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Prenatal Diagnosis of Nonrhizomelic Chondrodysplasia Punctata (Conradi-Hünermann Syndrome)

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Chondrodysplasia punctata has been classified into two major types including the rare autosomal recessive "rhizomelic type" and a more common but genetically heterogenous nonrhizomelic type (referred to by some authors as "Conradi-Hünermann (CH) type"). The former is typically lethal, manifesting serious anomalies, and allowing several instances of confident prenatal diagnosis. The latter being milder has more subtle anomalies and prenatal diagnosis has been uncommonly reported (confined to cases diagnosed incidentally by flat-plate X-ray examination of the mother in late third trimester, and a case found by directed ultrasound performed in a mandelian affected mother). Cases included 1) a young primigravida thought to be affected with Conradi-Hünermann syndrome presented at 16 weeks gestation for prenatal diagnosis and counseling. Ultrasound examination of the fetus detected assymetric limb shortness allowing the presumptive diagnosis of an affected fetus which was confirmed after delivery near term. 2) A normal 38-year-old multipara with unremarkable family history underwent routine fetal ultrasound evaluation at 18 weeks gestation. Disorganization of the spine, premature echogenicity of femoral epipheses, and frontal bossing with depressed nasal bridge were described. Neonatal examination confirmed suspicion of CH. Case 1 demonstrates the importance of solid clinical diagnosis in Mendelian malformation-affected parents for directing prenatal diagnostic efforts. Case 2 represents the first index case of CH diagnosed antenatally by ultrasound. Diagnostic clues which must be considered in establishing these diagnoses are discussed, as are some of the difficulties and limitations in antenatal counseling such cases. © 1993 Wiley-Liss, Inc.

KEY WORDS: skeletal dysplasia, Conradi-Hünermann syndrome, chondrodysplasia punctata, prenatal diagnosis, ultrasound

INTRODUCTION

Chondrodysplasia punctata is the name given to a group of congenital skeletal dysplasias characterized by locally disordered bone mineralization resulting in characteristic bone stippling observed on neonatal roentgenograms [Sheffield, 1976]. It was initially described by Conradi in 1914, but later was better characterized and subclassified [Spranger et al., 1971; Heselson et al., 1978] as two major types: these included a rare, and typically lethal autosomal recessive variety known as the "rhizomelic type," and a more common, nonrhizomelic, usually less severe, and genetically heterogeneous variety called the "Conradi-Hünermann," or "mild" type. More recently, as the inheritance patterns for this milder variety have been increasingly defined there have arisen some inconsistencies in the nomenclature as evidenced by the different opinions about which cases are "true" Conradi-Hünermann syndrome. Still, most authors seem to continue to group the chondrodysplasia punctatas into rhizomelic (autosomal recessive, with severe phenotype) versus nonrizomelic (Mendelian heterogeneity, with mild phenotype) types (Tables I and II).

Although rhizomelic chondrodysplasia punctata is rare, there are several reports of confident prenatal diagnosis by ultrasound [Connor et al., 1985; Duff et al., 1990; Wardinski et al., 1990]. Also, with the recent

