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REVIEW

Fetal chondrodysplasia punctata associated with maternal autoimmune diseases: a review

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Abstract: Chondrodysplasia punctata (CDP) is a skeletal abnormality characterized by premature calcification that is usually noticeable in the prenatal period and infancy. Etiologically, the condition is heterogeneous, and the causes include fetal conditions such as chromosome abnormalities, peroxisomal disorders, lysosomal storage disorders, cholesterol synthesis defects and abnormal vitamin K metabolism, as well as maternal diseases such as severe malabsorption and exposure to teratogens. An association between CDP and maternal autoimmune disease was first observed and reported by Curry et al and Costa et al in 1993 and expanded by Chitayat et al in 2010. This review lists the clinical characteristics and radiologic findings of all cases reported to date in English and discuss the possible etiology of this interesting fetal finding.

Keywords: stippled epiphyses, peroxisomal disorders, vitamin K, chromosome abnormalities, intrauterine growth restriction epiphysis, growth plate

Introduction

Chondrodysplasia punctata (CDP) is a skeletal abnormality characterized by premature foci of calcification, referred to as stippling, within the cartilage. It is most commonly found in the epiphysis of the long bone, vertebral column and other cartilaginous regions that do not normally calcify, including the trachea and the rib ends. These foci of calcifications can be visualized radiologically by fetal ultrasound and X-rays during the newborn and infancy periods. As the cartilage starts to calcify, these foci are no longer visible, and this diagnosis can be missed and can become challenging.

CDP is etiologically heterogeneous. Irving et al[1] divided the etiologies into four groups as follows: inborn error of metabolism, disruption of vitamin K metabolism, chromosomal abnormalities and a fourth group that includes maternal factors and a number of unclassified etiologies.

The inborn errors of metabolism associated with CDP include peroxisomal disorders, type 2 mucolipidosis, type 3 mucopolysaccharidosis and GM1 gangliosidosis. Peroxisomes are membrane-bound organelles found within almost all eukaryotic cells. Contained within the peroxisome matrix of mammalian cells are over 70 distinct enzymes required for normal lipid metabolism and a host of other biochemical processes critical for normal health and development.[2] Defects in peroxisome formation result in dysfunction of a group of metabolic diseases collectively known as peroxisome biogenesis disorders. This group of disorders is divided into two subtypes: Zellweger spectrum disorder and rhizomelic CDP (RCDP) type 1. The second group of peroxisomal disorders involves single enzyme defects. Other peroxisomal disorders associated with RCDP are RCPD

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type 2 and 3. CPD type 2 is caused by deficiency of the peroxisomal enzyme dihydroxyacetone phosphate acyltransferase, encoded by GNPAT (OMIM 602744). RCDP3 is caused by deficiency of the peroxisomal enzyme alkyl-dihydroxyacetone phosphate synthase, encoded by AGPS (OMIM 600121). Zellweger spectrum disorder and rhizomelic CDP types 1–3 share similar punctate cartilaginous changes.[3]

Abnormality of cholesterol metabolism is another cause of CDP. Defects in this pathway result in multisystem anomalies, attributable to the fact that cholesterol is an essential and ubiquitous chemical with an integral role in many developmental pathways and cell membranes. Cholesterol biosynthesis is a complex pathway that can be divided into two main parts. The so-called pre-squalene part leads to the biosynthesis of both isoprenoids (including the intermediate precursor named squalene) and sterols; the post-squalene metabolic steps are committed to the synthesis of cholesterol and vitamin D.[4,5] Ten disorders of the post-squalene pathway have been recognized, leading to a variable combination of intellectual disability and malformations with significant skeletal involvement. Smith–Lemli–Opitz syndrome (OMIM 270400), Conradi–Hünermann syndrome (OMIM 302960), Greenberg dysplasia (OMIM 125140) and congenital hemidysplasia with ichthyosiform erythroderma and limb defects, more commonly known by the acronym CHILD syndrome (OMIM 308050), are examples of this group of diseases.[5]

CDP is also seen in association with chromosomal abnormalities such as Turner syndrome, Down syndrome, trisomy 18 (Edwards's syndrome) and trisomy 9[6,7] and with maternal exposure to cytomegalovirus or rubella viruses.

