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Maternal Mixed Connective Tissue Disease and Offspring with Chondrodysplasia Punctata

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Abstract

Chondrodysplasia punctata (CDP) comprises a heterogeneous group of disorders that result in abnormal development of the fetal skeleton. The hallmark of the condition is radiographic presence of abnormal islands of calcification in areas of endochondral bone formation associated with premature closure of growth plates. Recently, several cases have been described in infants born to mothers with systemic lupus erythematosus (SLE).

Objectives—To describe the case of a mother with mixed connective tissue disease (MCTD) whose male and female offspring from two successive pregnancies had CDP in the absence of identifiable biochemical or genetic abnormalities or teratogen exposure.

Methods—Description of a male and female offspring from a mother with MCTD harboring high titer anti-RNP antibodies. Maternal autoantibody assays were performed employing quantitative multiplex suspension arrays and flow cytometry, and autoantibody titer and pattern were determined by indirect immunofluorescence. Assays of phytanic acid, plasmalogen and very long chain fatty acids were performed employing commercially available reagents. Chromosomal analysis was performed on both offspring employing standard cytogenetic analysis. Review of the relevant literature was performed (PubMed search 1966 through July 2008).

Results—Two children with CDP born to a mother with MCTD who harbored anti-RNP autoantibodies at high titer are described. Genetic and chromosomal studies, and biochemical analysis of peroxisome function and very long chain fatty acids excluded known biochemical or genetic defects or mutations as the cause of CDP in these children. Furthermore, detailed review of the clinical history failed to disclose any evidence of maternal teratogen exposure during the two pregnancies.

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Conflicts of Interest: none

Conclusions—Maternal MCTD is the most likely explanation for the occurrence of CDP in the two children reported here. Review of previously published cases of CDP associated with autoimmune disease suggests that placental crossing of maternal autoantibodies during pregnancy specifically affecting the normal development of fetal growth plates is responsible for CDP in the offspring in these cases.

INTRODUCTION

Chondrodysplasia punctata (CDP) refers to a heterogeneous group of genetic and non-genetic disorders that result in the abnormal development of fetal bone and cartilage. The condition is defined by the presence of premature islands of calcification occurring in the developing skeleton of an affected fetus. It is recognized at radiographic examination by the presence of stippling in regions of endochondral bone formation throughout the skeleton (1). Biochemical and genetic studies have identified several causes of CDP resulting from abnormal tissue levels of plasmalogens or specific sterols and discovered a pattern of inheritance in an autosomal or X-linked dominant pattern, respectively. A deficiency of the vitamin K dependent enzyme arylsulfatase E (ARSE), whose natural substrate is unknown, results in X-linked recessive CDP (2,3). Phenocopies of X-linked recessive CDP have been reported due to maternal warfarin ingestion, and in some cases, of maternal vitamin K deficiency (4). In the past few years an increasing number of case reports have highlighted the occurrence of CDP in offspring born to mothers with systemic lupus erythematosus (SLE) in the absence of any other identifiable genetic or biochemical abnormality or teratogen exposure. We describe here two siblings with CDP born to a mother with mixed connective tissue disease (MCTD) and thus expand the association of CDP to other maternal autoimmune diseases.

METHODS

Quantitative autoantibody analysis was performed on the mother's serum at Quest Diagnostics Laboratories (Philadelphia, PA) by multiplex suspension array assays employing a bead-based assay and flow cytometry (Bio-Rad Bioplex System, Bio-Rad Laboratories, Hercules, CA). Autoantibody titer and pattern was determined by indirect immunofluorescence of patient's serum on a Hep-2 cell line substrate (Bio-Rad). Biochemical studies were performed on both siblings shortly after birth. Determination of peroxisome function by assays of phytanic acid and plasmalogen, as well as assays for very long chain fatty acids were performed employing commercially available reagents at the clinical laboratories of the A. I. DuPont Hospital for Children (Wilmington, DE). Chromosomal analysis was performed on both offspring using standard cytogenetic analysis. The description of the cases was performed with the informed consent of the patient (mother), who also voluntarily provided the photographs of the ultrasound and radiography of her offspring. For review of the pertinent literature, a PubMed search was performed encompassing years 1966 through July 2008 employing the search terms "chondrodysplasia punctata" AND "autoimmune disease", "chondrodysplasia punctata" AND "systemic lupus erythematosus", and "chondrodysplasia punctata" AND "mixed connective tissue disease".