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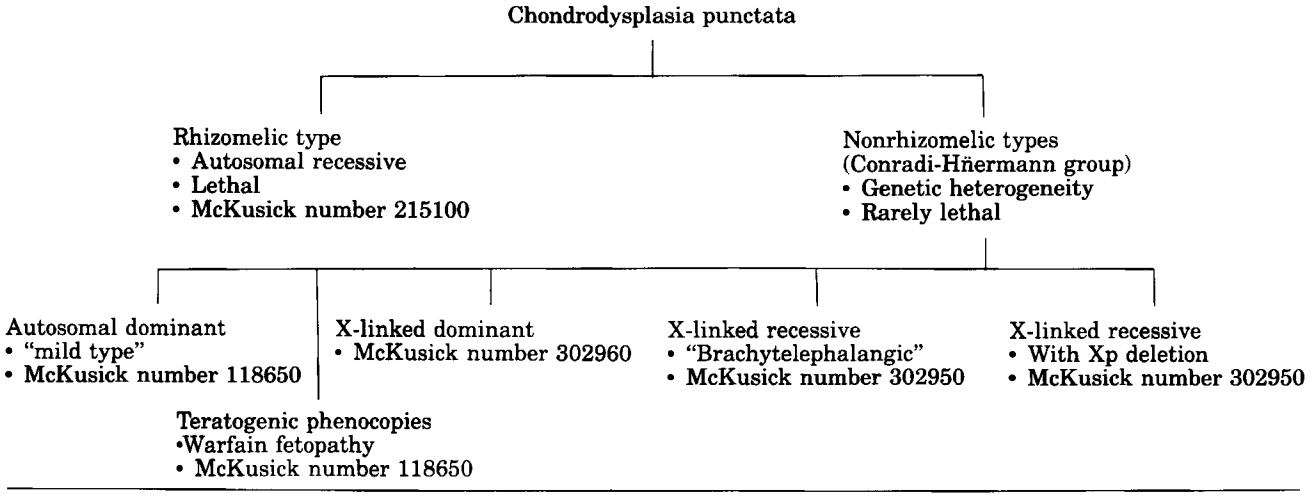
TABLE I. Classifcation of Chondrodysplasia Punctata



appreciation of its associated underlying disorder of peroxisomal metabolism, several cases have been reported having biochemical confirmation [Hoefler et al., 1988; Schutgens et al., 1989]. In contrast, prenatal diagnosis of the more common nonrhizomelic type has been rarely reported, including a case found by directed ultrasound performed in a known Mendelian affected mother having an anticipated fetal risk of up to 50% [Tuck et al., 1990], and several cases diagnosed incidentally by flat-plate X-ray examination of the mother in the late third trimester [Hyndman et al., 1976; Josephson and Oriatti, 1961]. To our knowledge there have been no published reports of index cases discovered by ultrasound evaluation of the fetus.

We report two cases of nonrhizomelic (traditionally, Conradi-Hünermann) type chondrodysplasia punctata diagnosed sonographically in the second trimester. Our first case, similar to that reported by Tuck et al. [1990], was a diagnosis made by *directed ultrasound* looking for early signs of similar developmental abnormalities in the fetus as were present in the mother thought to be affected with the X-linked dominant variety of the disorder. However, our second case was identified in a pregnancy carried by a patient having no known genetic risk factors and therefore represents the first *index case* discovered by ultrasound evaluation of the fetus. Problems and diagnostic clues which must be considered in establishing this diagnosis are discussed, as are some of the difficulties and limitations in antenatal counselling such cases.

Clinical Reports

Patient 1. The patient was a 26-year-old African-American G5 P0 woman referred for genetic counseling at 16 weeks of gestation due to history of a previous anomalous pregnancy aborted at 17 weeks of gestation after the ultrasound findings of asymmetrical limb shortness, scoliosis, and mild fetal cerebral-ventriculomegally. Fetopsy had confirmed the anticipated anomalies and karyotype was normal (46,XX). Her current pregnancy history was negative for exposures to drugs or known teratogens, and her past obstetrical history was otherwise remarkable for three voluntary first trimester abortions. Her partner was also African-American, and there was no knowledge of consanguinity. Both family histories were negative for known genetic diseases, or congenital anomalies prior to their previous abnormal pregnancy.

Physical examination of the patient by E.B. demonstrated severe scoliosis, slight epicenthial folds, shallow nasal bridge, and mild asymmetry of both upper and lower limb lengths. These findings prompted review of earlier records which revealed that at 3 days of age she had been given the diagnosis of congenital chondrodysplasia punctata, Conradi-Húnermann type, based on the findings of severe scoliosis, punctate calcifications of the spine and femoral epipheses, asymmetric limb shortness, post-axial polydactyly, left eye cataract, irregular macular skin hyperpigmentation, and normal karyotype.