Fetal exposure to warfarin, an anticoagulant that is a commonly used for the prevention and treatment of thrombosis, carries the risk of developing warfarin embryopathy. The condition is primarily characterized by nasal bone hypoplasia and skeletal abnormalities, including short limbs and digits (brachydactyly), and stippled epiphyses.[8] Warfarin functions by inhibiting vitamin K epoxide reductase complex 1, an essential enzyme through which vitamin K is recycled, leading to deficiency of vitamin K and as a result reduction in the function of vitamin K-dependent enzymes.[9] Vitamin K acts as a coenzyme for a carboxylase that functions to activate several coagulation factors, coagulation inhibitors and other proteins such as osteocalcin, matrix-Gla protein and periostin. The latter three proteins are involved in the mineralization process of bones and teeth. Deficiency of vitamin K leads to undercarboxylation of Gla proteins, which, in turn, leads to abnormal calcium deposition and aberrant growth of cartilage.[10–12]

Another enzyme that is dependent on vitamin K is arylsulfatase E (*ARSE*), a member of the sulfatases group that is essential for bone and cartilage development. Deficiency of this enzyme results in X-linked recessive CDP.[13]

The association of CDP and maternal autoimmune diseases, namely, systemic lupus erythematosus (SLE), was first presented by Curry et al at the David Smith meeting in 1993[14] and by Costa et al (1993), at the first meeting of the International Skeletal Dysplasia Society.[15] Subsequently, 29 cases were reported, in association not only with SLE but also with mixed connective tissue disease (MCTD) and Sjögren syndrome. This article reviews the clinical, radiologic and biochemical characteristics of all reported cases with CDP born to mothers with autoimmune diseases.

CDP and SLE

SLE is a chronic autoimmune disease that affects various body systems. Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic or central nervous system involvement. A revised diagnostic criterion has been proposed by the SLE International Collaborating Clinics in 2012.[16] This criterion requires that a patient either satisfy at least 4 of 17 criteria, including at least 1 of the 11 clinical criteria and 1 of the 6 immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANAs) or anti-double-stranded DNA antibodies.

ANAs are antibodies that target normal proteins within the nucleus of the cell. The presence of these antibodies in abundance indicates an autoimmune disease. There are many subtypes of ANAs, such as anti-Ro antibodies, anti-La antibodies, anti-Sm antibodies, anti-nRNP antibodies and anti-double-stranded DNA antibodies. Each of these subtypes of antibody binds to different proteins or protein complexes within the nucleus. Pregnancies in women affected with SLE carry a higher maternal and fetal risk. About 1%–2% of babies born to women with SLE develop neonatal lupus.[17] Following the report of McCuistion et al showing that SLE-like skin changes are found in newborns to mothers with SLE,[18] it was recognized that fetuses/neonates can have manifestations associated with maternal SLE. Neonatal lupus is a disease caused by passively transferred maternal autoantibodies leading to immunologic injury with most manifestations in the newborn being transient. These babies display cutaneous, hematologic, liver and cardiac manifestations. Skeletal manifestations include epiphyseal stippling, distal phalangeal hypoplasia and midface hypoplasia with hypoplastic nasal bone. We reviewed all cases of neonates with CPD born to mothers with SLE reported to date[15,19–27] and have summarized their antenatal history, clinical and radiologic findings in Table 1.

Table 1 Clinical and radiologic features of infants born to mothers affected with SLE

Clinical features	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	Mansour et al[20]	Elcioglu et al[21]	Elcioglu et al[21]	Austin-Ward et al[22]	Kelly et al[23]	Kozlowski et al[24]
Gestational age	29 weeks	25 weeks dizygotic twin	Still born at 36 weeks	Still born at 24 weeks	33 weeks	33 weeks+5 days	7 months
Gender	Female	Male	Male	Male	Female	Male	Male
Parental ethnic origin	Sri Lanka	West Indian	Black African	Black African	Chilean	African American	Cape town
Consanguinity	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous	Not reported	Not consanguineous
Maternal disease	SLE diagnosed prenatally	SLE diagnosed postnatally	SLE	SLE	SLE diagnosed at 16 years	SLE diagnosed postnatally	SLE diagnosed in early adulthood
Medications in pregnancy	Prednisone	None	Intermittent steroid use	• Prednisone • Aspirin	• Hydroxychloroquine • Aspirin • Prednisolone	Not applicable	Chloroquine Prednisone
Mother's antibodies	• Positive anti-Ro and anti-La antibodies • Positive anti-RNP antibodies • Positive ANA	Not reported	Not reported	Not reported	• Positive ANA • Positive anticardiolipin antibodies • Positive ENA • Positive RNP • Positive anti-Ro • Positive anti-dsDNA	Positive ANA Positive RNP Negative for Sm, Ro, La and dsDNA antibodies	Not reported
Pregnancy history	Not reported	Uneventful	Anatomy scan showed nasal hypoplasia, short long bones (below third centile), a sacral abnormality and polyhydramnios	• Maternal flare-up of SLE renal failure, hypertension and neurologic impairment • Anatomy scan showed femoral length below third centile	Not reported	No prenatal care before 30 weeks gestation	Not reported
Birth weight	Below third centile	820 g (50%)	1485 g (below fifth centile)	190 g (below fifth centile)	1500 g	1.8 kg	2020 g
Birth HC	Not reported	Not reported	31cm (10th centile)	16 cm (below fifth centile)	Not reported	30.5 cm	33 cm
Birth length	Not reported		27.5 cm (below fifth centile)	20.7 (below fifth centile)	39.5 cm	42 cm	33 cm

