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LETHAL CHONDRODYSPLASIA PUNCTATA IN TWO SIBLINGS*

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Chondrodysplasia punctata was first described in 1914 by Conradi who called the syndrome "Chondrodystropica fetalis hypoplastica". This syndrome has been subdivided into two major types: the lethal type (rhizomelic) and the milder Conradi-Hünermann type[1]. The rhizomelic type carries a very poor prognosis and usually leads to death in the first few years of life[2]. There is gross long bone shortening, metaphyseal splaying and epiphyseal stippling of humeri and femora. This type of disorder has a higher frequency of associated cataracts, psychomotor retardation and spasticity[2,3] and it appears to be transmitted as an autosomal recessive trait[4].

This paper presents two siblings with the lethal rhizomelic type of chondrodysplasia punctata. To our knowledge these are the first cases of this rare syndrome occurring in two siblings reported in our country.

Case Reports

Case 1

A one-day-old male infant was born at 40 weeks gestation to a 24-year-old multigravida woman. The mother had not been exposed to any drugs during pregnancy. The parents were first cousins. The patient was the eighth child in the family. The mother had four spontaneous abortions and two stillbirths.

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Birth weight was 3000 g; length 45 cm; head circumference 35.5 cm, respiration rate 52/min, irregular; pulse 124/min rhythmic; body temperature 37 °C (axillary). His general condition was poor and he was cyanotic. Intercostal retraction was present. The infant had hypertonicity and lacked the usual newborn reflexes. He was found to have marked micrognathia, a complete cleft palate, and an abnormally flat face with depression of the nasal bridge. He also had symmetrical proximal shortening and flexion contracture of the limbs. The penis was small and the preputium short (Fig. 1).

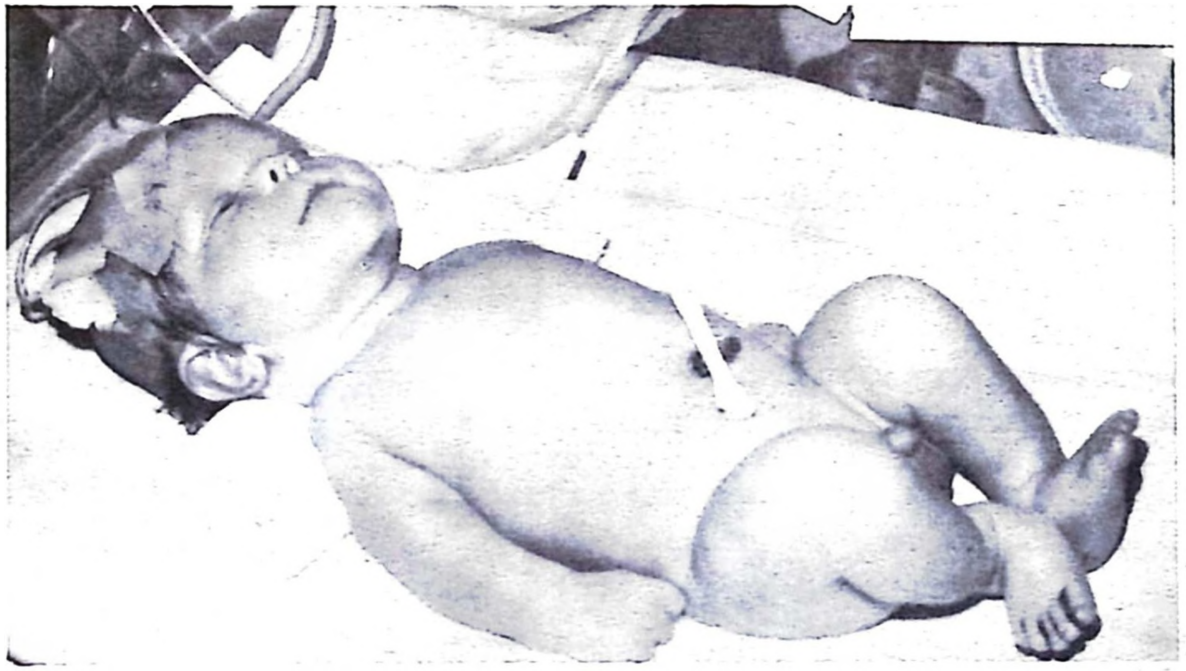

Fig. 1 : Case 1. Flat face with depression of the nasal bridge. Symmetrical shortening of the proximal limbs and flexion contracture of the lower limbs.

