may be impossible. Sonographic views of the fetal profile may be helpful in distinguishing the characteristic flattened mid-face and nose seen in the tibia-metacarpal form. The abdominal and placental calcifications may also prove to be distinguishing manifestations. Although rhizomelic chondrodysplasia punctata causes shortness of proximal long bones, cases of micromelia in the rhizomelic form have been described¹². Patients need to be offered specific testing for rhizomelic chondrodysplasia punctata to verify the clinical impression.

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