(*Continued*)

Table 1 (*Continued*)

Clinical features	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	Mansour et al[20]	Elcioglu et al[21]	Elcioglu et al[21]	Austin-Ward et al[22]	Kelly et al[23]	Kozlowski et al[24]
Pattern of stippling	Stippling at: • The proximal femoral epiphyses • Both heels	Stippling at: • The lumbosacral spine • The proximal end of second metacarpals	Stippling at: • The laryngeal cartilage • Anterior and lateral to the vertebral bodies • The proximal femora • The elbows • The ends of the first, second, third and fourth metacarpals • The tarsal bones and the proximal ends of the first, second and third metatarsals	Stippling at: • The laryngeal cartilage • The anterior spinous ligament • The anterior part of the vertebral body • The distal end of the humeri and proximal ends of the femora • The tarus	Stippling at: • Sacrococcygeal region • Heels	Stippling at • The right proximal humerus • Sacrum • Distal phalanges • Tarsal centers	Stippling at • The tarsal regions • Spine
Vertebral body defects	Not reported	Sagittal clefts	Sagittal clefts of several upper thoracic vertebral bodies	Coronal clefts	Not reported	Not reported	• Round and irregular • Anterior wedges
Other radiologic findings	None	• Tiny distal phalanges • Sort second metacarpals	• Short long bones (below fifth centile) • Pronounced humeral shortening • Poorly ossified skull vault	• Short long bone (below the fifth centile) • Poor ossification of the vault • Short first metatarsals • Short third and fourth metacarpals	Not reported	• Brachydactyly • Deformity of the proximal phalanges of the first and second digits • Deformity of the proximal phalanx of the great toe	• Generalized osteopenia • Hypoplastic distal phalanges
Facial features	• Flattened nose • Skin tag on the left cheek	• Nasal hypoplasia • Depressed nasal bridge • Anteverted nares • Bilateral alar grooves	Poorly developed nasal bridge		• Poorly developed brow ridges • Depressed nasal bridge • Nasal hypoplasia • Large philtrum • Thin pinnae • Prominent occiput	• Small ears • Upward-slanting palpebral fissures • Midface hypoplasia • Short columella	• Narrow face • Prominent ears • Mandibular prognathism • Crowded teeth
Skin rash	Lupus facial rash	Not reported	Not reported	Not reported	Erythematoviolaceous, scaly facial rash	Lupus rash over the neck, wrists, ankles and anterior thorax	Not reported

(*Continued*)

Table 1 (*Continued*)

Clinical features	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	Mansour et al[20]	Elcioglu et al[21]	Elcioglu et al[21]	Austin-Ward et al[22]	Kelly et al[23]	Kozlowski et al[24]
Musculoskeletal exam	Not reported	Brachydactyly with drum stick swelling	• Symmetrical, mild limb shortening • Short fingers and camptodactyly • The toes overlapped with hypoplastic nails on the feet	• The limbs are slightly short • Short, malpositioned fingers • Underdeveloped right palmar creases	Not reported	• Generalized hands brachydactyly • Short first, second and fourth proximal phalanges	Pectus excavatum
Developmental history	Normal	Normal development at 15 months	Not reported	Not reported	Not reported	Not reported	Intellectual delay
Growth parameters	Proportionally small	Not reported	Not reported	Not reported	Not reported	At 35 months: • Weight and height below fifth centile • HC was below 10th centile	Not reported
Chromosomal analysis	Not reported	46, XY	Not performed	Not performed	46, XX	46, XY	46, XY
Metabolic work up	Not reported	Not reported	Not performed	Not performed	Not reported	VLCFA normal	Not done
Antibodies level	Not reported	Not reported	Not reported	Not reported	Not reported	Positive ANA Positive anti-RNP	Not reported

	Kozlowski et al[24]	Shanske et al[25]	Chitayat et al[19]	Chitayat et al[19]	Tim-aroon et al[26]	Roy et al[27]
Gestational age	Term	36 weeks	IUFD at 21 weeks	35 weeks	37 weeks	Term
Gender	Male	Male	Male	Male	Male	Male
Paternal ethnic origin	Cape Town	Dominican republic	German	Caucasian	Thailand	Indian Hindu
Consanguinity	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous		Not consanguineous
Maternal disease	SLE	SLE diagnosed postnatally	SLE	SLE	SLE	SLE diagnosed postnatally
Medications in pregnancy	• Quinine • Chloroquine • Epanutin		• Prednisone • Azathioprine • Hydroxychloroquine sulfate • Methyldopa • Amlodipine	Prednisone	• Prednisolone • Fraxiparin	No medications