Based on this historical information the patient was counseled that she was likely a carrier of a new X-linked (or less likely autosomal) dominant mutation and she was appraised of the attendant transmission risks to her fetus. High-resolution ultrasound was performed demonstrating a biparietal diameter of 33 mm which was biometrically consistent with her gestational age of 16 weeks as estimated by menstrual dates. However, marked asymmetry was noted in the lower limbs with the right femur measuring 13 mm compared with the left measuring 18 mm. No other abnormalities were appreciated. A presumptive diagnosis of fetal Conradi-Hünermann syndrome was made. Karyotype of fetal amniocytes was normal (46,XX). The patient elected to continue the pregnancy.

At 32 weeks premature contractions were noted for which tocolysis was initiated. Ultrasound examination at that time documented moderate severity polyhydramnios. At 36 weeks gestation the patient vaginally delivered a 2,020 g female with apgar scores of 9 and 9 at 1 and 5 minutes, respectively. Physical examination after delivery demonstrated "saddle-nose" de-

TABLE II. Comparitive Manifestations of Nonrizomelic Chondrodysplasia Punctata Subtypes by Inheritance Patterns

Inheritance	Synonyms	Punctate calcifications	Limb shortness	Saddle nose deformity	Skin Changes: (Ichthyosiform erythroderma)	Cataracts	Mental retadation	Other	Overall prognosis
Autosomal dominant	1. Chondodystrophia calcificans congenita 2. McKusick number 118650	Variable severity, assymetric	Mild or none	Present	Present 28%	Symmetric present 17%	None or minimal	Skeletal dysplasia	Good
X-linked recessive (without chromosome deletion)	1. Brachytele-phalangic Chon-drodysplasia Punctata 2. McKusick number 302940	Mild severity, symmetric	Mild overall growth lag	Variable severity	No changes	None	None or mild	Uniform distal phalangeal hypoplasia	Good
X-linked recessive (with Xp deletion)	1. CPXR 2. McKusick #302950	Extensive, bilateral symmetric	Shortness of stature	Typically severe with nasal hypoplasia	Marked skin changes	Occasional	IQ range 50–70	Steroid sufatase deficiency, and frequent distal phalangeal hypoplasia	Survival good, but neurodevelop-mentally impaired
X-linked dominant	1. CPXD 2. McKusick number 302960	Variable assymetric	Proximal, variable, asymetric	Present	Marked cicatrical "patchy" changes	Assymetric	Normal	Occasional scoliosis	Lethal in hemizygous males
Teratogenic phenocopy	1. Vitamine K-dependent coagulation defect 2. Warfarin embryopathy 3. McKusick number 277450	Irregular assymetric pattern variable severity	Moderate to severe	Moderate to severe with frequent nasal hypoplasia	None	None	Mild or none	Common mild distal phalangeal hypoplasia	Good

formity, ichthyotic skin changes, and assymetric shortness of upper and lower limbs. Roentgenograms demonstrated typical epiphyseal stippling confirming the diagnosis of Conradi-Hünermann syndrome. The infant had no respiratory or nutritional difficulties and uneventful neonatal course. She has normal psychomotor development at age 2 years but is receiving orthopedic management for scoliosis and assymetry of the lower limbs.

Patient 2. The patient was a healthy, 38-year-old G7 P5, African-American woman referred for genetic counseling at 18 weeks of gestation for the indication of advanced maternal age. Her current pregnancy course had been unremarkable and she denied exposures to medications or known teratogens. Previous medical history was likewise negative, and her obstetrical history was notable for uncomplicated deliveries of five reportedly healthy and normal children. Her partner was also African-American, and there was no knowledge of consanguinity. Both family histories were negative for genetic diseases or birth defects.

High-resolution ultrasound examination of the fetus prior to amniocentesis showed the unexpected finding of disorganization of the fetal spine which was initially poorly defined and seemed mostly to affect the sacral region. No other anomalies were appreciated and follow-up ultrasound was scheduled. Karyotype of cultured amniocytes was normal (46,XY), amniotic fluid alpha-fetoprotein was normal, and acetylcholinesterase was negative. At 21 weeks of gestation a second ultrasound examination was performed: Marked structural disorganization of the spine was appreciated with evidence of malsegmentation involving virtually its entire length (Fig. 1), although there was no definitive scoliosis or shortness. Examination of the profile of the fetal face was notable for the impression of frontal bossing and flattening of the nasal bridge (Fig. 2). Additionally, there were hyperechoic regions in the femoral epipheses bilaterally suggestive of premature calcification (Fig. 3). Careful measurement of the long bones bilaterally did not indicate evidence of limb shortness, and fetal echocardiagram was normal.