Laboratory studies including a complete blood count, blood sugar, serum electrolytes, calcium, phosphorus, alkaline phosphatase, blood and amino acids in urine were all normal. A remarkable laboratory finding was respiratory acidosis with blood pH: 7,14, PCO_2 76 mm Hg, PO_2 51 mm Hg.

The serological tests for cytomegalovirus, toxoplasmosis, rubella and syphilis were all negative. X-ray studies of the skeleton revealed that both humeri and femora were markedly shortened (Fig. 2).

The metaphyses of the proximal tubular bones were splayed and studded with irregular calcium deposits and stippling was present in the joints of the long tubular bones. The vertebral bodies were flat, the intervertebral spaces widened and the dorsal ends of the ribs splayed.

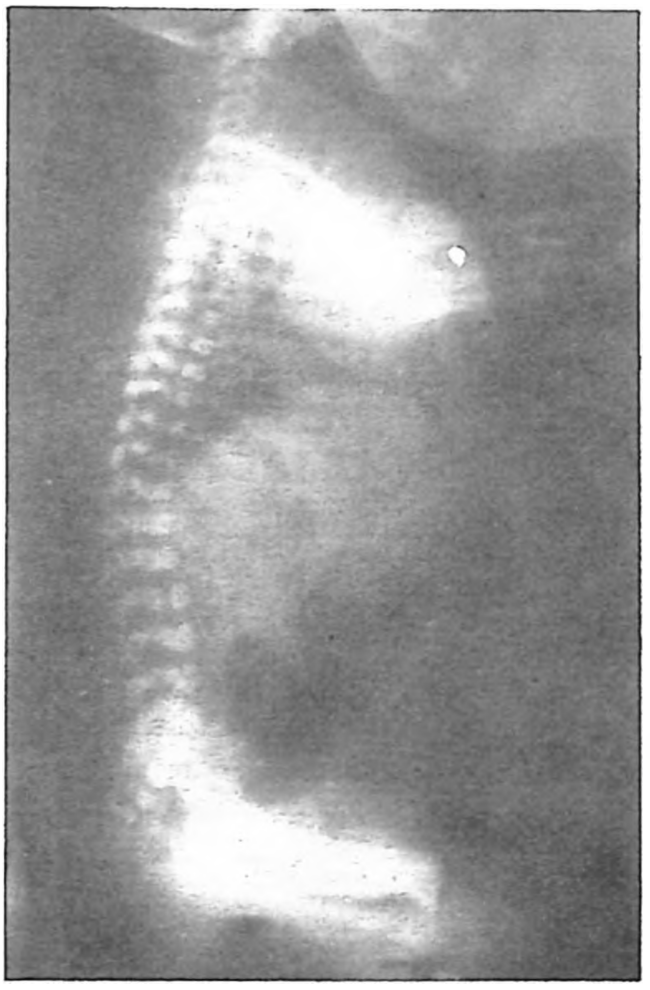

Fig. 2: Case 1. Lateral vertebral radiograms of the patient show flat vertebral bodies, widened intervertebral spaces and splayed dorsal ends of the ribs.

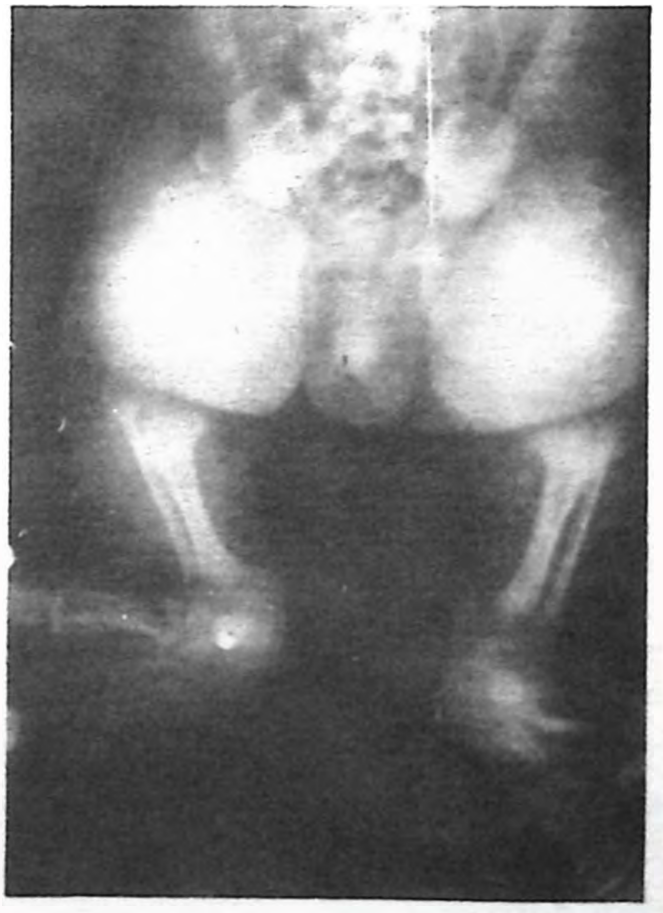

Fig. 3: Case 2. Femoral shortening, metaphyseal splaying and epiphyseal and juxta-epiphyseal stippling are pronounced.