(*Continued*)

Table 1 (*Continued*)

	Kozlowski et al[24]	Shanske et al[25]	Chitayat et al[19]	Chitayat et al[19]	Tim-aroon et al[26]	Roy et al[27]
Mother's antibodies	Not reported	• Positive ANA • Positive anti-RNP antibodies • Positive anti-RO and anti-LA antibodies	Not reported	Not reported	• Positive ANA • Positive anti-RO and anti-La antibodies • Positive anti-RNP • Positive anticardiolipin • Positive anti-dsDNA	• Positive ANA • Positive anti-SM antibodies • Positive anti-RNP • Positive anti-Ro antibodies
Pregnancy history	Epilepsy	UTI	High blood pressure Anatomy scan showed short long bones and an abnormal head shape	Anatomy scan showed discrepancy of 4 weeks in femoral length and 2 weeks in humeral length	Not reported	Uneventful No exposure to infection
Birth weight	3080 g	2176 (25th centile)	127 g	Not reported	2970 g (50th centile)	2459 g (10th–25th centile)
Birth HC	38 cm	33 cm (50th centile)	Not reported	Not reported	35 cm (75th centile)	33 cm (50th centile)
Birth length	34 cm	42 cm (below 10th centile)	Not reported	46 cm (50th centile)	45 cm (10th centile)	42.5 cm (below 10th centile)
Pattern of stippling	Stippling at: • Epiphyses of the knees • Tarsal regions • The pine • Left wrist and terminal phalanges	Stippling at: • Vertebral bodies • Carpal bones and phalanges • The shoulders and hips • The elbows and knees • All of the tarsal bones and phalanges	Stippling at: • The vertebral column • The sacral ossification centers	Multiple stippled epiphyses	Stippling at: • The proximal humeri • Elbows • Metacarpals • Hips • Knees • Vertebrae	Stippling at: • The shoulders • The elbow • The hips • The knee joints • Anterior arch of foramen magnum
Vertebral body defects	Hypoplasia and dysplasia of vertebral bodies	• Decreased ossification • Small vertebrae with vertical clefts	Nor reported	Not reported	• Non-ossification of the vertebral bodies of cervical spines • Partially ossified thoracic and lumbosacral vertebral bodies • Wedge-shaped midthoracic vertebrae • Sagittal cleft of lumbar vertebrae	• The spine exhibited minimal ossification • Coronal clefts of the vertebral bodies

(*Continued*)

Table 1 (*Continued*)

	Kozlowski et al[24]	Shanske et al[25]	Chitayat et al[19]	Chitayat et al[19]	Tim-aroon et al[26]	Roy et al[27]
Other radiologic findings	Short dysplastic terminal phalanges	• Short tibias • Unusual cartilaginous extensions from the tibial growth plate into the upper tibias	• Bell-shaped chest • Mild bowing of the tibiae and femora • Shortening of the middle phalanges, the first metacarpal and the proximal phalanx of the thumbs bilaterally • The second, third and fourth distal phalanges bilaterally showed broadened tufts with proximal tapering • Increased density at the bases of the third distal phalanges	Asymmetric femur length		• Rhizomelic shortening of extremities • Metaphyseal flaring in humerus and femur
Facial features	• Prominent forehead • Simple ears • Midface hypoplasia • Depressed nasal bridge • Micrognathia	• Upward palpebral fissures • Epicanthal folds • Midface hypoplasia • Depressed nasal bridge • Hypoplastic nasal bone • Anteverted nares	• The nose was flat • The chin was prominent	• Broad low nasal bridge • Long philtrum • Thin upper lip • Micrognathia	• Flattened nasal bridge • Hypoplasia of the nasal bone • Midface hypoplasia • Thin upper lip • Long/smooth philtrum	• Midface hypoplasia • Depressed nasal bridge • Anteverted nares • Cataracts in both eyes
Skin rash	Not reported	Not reported	Not reported	Not reported	Erythematous lupus rash over face, trunk and extremities	Not reported
Musculoskeletal exam	• Rhizomelia of the upper and lower limbs • Brachydactyly • Talipes equinovarus • Short and bell-shaped thorax	• Rhizomelic shortening of the arms and legs • Bilateral brachydactyly of the second and third fingers	Short limbs		• Small thorax • Pectus carinatum • Wide internipple distance • Mild rhizomelia of the upper and lower extremities • Decreased U/L segment ratio • Severe kyphosis of the thoracic spine	• Barrel-shaped chest • Proximal shortening of both the upper and lower limbs
Developmental history	Developmental delay	Mild psychomotor delay with borderline cognitive function	Not reported	Normal	Appropriate for age	Not reported