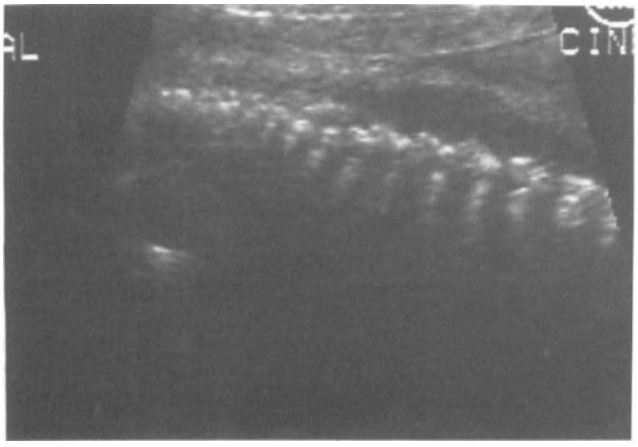


Fig. 1. Patient 2, ultrasound examination at 17 weeks of gestation demonstrates a scalloped or wrinkled appearance of vertebral disorganization.

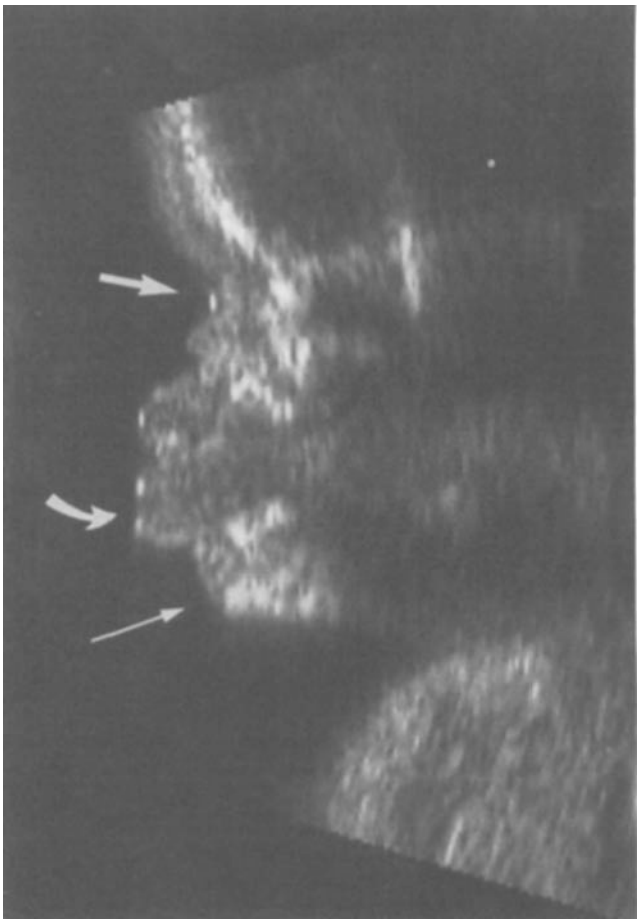


Fig. 2. Patient 2, ultrasound imaging of the fetal profile at 21 weeks of gestation demonstrates virtual absence of nasal bridge and nasal hypoplasia suggestive of the "saddle-nose" defomity. Mandible, lips, and depressed nasal bridge are indicated by the narrow, curved, and large arrows, respectively.

The patient and her partner had normal stature with no evidence of skeletal anomalies, skin abnormalities, or cataracts.

Extensive counseling was given regarding diagnostic possibilities emphasizing the leading possibility of nonrhizomelic (Conradi-Hünermann) chondrodysplasia punctata. At 30 weeks of gestation ultrasound demonstrated persistence of previously described anomalies, definitive depression of the nasal bridge, a question of abnormal posturing of the hands, and evolution of polyhydramnios.