RESULTS (PATIENT HISTORIES)

Maternal

SP is a 37 year old female diagnosed initially with systemic sclerosis (SSc) at age 19 following several years of Raynaud phenomenon symptoms and skin induration and tightening resulting in numerous non-healing digital ulcerations. At age 20 she began to experience additional symptoms including a malar facial rash, arthralgias, dysphagia and muscle weakness. Her diagnosis was changed from SSc to MCTD owing to the appearance of facial skin rash with a malar distribution, inflammatory myopathy and polyarthritis coupled to serologic studies

showing a high anti-nuclear antibody (ANA) titer ($> 1:1280$) with a speckled pattern and anti-RNP specificity with an anti-RNP titer of > 8 (normal < 1). Repeated assays for RNP antibodies yielded positive results with high titers. Other autoantibodies were not present. The results of the serologic studies and a summary of her clinical manifestations are shown in Table 1. She was treated with oral prednisone and hydroxychloroquine. At age 29, she experienced a rapid and diffuse progression of skin induration involving the face, chest and extremities. A short course of D-penicillamine was started but discontinued owing to elevated liver function tests. Her persistent systemic disease included severe Raynaud symptoms associated with digital ulcers eventually requiring sympathetic blockade, induration of the skin in her fingers and dorsum of hands, and recurrent dysphagia with dysfunction of lower esophageal sphincter and abnormal esophageal peristalsis. A proton pump inhibitor, metoclopramide, ursodiol and a vasodilating agent were added to her therapy. The patient was never exposed to warfarin, phenytoin or had any symptoms or signs of bowel malabsorption or vitamin deficiencies.

Child 1

The maternal disease stabilized and at age 31 the patient became pregnant with a non-consanguineous partner following the use of a five day course of clomiphene (50 mg daily). The pregnancy was complicated by early gestational diabetes mellitus and hypertension. At 4 months gestation, an ultrasound of the fetus demonstrated the presence of a depressed nasal bridge (see Figure 1A), epiphyseal stippling of the long bones and other features consistent with the presence of CDP. A female child was born at 34 weeks gestation following an induced vaginal delivery for maternal hypertension. Her birth weight was 1980 g (10th – 50th percentile Tanner growth chart (TGC)), length 40.6 cm (3rd – 10th percentile, TGC) and head circumference 33cm (50th – 90th percentile, TGC). Dysmorphic features included a flat nasal bridge, shortened columella and the appearance of rhizomelic shortening of the extremities. Radiographic studies revealed stippling of epiphyses in the left proximal humerus, both proximal femora, carpal and tarsal bones, and within multiple vertebral bodies (Figures 1-B and 1-C). Brachytelephalangy was found with notable shortening of the second proximal phalanx in both hands (Figure 1B). Chromosome analysis demonstrated a normal 46, XX karyotype with normal subtelomeric fluorescent in situ hybridization (FISH). Biochemical studies showed normal plasmalogens, phytanic acid, very long chain fatty acids (VLCFA), and sterol panel including normal 8(9)-cholesterol, 8-dehydrocholesterol and methyl sterols, thus eliminating the X-linked dominant forms of CDP in this female child. Assays for autoantibodies were not performed. At 18 months the child was in the 10th percentile for weight and in the 3rd percentile for height on the TGC. Cervical spine radiographs showed kyphosis, asymmetric vertebrae with coronal clefting and odontoid hypoplasia requiring the use of a soft collar for spinal stability. The patient suffered from periods of sporadic apnea and was diagnosed later as having obstructive sleep apnea. A moderate degree of conductive hearing loss was identified; cataracts were not present. Developmental milestones were age appropriate, although speech delays and articulation deficits were noted at age 3. The child has currently adapted well to enrollment in preschool and functions with twice weekly physical therapy.