On the 14th day of life, the infant developed sepsis and died when he was 35-days-old. On postmortem examination, histologically the epiphyseal cartilage showed areas of degenerating cartilage which were calcified, vascularized and poorly ossified.

Case 2

The female sibling of Case 1 at delivery weighed 2450 g, her length was 45 cm and head circumference 31 cm. The newborn died on the same day of birth as a result of respiratory difficulty. She had meconium aspiration at birth and appeared to have mild hypertelorism. Physical examination revealed short arms and legs, a flattened bridge of the nose and a short neck. X-ray examination showed that the iliac crests and basillar portions of the pelvic wings were similar in width giving the iliac wings a trapezoid shape in frontal projections. The ossification of the femoral head, necks and trochanters was grossly retarded and only discrete islands of ossified tissue appeared in the femoral necks. The femora were markedly shortened but the tibiae were less affected (Fig. 3).

Discussion

Chondrodysplasia punctata as originally described by Conradi (1914) and Hünermann (1931) is characterized by a finely stippled "flecks of spattered paint" appearance in the epiphyseal area radiologically. Coarse stippling and chondrodysplasias may suggest a number of conditions. These include Zeilweger syndrome, trisomy 13-15, trisomy 17-18, trisomy 21, diastrophic dwarfism, multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia, prenatal infection, and warfarin, alcohol and dicumarol ingestions during early pregnancy[2,5-11]. Most of these conditions have their own characteristic radiological features. The absence of periepiphyseal stippling is an important additional point in the differential diagnosis of chondrodysplasia punctata. This syndrome has been subdivided into two major types; rhizomelic (lethal) and Conradi Hünermann (milder)[1].

The genetic inheritance of these disorders differ. The Conradi-Hünermann type is usually inherited as autosomal dominant, but the rhizomelic type follows the autosomal recessive mode of inheritance. An X-linked dominant form of the Conradi-Hünermann type, which is characterized by ichthyotic skin lesions, has also been reported[2,7]. The clinical features of these two forms also differ from each other.

The Conradi-Hünermann type has a higher frequency of associated cataracts, psychomotor retardation and spasticity, but cataract is said to be much less common than in the rhizomelic form[3,7]. In contrast to the Conradi-Hünermann

type, the bone lesions in the rhizomelic form are symmetric, even in older infants and children[12]. The humeri and femora are more severely shortened, the metaphyses are more irregular and epiphyseal ossificiation is more severely retarded and distorted[12]. The vertical radiolescent bars of multiple vertebral bodies and the trapezoid shape of the iliac wings are not present in the Conradi-Hünermann type[12,13]. Because of the presence of stippled epiphyses in both types, these two conditions have long been regarded as variants of the same entity[1]. Characteristic radiologic findings permit their identification as separate disorders[1,12-15]. This differentiation is important in view of the different genetics and prognosis[1,12]. The presence of an abnormal face, short proximal limbs, flexion contractures and radiologic findings suggest the rhizomelic type of chondrodysplasia in our cases.

Intrauterine infection and ingestion of drugs such as warfarin and alcohol during early pregnancy have been known causes of epiphyseal stippling[2,6]. But our patient's mother had not been exposed to any drugs during pregnancy and serological tests for intrauterine infections were negative. The rhizomelic type of chondrodysplasia punctata is rare. A case whose clinical findings are similiar to the cases we have presented has also been reported from our hospital[16]. The majority of affected infants die in the neonatal period as in our cases[2].

The rhizomelic type of this disorder is inherited as autosomal recessive so there is a one in four chance that subsequent siblings will develop this disease. Fabris et al[4] has described two siblings affected by the rhizomelic type of this syndrome. They were similar to our cases and born from healthy parents. The rhizomelic type of chondrodysplasia punctata, although rare, is the most common fatal form of this disease. Radiologic features are present at birth and early diagnosis is possible. Diagnostic precision is therefore crucial for effective genetic counseling.

Summary

This report describes two siblings affected by the rhizomelic type of chondrodysplasia punctata who were born of healthy parents. To our knowledge these are the first cases in two siblings presenting with this rare syndrome reported in our country.

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