At 37 weeks of gestation a 3,000 g boy was delivered vaginally with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. Physical examination by E.B. confirmed sonographic findings of severely depressed nasal bridge ("saddle nose deformity"), short columella, macrocephaly with occipitofrontal head circumference of 37.5 cm, and the unanticipated finding of hypoplasia of the distal phalanges of the fingers and toes bilaterally. The skin was normal and there were no cataracts. Extensive radiologic evaluation confirmed the symmetric stippled mineralization pattern of the femoral epiphyses and vertebrae characteristic of chondrodysplasia punc-

Fig. 3. Patient 2, ultrasound imaging of the fetal femus at 21 weeks of gestation demonstrates echogenic epipheses (arrow) suggestive of premature and disorder mineralization.

tata. Also confirmed were the antenatally appreciated vertebral malsegmentation. CT of the head demonstrated a small foramen magnum and mild dilatation of the lateral ventricles bilaterally. The finding of distal phalangeal hypoplasia prompted high-resolution prophase banding karyotype evaluation of the infant's lymphocytes which did not demonstrate and X-chromosomal microdeletion.

The infant's course was initially complicated by failure to thrive and persistent upper airway problems attributable to his extreme nasal hypoplasia. He ultimately required placement of a tracheostomy and placement of a ventriculoperitoneal shunt. He also required nasogastric tube feeding after which he was able to gain weight appropriately and was discharged home. At age 4 months he has continued tracheostomy dependence but he is now successfully bottle-feeding. To date, there are no detectable neurologic abnormalities and psychomotor development is within the normal range.

DISCUSSION

Confident antenatal diagnoses in cases in which ultrasound examination of the fetus documents evidence of skeletal dysplasia remain difficult despite recent advances in ultrasonographic imaging technology [Romero and Nores, 1992]. The lists of differential diagnostic possibilities for vertebral malsegmentation disorders and/or short limbs are lengthy and often have considerable phenotypic overlap. Thus, sonographic findings may only give clues about diagnosis, or allow the formulation of lists of diagnostic possibilities. Because accurate prognostication is a major goal of antenatal diagnosis, and because accurate prognostication relies on accurate diagnosis, it is very important to narrow as much as possible this list of differential diagnostic possibilities in each individual case.

When considering the antenatal diagnosis of chondrodysplasia punctata it is important to distinguish each case according to type [Spranger et al., 1971]. We propose a classification and differential diagnosis scheme as shown in Table I: The rare "rhizomelic type" is characterized by severe symmetrical rhizomelic limb shortness, puncatate calcifications of the epipheses and soft tissues, facial abnormalities, and typically lethal outcome. The most common and genetically heterogeneous "nonrhizomelic types" (formerly designated "Conradi-Hünermann type" by some authors) are characterized by asymmetric, dysplastic skeletal changes, punctate calcifications of the epipheses, variably severe asymmetric limb shortness or normal limb lengths, "saddle-nose" deformity, varaible upper airway embarrassment, skin changes, cataracts, and generally good prognosis.

Because of the profound degree of limb shortness in the rhizomelic type, it is much more easily detected by screening ultrasound, and because of the severity of disordered ossification characteristic of the disorder, it is more easily distinguished from other skeletal dysplasias. Therefore, confident antenatal diagnosis has been made and reported in several instances [Connor et al., 1985; Duffet al., 1990; Wardinski et al., 1990]. On the other hand, in nonrhizomelic cases the severity of limb shortness can be mild, asymmetric, or not present. Vertebral malsegmentation and disordered bone mineralization also can be very subtle. Thus, it can be difficult to detect any anomaly by sonographic screening, and when an abnormality is detected, it is difficult to characterize and provide precise diagnosis.