Child 2

At the age of 33 SP remained clinically stable from MCTD on the same treatment and became pregnant for the second time. At 20 weeks of pregnancy a prenatal screening ultrasound detected a viable male fetus with a depressed nasal bridge, stippled epiphyses and a strong suspicion of CDP. This pregnancy was also complicated with gestational diabetes and hypertension and was delivered vaginally after induced rupture of membranes at 37 weeks gestation. A male child was born with a weight of 2608 g and length of 45.7 cm, and at 12 days after birth remained in the 3rd percentile for weight and height on the TGC. Dysmorphic features included midfacial hypoplasia with flattening of the nasal bridge, rhizomelia of all four extremities, bowing of the humerus and broad phalanges with shortened 2nd metacarpals,

1st metatarsals and brachytelephalangy. A mild pectus excavatum was also noted. Radiography showed stippling within the humerus and femur bilaterally (Figure 1 D) and confirmed the presence of telebrachyphalangy and shortening of the proximal and middle phalanges of both second digits (Figure 1E). Platyspondyly and clefting was present in all levels of the spinal column (Figure 1F). Assays for autoantibodies were not performed. The child was last seen at age 18 months and did not have developmental delays, cataracts, or hearing deficits.

DISCUSSION

CDP comprises a heterogeneous group of osseous developmental disorders resulting in islands of calcification in the end plates of long bones and in vertebral bodies and other areas of fetal skeletal formation. The condition is classically represented by epiphyseal stippling noted on prenatal ultrasound or more commonly during the first 6-9 months of life by radiographic studies (1). CDP can be associated with numerous dysmorphic features including mid-facial hypoplasia, tracheal and other cartilaginous calcifications, limb shortening, brachytelephalangy, nail hypoplasia and vertebral abnormalities often accompanied by respiratory distress, cataracts, sensorineural hearing loss and development delays. The location, symmetry and severity of the stippling noted on radiography and the pattern of inheritance may suggest the etiology of CDP (1,5). A differential diagnosis of radiographic stippling includes specific forms of CDP such as brachytelephalangi CDP, rhizomelic CDP, and others that are caused by unique genetic mutations that can either follow autosomal or X-linked inheritance. These genetic forms can be diagnosed by gene sequencing or biochemical testing for plasmalogen and sterol levels (2,3). Other CDP-like syndromes result in offspring of mothers exposed during pregnancy to teratogens such as alcohol, rubella, dilantin and warfarin and must be addressed through careful exposure histories (4). Maternal deficiencies of vitamin K resulting from enzyme deficiencies, impaired intestinal absorption and poor diet during fetal development have also been associated with CDP (6).

Recent attention has been drawn to mothers with SLE who gave birth to children with CDP in the absence of any known genetic or enzymatic abnormalities or teratogenic exposures. The first report described two mothers with SLE who both gave birth to pre-term infants with radiographic evidence of diffuse stippling and an eventual diagnosis of CDP in the absence of any typical genetic or biochemical abnormalities (7). Eight other additional cases of CDP occurring in male and female offspring of mothers with SLE also lacking any known biochemical or genetic causes of the disorder have been reported (5,8-12). Some of the cases described were stillbirths (10), however, nine of the twelve children described have survived at least to childhood. A detailed review of the clinical features of the previously described cases is shown in Table 2.

The case reported here representing the association between MCTD and CDP raises several interesting associations worth discussion and expands on an oral communication by Lim et al reporting the presence of CDP in 4 offspring of a woman with MCTD (13). As in previous cases, the development of CDP in both infants occurred in the absence of any known genetic or biochemical abnormalities or maternal teratogen exposure. Specifically, erythrocyte plasmalogen levels and plasma sterol profiles were normal in the older infant. Gross genetic alterations were excluded by the presence of a normal karyotype. Furthermore, the presence of an affected female made X-linked recessive inheritance of the ARSE mutation unlikely. Maternal exposure to medications that cause vitamin K deficiency, such as warfarin and phenytoin, was also excluded. Other potential mechanisms by which SLE can cause or contribute to the occurrence of CDP as discussed in detail by Toriello (14), including maternal hypoprothrombinemia, presence of anti-cardiolipin and anti-B₂-glycoprotein I antibodies, or lupus anticoagulant were not observed.