(*Continued*)

Table 1 (*Continued*)

	Kozlowski et al[24]	Shanske et al[25]	Chitayat et al[19]	Chitayat et al[19]	Tim-aroon et al[26]	Roy et al[27]
Growth parameters	Not reported	Height and weight below third centile	Not reported	At 5 months of age: • Height was 54.5 cm (−4.5 SD) • Weight 6.6 kg (25th centile) • HC 41.5 cm (40th centile)	• Progressive kyphosis • At the age of 3 years: 1. Height 80 cm (below third centile) 2. Weight 11.4 kg (third centile) 3. HC 49 cm (50th centile)	Not reported
Chromosomal analysis	46, XY	Not reported	Not reported	Not reported	46, XY	Not reported
Metabolic work up	Not done	• Normal plasmalogen level • Normal VLCFA • Normal total plasma lipids • Normal phytanic acid level	Not reported	Not reported	• Normal VLCFA • Normal plasmalogen	• Normal plasmalogen • Normal VLCFA • Normal phytanic acid
Antibodies level	Not done	Not reported	Not reported	Not reported	• Positive anti-Ro and anti-La antibodies • Positive anti-RNP • Positive ANA antibodies	Not reported

Abbreviations: ANA, antinuclear antibody; dsDNA, double-stranded DNA; HC, head circumference; IUFD, intrauterine fetal death; RNP, ribonucleoprotein antibodies; SLE, systemic lupus erythematosus; UTI, urinary tract infection; VLCFA, very long chain fatty acid.

CDP and MCTD

The concept of MCTD as a separate immune-mediated connective tissue disease was first introduced by Sharp et al >40 years ago,[28] but there is still no consensus regarding the disease definitions, classification, criteria or the relationship with other autoimmune conditions.[28,29] Different set of diagnostic criteria were proposed. MCTD may begin with any clinical manifestation associated with SLE, systemic sclerosis, polymyositis or rheumatoid arthritis at the initial presentation or during the clinical course. The most common clinical features are polyarthritis, Raynaud's phenomenon, sclerodactyly, swollen hands, muscle disorders and esophageal dysmotility. The anti-U1-RNP antibodies are the hallmark of the disease. Patients with high titers without any criteria of MCTD or other defined connective tissue disease usually evolve into MCTD in about 2 years.[29] Seven affected women who gave birth to neonates with CDP have been reported to date. Table 2 lists the clinical, radiologic and biochemical manifestations of these cases.[14,15,19,30]

Sjögren syndrome and CDP

Sjögren syndrome is a chronic disease in which the body's immune system abnormally attacks secretory glands. The clinical presentation can extend to systemic involvement (extraglandular manifestations). Martin et al[31] reported the first and the only case of a child with CPD born to a mother with Sjögren syndrome. The mother was diagnosed with the syndrome at the age of 21 and got pregnant at the age of 36. At that time, she was on prednisone and hydroxychloroquine that were discontinued after her pregnancy was confirmed at 4 weeks' gestation. Fetal scan at 20 weeks' gestation showed sacral hypoplasia suggestive of a possible caudal regression syndrome. A female infant was delivered at 40 weeks with a birth weight of 2210 g and a length of 43 cm (both below first centile) and the head circumference was 33.5 cm (34th centile). She had large anterior fontanelle, sparse hair, marked nasal hypoplasia, wide mouth and short neck. The limbs were short with brachydactyly. She had deviated the second to fourth fingers and short middle and distal phalanges. The skeletal survey showed stippling of the carpal bones, tarsal bones, many vertebral bodies and the hyoid bone. The distal and middle phalanges on both hands were markedly hypoplastic, and the first metacarpal bone was short. Spine magnetic resonance imaging showed anomalies involving the cervical, lumbar and sacral vertebral bodies and mild spinal stenosis at C2–C3. Serological investigations of the newborn showed positive anti-Ro antibodies, anti-La antibodies and ANA titers. Biochemical

tests of peroxisome function, including plasmalogen, very long chain fatty acid and phytanic acid, were within normal limits. 7-Dehydrocholesterol and plasma cholesterol were also normal. Chromosome analysis showed a normal female karyotype (46, XX), and molecular analysis of *ARSE* gene failed to identify a mutation. On follow-up assessments, the child's development was within normal range.