Our cases demonstrate clues which allowed antenatal diagnosis of the nonrhizomelic (Conradi-Hünermann) type chondrodysplasia punctata in the second trimester by fetal ultrasound examination. In the first case, the recognition of a malformation syndrome in the mother prompted careful review of her medical records which revealed evidence that she had herself been diagnosed as an infant (somehow unbeknowst to her) with "Conradi-Hünermann disease". Given her previously unremarkable family history and clinical picture (see Table II), we could assume that she was likely a monogenic new mutation, and due to the assymetry of her limb shortness, absence of male progeny, and unilateriality of lenticular cataracts, it was thought that she was more likely affected with the X-linked dominant type rather than the autosomal dominant type. This allowed a high degree of confidence in our antenatal diagnosis of an affected pregnancy when asymmetric limb shortness was clearly appreciated by directed ultrasound examination of the female fetus.

In the second case, there was no genetic history to direct diagnostic efforts. However, at the first screening ultrasound examination there was suspicion of fetal spine disorganization. Although the finding was vague and its significance uncertain, it prompted a careful ongoing study of the fetus. With the second sonographic examination only 3 weeks later, vertebral malsegmentation was clearly evident, thus modifying the differential diagnosis. Additionally, and perhaps of greatest diagnostic significance, increased echogenicity of the femoral epipheses was observed (Fig. 3). This suggested a disorder affecting the timing and pattern of bone mineralization in a pattern very consistent with that described in the roentgenograms of condrodysplasia punctata affected newborn infants. Finally, careful examination of the fetal profile demonstrated diminu-

tion of the nasal bridge with an appearance of frontal bossing suggesting the well described "saddle-nose" deformity. Taking all of these individual anomalies together allowed narrowing of the differential diagnosis to a very strong suspicion of a nonrhizomelic type condrodysplasia punctata which was ultimately corroborated by examination of the infant.

An interesting finding identified after delivery in case 2, but missed by serial ultrasound examinations of the fetus, was that of distal phalangeal hypoplasia. Maroteaux [1989] reported this finding in a series of four karyotypically normal nonrhizomelic chondrodysplasia punctata affected males and noted that it had also been mentioned in four males in Sheffields [1976] previous series. All of these reported individuals manifested typical punctate calcifications, and saddle-nose deformity, as well as the phalangeal anomaly but did not manifest the ichthyotic skin abnormalities and cataracts so often identified in other forms of Conradi-Hünermann syndrome. He proposed a second variety of X-linked recessive nonrhizomelic chondrodysplasia punctata which he called "brachytelephalangic chondrodysplasia punctata" to distinguish it from a previously documented X-linked recessive type in which a characteristic Xp deletion is present. It is an important observation that in cases having the Xp deletion there is uniform detection of steroid sulfatase deficiency as well as cataracts, ichthyotic skin changes, and mental retardation [Curry et al., 1984], demonstrating probably absence of multiple contiguous genes located in the region of the deletion. This is in contrast to the findings in the brachytelephalangic X-linked recessive type in which the abnormalities are confined to those affecting skeletal development suggesting a single gene disorder (perhaps involving one of the genes located in the deletion found in Curry's cases). Our case was a male manifesting the typical general skeletal defects of nonrhizomelic chondrodysplasia punctata with the additional finding of distal phalangeal hypoplasia (in the absence of skin changes, cataract, or X-chromosomal microdeletion) and therefore probably represents another instance of "brachytelephalangic chondrodysplasia punctata." In the absence of suspicious family history, this infant may be manifesting a de novo single gene Xp mutation.

The difficulties in counselling patients after antenatal diagnoses of fetal anomalies having variability in severity of outcomes have been discussed elsewhere [Pryde et al., 1992]. Our two cases of antenatally diagnosed Conradi-Hünermann syndrome emphasize some of these problems: In the first case the mother herself was affected and had some idea of what to expect although the possibility of a more severely affected child (intellectually, orthopedically, or airway atresias) could not be ruled out. In the second case, although some of the abnormalities noted by ultrasound were in themselves severe in degree (e.g., profound vertebral malsegmentation and nasal hypoplasia), the suspected disorder itself is not usually thought to be lethal or severely disabling. Not only was it impossible to predict the definite diagnosis (specific disorder or subtype) with certainty, but the severity of disability which might accompany the disorder was also felt to be uncertain as outcomes can be quite variable between subgroups as well as within subgroups.

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