The occurrence of CDP in offspring from mothers with another autoimmune disease besides SLE as described here supports the hypothesis that in these offspring, CDP is an acquired process resulting from the presence of a circulating maternal antibody capable of crossing the placental barrier and affecting the normal development of the growth plates in the long bones and other osseous structures. The transplacental crossing and passive acquisition of maternal SSa and SSb antibodies has long been associated with the development of neonatal lupus syndromes and case reports also implicate the isolated presence of maternal anti-U1RNP antibodies in neonatal skin disease (15). A similar process is highly likely in the cases described here. In the report by Shanske et al (5), the mother of the affected child harbored high titers of anti-Ro SSa antibodies, and the authors proposed that transplacental crossing of maternal Ro/SSa antibodies in early development resulted in CDP, possibly involving the inhibition of the calcium binding protein, calreticulin. In contrast, in the patient reported here, serologic studies failed to show the presence of Ro/SSa or La/SSb auto-antibodies on multiple occasions and instead disclosed high titers of anti-RNP antibodies. Interestingly, all the known ANA patterns in SLE mothers with CDP-afflicted offspring have been speckled, and five of the six cases with available full antibody profile have been associated with high titers of RNP auto-antibodies. Thus, we propose here that the transplacental crossing of anti-RNP, or possibly another yet unidentified antibody, mediates the pathogenesis of CDP. Although this notion remains speculative and the antigen target yet unknown, the presence of CDP in children born to mothers with SLE or MCTD in the absence of other known mechanisms raises intriguing questions about still unknown consequences of fetal passive transplacental acquisition of maternal auto-antibodies in these conditions.

CDP can be a severe and life-threatening disorder, but early recognition can help to optimize medical care. Given the sometimes subtle physical findings at birth and the disappearance of the hallmark stippling by radiography after childhood, the timely diagnosis of CDP may be missed in many patients and retrospective diagnosis is challenging. The occurrence of CDP among children of mothers with autoimmune disorders such as SLE and MCTD may be substantially higher than that currently reported. Nevertheless, the infrequency of cases describing CDP in offspring of mothers with autoimmune disease suggests that occurrence of CDP in affected offspring may be the result of a combination of factors that may include the existence of a rare and currently un-identified antibody capable of affecting fetal growth plates, a subtle maternal exposure not identified to date, or a genetic mutation distinct from the well recognized genetic mutations causing CDP. Furthermore, although unlikely, the possibility exists that the cases reported here are the result of autosomal recessive inheritance from an undelineated genetic form of CDP. Also, CDP could have been caused by the presence of hyperglycemia resulting from the mother's gestational diabetes in both pregnancies or possibly a complex interaction from an unknown maternal medicinal therapy or a medicine such as ursodiol. Physicians caring for female patients with autoimmune diseases must be aware of the potential occurrence of CDP in their offspring and should recognize that if fetal development is abnormal, detailed maternal antibody panels including ANA titer and pattern, and assessment of SSa, SSb, Smith and RNP antibodies should be performed during gestation. Physicians should also encourage routine prenatal ultrasound screenings and further genetic counseling on the risk of CDP in future pregnancies for the SLE/MCTD patient if CDP has been diagnosed in one of her children. Although currently there is no available intervention which may prevent the development of CDP in the offspring of patients with SLE or MCTD, it is possible that if the hypothesis that the transplacental transfer of a specific maternal antibody is the cause of CDP in the offspring is confirmed, then removal of such antibody or a therapeutic intervention to deplete or decrease the maternal autoantibody load (16-18) may prove to be beneficial.