Discussion

Maternal collagen vascular disorders can be associated with a number of fetal complications including recurrent miscarriages, intrauterine deaths, intrauterine growth restriction, prematurity and heart block which can lead to hydrops fetalis. Postnatally, these disorders can result in a transient rash, congenital heart block, hematologic cytopenias and hepatobiliary and central nervous system abnormalities.[17,19]

CDP is a skeletal abnormality characterized by calcification of the epiphysis of the long bones, the vertebrae and other areas such as rib ends, trachea and hyoid bone. It is associated with characteristic facial features which resemble the one seen in warfarin embryopathy and with variable degrees of long bones and phalangeal shortening. CPD is seen in various genetic diseases and in association with certain exposures. To date, a total of 21 neonates with CDP, born to women with autoimmune diseases, including SLE, MCTD and Sjögren's syndrome, have been reported. These reports support the association between maternal autoimmune disease and fetal/newborn CDP. However, it remains a diagnosis of exclusion. Chromosome analysis, single-gene disorders, and maternal diseases and exposure should be ruled out before concluding that the etiology is maternal autoimmune disease. The differential diagnosis was outlined by Chitayat et al,[16] and the diagnosis, especially in fetuses, relies on the clinical and pathologic/radiologic manifestations and should include a thorough investigation to exclude chromosomal abnormalities and one of the inherited conditions such as peroxisomal disorders, arylsulfatase A and Smith–Lemli–Opitz among others, using chromosome analysis, metabolic studies, DNA analysis and, if needed, whole exome sequencing.

Observations of these cases showed that the majority (two-thirds) were males (Tables 1 and 2). Most affected neonates were born prematurely, two were still born and two died in utero.[19,21] Despite diversity of ethnicity, African origin seemed predominant, which could be explained by the higher prevalence of autoimmune diseases among African-American women.[14,19,21,23,24] The stippling, in these cases, did not have a specific pattern of distribution and happened anywhere across the skeleton. Vertebral abnormality is another major finding and includes reduced ossification, abnormal shapes (wedge, cone, flat and broad) and clefts. The changes in spine curvature noted in these patients are probably secondary and reflect the degree of vertebral involvement. It is difficult to comment on the final height due to lack of regular and constant follow-up of the growth parameters. Shortening of the proximal long bones was also reported in three cases;[21,25] however, peroxisomal disorders were ruled out biochemically in one of the three cases only.[25] Intrauterine growth restriction is another risk factor for long bone shortening. The involvement of the fingers and toes is variable in the degree of hypoplasia and the bones involved. The most common facial findings include midface hypoplasia with a poorly developed nasal bone and creases over the alae nasi and some malar flattening, similar to what is seen in fetuses exposed prenatally to warfarin. Intellectual development seems to be unaffected in these cases, although long-term follow-ups are lacking to confirm this observation.[14,19,20,26,30] However, other risk factors including placental insufficiency and prematurity can increase these children's risk for developmental delay. None of the cases reported had a history of prenatal exposure to teratogens including viral infections or warfarin. Although some of the mothers received medications to treat the autoimmune condition during pregnancy, none of these medications are known to cause CDP.

The reason for the stippled epiphyses in maternal autoimmune conditions has not been delineated, and a variety of explanations have been proposed. Austin-Ward et al[22] suggested that the maternal antibodies interfere with calcium-binding proteins, and Toriello[32] proposed genetic susceptibility as the cause for CDP in view of the rarity and the occurrence in sibs.

We know from neonatal SLE experience that the presence of anti-Ro/SSA antibodies, with or without anti-La, rather than the type of maternal autoimmune disease, is the risk factor for the development of the disease.[33] We do believe that in the cases of CPD, the maternal antibodies that cross the placenta have a major role in the pathophysiology of the condition, yet the precise mechanism has not been delineated. Although not all the reported cases underwent screening for autoantibodies, the ones who did, had positive anti-RNP antibodies in common. In the mother reported by Schultz et al,[30] serological studies failed to show the presence of anti-Ro/SSA or anti-La/SSb autoantibodies and instead disclosed high titers of anti-RNP antibodies. This observation suggests that the transplacental crossing of anti-RNP or possibly another yet unidentified antibody mediate CDP.

Table 2 Clinical and radiologic features of infants born to mothers with mixed connective tissue diseases