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Figure 1. Features of CDP demonstrated in Child 1 and Child 2 in pre-natal ultrasound and by radiography shortly after the birth of both infants

A, three-dimensional prenatal ultrasound of Child 1 demonstrating the depressed nasal bridge and midfacial hypoplasia. **B**, frontal radiograph of Child 1 showing pelvic and femoral stippling with hand view demonstrating carpal stippling, shortening of the second proximal phalanx and telebrachyphalangy. **C**, Radiograph of Child 1 showing tarsal punctata in right foot. **D**, whole body skeletal radiograph of Child 2 demonstrating femoral shortening/proximal punctata and vertebral stippling. **E**, hand radiograph of Child 2 showing carpal stippling and presence of telebrachyphalangy and shortening of the proximal and middle phalanges of the second digit. **F**, lateral spinal radiograph of Child 2 demonstrating vertebral clefting.

Table 1

Summary of Clinical Features and Laboratory Studies of Mother *

	Mother (SP)
Disease Features	
Malar skin rash	Yes
Sclerodactyly	Yes
Proximal Skin Induration	No
Raynaud Phenomenon	Yes
Hair Loss	Yes
Oral Ulcers	Yes
Synovitis	Yes
Arthritis	Yes
Myopathy	Yes
Dysphagia	Yes
Pulmonary Fibrosis	Yes
Serositis	No
Renal Involvement	No
Antibodies	
ANA	1:1280
Pattern	Speckled
SSa	neg
SSb	neg
Smith	neg
RNP	>8.0 (normal < 1.0)
Scl-70	neg
Anti-centromere	neg
C3/ C4	normal

* ANA = anti-nuclear antibody

Table 2

others with diagnosed autoimmune disease *

Pattern/Specificity	Sex	Offspring	Gestation (wks)	Height (cm)/Weight (kg)	Radiographic Stippling	Vertebral Abnormalities	Cranio-Facial Abnormality	Genetic Mutation/ Biochemical Abnormality/ Maternal Exposure	MISCELLANEOUS
SSb +	F		29	N/A	tarsal/sacral	N/A	N/A	no/no/no	NSLE skin findings on infant
	M		36	N/A	humeral/femoral	coronal clefting	N/A	no/no/no	Died at 6 months (encephalopathy)
	M		25	N/A/0.92	carpal/lumbar/sacral	sagittal clefting	yes	N/A	Second of dizygotic twins/Mother diagnosed with SLE after pregnancy
SSa+/RNP +	F		33	39.5/1.5	tarsal/sacral	N/A	yes	no/no/no	NSLE skin findings on infant (annular facial plaques)
	M		36	27.5/1.49	carpal/tarsal/sacral/long bone	sagittal clefting	yes	no/no/no	Fetal stillbirth at 36 weeks
	M		24	IUGR	long bone/respiratory cartilage/tarsal	coronal clefting	yes	no/no/no	Fetal stillbirth at 24 weeks
RNP+/SSa -	M		34	42/1.9	long bone/sacrum	N/A	yes	no/no/no	NSLE skin findings on infant/infant RNP +, SSa/SSb - /- Mother diagnosed after pregnancy
	M		30	33/2.0	long bone/tarsal/vertebral	irregular shape	yes	no/no/no	Infant intellectual delay/Respiratory insufficiency
	M		38	34/3.1	long bone/tarsal/wrist	hypoplastic	yes	no/no/yes (phenytoin)	Infant intellectual delay/Respiratory insufficiency
SSb+ S m/RNP+	M		36	42/2.2	Carpal/tarsal/vertebrae/long bone	vertical clefting	yes	no/no/no	Infant intellectual delay/Mother diagnosed after pregnancy
RNP+ SSa/SSb-	F		34	40.6/1.98	long bones/carpal/vertebral	coronal clefting	yes	no/no/no	Respiratory insufficiency
e	M		37	43.9/2.6	long bones/carpal	platyspondyly	yes	no/no/no	

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*TD = mixed connective tissue disease; N/A = data not available; M = male; F = female; NSLE = neonatal systemic lupus erythematosus;