	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	**Chitayat et al[19]**	**Chitayat et al[19]**	**Curry et al David Smith meeting 1993[14] Chitayat et al[19]**	**Curry et al David Smith meeting 1993[14] Chitayat et al[19]**	**Schulz et al[30]**	**Schulz et al[30]**
Gestational age	36 weeks	Fetal demise at 22 weeks	34 weeks	32 weeks	32 weeks	34 weeks	37 weeks
Gender	Male	Male	Female	Female	Female	Female	Male
Paternal ethnic origin	Caucasian	Liberian	Not reported	African-American	African-American	Not reported	Not reported
Consanguinity	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous	Not consanguineous	Not reported
Maternal disease	MCTD	MCTD	MCTD	MCTD	MCTD	MCTD	MCTD
Medications in pregnancy	• Prednisone • Verapamil	Not reported	• Amlodipine • Fexofenadine hydrochloride • Acetazolamide	Prednisone	Prednisone	Not reported	Not reported
Mother's antibodies		• Positive ANA • Positive anti-RNP • Positive anti-RO	• Positive ANA • Positive anti-RNP	• Positive ANA • Positive anti-RNP	• Positive ANA • Positive anti- RNP	• Positive ANA • Positive anti RNP	• Positive for ANA • Positive for anti-RNP
Pregnancy history	Skin rash and arthralgia in the third trimester	• Maternal flare up at 22 weeks' gestation • Fetal demise at22 weeks	• A fetal ultrasound at 20 weeks' gestation showed • Epiphyseal stippling • Flat vertebrae • Nasal bone hypoplasia	Not reported	Not reported	• Gestational diabetes • Hypertension • Anatomy scan showed: • Depressed nasal bridge • Epiphyseal stippling of the long bones	• Gestational DM • Hypertension • Fetal U/S showed: • Depressed nasal bridge • Stippled epiphyses
Birth weight	2080 g (third centile)	584 g	Not reported	1700 g (50th centile)	1.32 kg (10th centile)	1980 g (10th–50th centile)	2608 g
Birth HC	Not reported	Not reported	Not reported	30 cm (25th centile)	29.5 cm (25th centile)	33 cm (50th–90th centile)	Not reported
Birth length	43 cm (below third centile)	Not reported	Not reported	42 cm (below third centile)	38 cm (below third centile)	40.6 cm (3rd–10th centile)	45.7 cm
Pattern of stippling	Stippling at: • Proximal humeri • Proximal femoral heads • Vertebral bodies	Stippling: • Cervical and thoracic vertebrae • Proximal femurs and Taluses	Stippling at: • Feet • Hips • Vertebrae • Sacrum	Stippling at: • Tarsal bones • Sacrum • Vertebral body • Greater trochanter bilaterally • The base of distal phalanges	• Stippled proximal femoral epiphysis • Stippled metacarpals and calcanei bones • Stippled vertebral bodies	• Stippling in the left proximal humerus • Stippling of both proximal femora • Stippling of carpal and tarsal bones • Stippling of multiple vertebral bodies	• Stippling of humeri • Stippling of femura

(*Continued*)

Table 2 (*Continued*)

	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	Chitayat et al[19]	Chitayat et al[19]	Curry et al David Smith meeting 1993[14] Chitayat et al[19]	Curry et al David Smith meeting 1993[14] Chitayat et al[19]	Schulz et al[30]	Schulz et al[30]
Vertebral body defects	Coronal clefts	Not reported	Not reported	• Vertical clefts of T3, T6 and T8 vertebral bodies • Broad flat L5 vertebra	Not reported	• Kyphosis • Asymmetric vertebrae • Coronal clefts • Odontoid hypoplasia	• Platyspondyly • Clefts at multiple levels
Other radiologic findings	Not reported	• Hypoplasia of the distal phalanges • Generalized brachydactyly	• Hypoplasia of the distal phalanges • Brachydactyly	• Short first, second and fourth distal phalanxes bilaterally • Cone-shaped epiphyses in the distal phalanges of the thumbs • Mild shortening of the middle phalanx of the index finger	Not reported	• Short second proximal phalanx bilaterally	Short proximal and middle phalanges of the second digits
Facial features	• Upturned nares • Retrognathia • Long philtrum • Hypoplastic nose	• Nasal hypoplasia • Malar hypoplasia	• Large anterior and posterior fontanelles • Flattened nasal bridge • Short nose	• Nasal hypoplasia • Large anterior fontanelle • Long philtrum • Small ears	• Prominent eyes • Displaced inner canthi • Flat nasal bridge • Nasal hypoplasia • Small unilateral cortical cataract	• Flat nasal bridge • Shortened columella	• Midface hypoplasia • Flat nasal bridge
Skin rash	Not reported	Not reported	Not reported	None	None	Not reported	Not reported
Musculoskeletal exam	• Narrow chest • Hip contractures • Hyperextended left knee • Overlapping fingers • Club feet		• Brachydactyly • Radial deviation of the distal phalanges • Bilateral shortened first toes • Prominent thorax	• Radially deviated index fingers • Short proximal phalanges • Short first metatarsals • Flat feet • Joint hypermobility • Mild pectus carinatum	• Hypoplasia of the distal phalanges • Clinodactyly of the second fingers • Hypoplastic finger and toenails • Mild rhizomelic shortening of the humeri	• Rhizomelic shortening of the extremities	• 4 limbs rhizomelia • Bowed humerus • Broad phalanges • Short second metacarpals and first metatarsals • Pectus excavatum
Developmental history	Developmental delay	Not reported	Not reported	Normal	• Normal development • Unilateral sensory neural hearing loss	• Normal motor development • Mild speech delay	Normal development

(*Continued*)

Table 2 (*Continued*)

	Costa et al[15] Skeletal dysplasia meeting 1993 Chitayat et al[19]	**Chitayat et al[19]**	**Chitayat et al[19]**	**Curry et al David Smith meeting 1993[14] Chitayat et al[19]**	**Curry et al David Smith meeting 1993[14] Chitayat et al[19]**	**Schulz et al[30]**	**Schulz et al[30]**
Growth parameters	Not reported	Not reported	At 7 weeks: • Length on 10th–25th centile • Weight on 50th–75th centile • HC on 90th centile	At age 7–10 years: • Height 118 cm (10th centile) • Weight 34 kg (95th centile)	Normal	At 18 months: • Weight on10th centile • Height on third centile	Not reported
Chromosome analysis	Not reported	46, XY	46, XX	Not reported	46, XX	46, XX	Not reported
Metabolic work up	Not reported	Not reported	Normal blood cholesterol levels	Not reported	Not reported	• Normal plasmalogen • Normal phytanic acid • Normal very long chain fatty acid • Normal sterol panel	Not reported
Antibodies level	Not reported	Not reported	Not reported	Not reported	• Positive ANA • Positive anti-Ro • Positive anti-RNP • Positive anticardiolipin antibodies	Not done	Not done

Abbreviations: ANA, antinuclear antibody; DM, diabetes mellitus; HC, head circumference; MCTD, mixed connective tissue disease.

The similarity of phenotype in patients born to autoimmune disease-affected mothers with patients exposed to warfarin and patients with X-linked recessive brachytelephalangic type of CDP (CDPX1) suggests that the antibodies target proteins in the vitamin K pathway or in the pathways dependent on vitamin K.

Vitamin K possesses a capacity to stimulate bone formation while simultaneously suppressing bone resorption, which is not attributable to carboxylation. Studies have demonstrated that it inhibits the synthesis of prostaglandin E2, a bone resorption-inducing agent, and it inhibits the osteoclast activity by suppressing the nuclear factor κB.[10,34]

Several reports have suggested candidate targets for the antibodies based on their role in bone morphogenesis and the knowledge gained form warfarin embryopathy. The candidate proteins include osteocalcin, the matrix GLA protein (MGP) and the enzyme *ARSE*. Osteocalcin, also called bone Gla protein, and the MGP are two extracellular matrix proteins that contain glutamyl groups, which are posttranslationally modified by a vitamin K-dependent gamma glutamate carboxylase into gamma carboxyglutamic acid residues. The gamma carboxyglutamic acid residues promote the binding of calcium and phosphate ions; this shows that these extracellular matrix proteins are essential for calcium control.[35]

Although some reports suggested that inhibition of carboxylation of osteocalcin is the mechanism proposed for the stippling and the skeletal features seen in warfarin embryopathy, experimental studies found that mice lacking a functional MGP gene are viable, but exhibit increased calcification of growth plate cartilage, short stature, osteopenia and fractures.[36–38] Furthermore, treatment of rats with warfarin results in excessive mineralization of growth plate cartilage. In humans, mutation in the *MGP* gene causes Keutel syndrome, a rare autosomal recessive disorder that shares phenotypic similarities with warfarin embryopathy and CDPX.[39] All these findings were attributed to the anticalcification activities of *MGP*.[40-41]

The *ARSE* is a sulfatase enzyme located in the Golgi apparatus; its deficiency causes X-linked CDP. Decrease in the enzymatic activity level was observed with the administration of warfarin. This enzyme could well be a target for the antibodies that cross the placenta to the fetus.[42]

Although autoantibodies may be the largest risk factor for the development of CDP, it might not be the only cause to predict the development of the disease. The very low incidence of the condition in infants of mothers with autoimmune diseases and the recurrence of the condition in a male and female offspring of a mother with MCTD[30] point to the possibility of a genetic predisposition. Further studies are required to identify the maternal antibodies associated with CDP and the fetal antigen/pathway disrupted by it.

Thus, CDP should be added to the counseling regarding the fetal potential complications associated with maternal autoimmune diseases. Obstetricians/sonographers taking care of pregnant women with autoimmune conditions should be aware of this complication. The insufficient long-term follow-up data on these children interfere with our ability to provide prognostic information to the couples/mothers during the prenatal counseling.

Conclusion

CDP is associated with maternal autoimmune diseases, and stippling could be identified on prenatal ultrasound and could identify the affected fetuses. It remains a diagnosis of exclusion until more objective tests are available to confirm the association.

Disclosure

The authors report no conflicts of interest in this work.

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