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. 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. 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
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).

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. 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.

CPD is also seen in association with chromosomal abnormalities such as Turner syndrome, Down syndrome, trisomy 18 (Edwards’ syndrome) and trisomy 9 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. 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. 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 peristin. 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.

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 CPD.

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 and by Costa et al (1993), at the first meeting of the International Skeletal Dysplasia Society. 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. 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. Following the report of McCuistion et al showing that SLE-like skin changes are found in newborns to mothers with SLE, 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 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<sup>18</sup> | Mansour et al<sup>19</sup> | Elcioglu et al<sup>20</sup> | Elcioglu et al<sup>21</sup> | Austin-Ward et al<sup>22</sup> | Kelly et al<sup>23</sup> | Kozlowski et al<sup>24</sup> |
|-------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| **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 | • Hydroxychloroquine | • Aspirin | Chloroquine |
| **Mother’s antibodies** | • Positive anti-Ro and anti-La antibodies | Not reported | Not reported | Not reported | Not reported | Positive RNP | Prednisone |
| **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 | 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 | 31 cm (10th centile) | 16 cm (below fifth centile) | Not reported | 30.5 cm | 33 cm |
| **Birth length** | Not reported | 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 al15 Skeletal dysplasia meeting 1993 Chitayat et al19 | Mansour et al20 | Elcioglu et al21 | Elcioglu et al21 | Austin-Ward et al22 | Kelly et al22 | Kozlowski et al24 |
|-------------------|---------------------------------------------------------------|-----------------|-----------------|-----------------|-------------------|---------------|-------------------|
| **Pattern of stippling** | • The proximal femoral epiphyses • Both heels | • The lumbosacral spine • The proximal end of second metacarpals | • 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 | • 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 | • The right proximal humerus • Sacrum • Distal phalanges • Tarsal centers | • The tarsal regions • Spine |
| **Vertebral body defects** | Not reported | Sagittal clefts | Coronal clefts | Not reported | Not reported | | |
| **Other radiologic findings** | None | • Tiny distal phalanges • Short second metacarpals | • Short long bones (below fifth centile) • Pronounced humeral shortening • Poorly ossified skull vault | • Short long bone (below 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 | |
| **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 Erythematoviolaceous, scaly facial rash | • Small ears • Upward-slanting palpebral fissures • Midface hypoplasia • Short columella | | |
| **Skin rash** | Lupus facial rash | Not reported | Not reported | | Lupus rash over the neck, wrists, ankles and anterior thorax | Not reported | |

(Continued)
Table 1 (Continued)

| Clinical features                  | Costa et al 1993 | Mansour et al19 | Elcioglu et al21 | Elcioglu et al21 | Austin-Ward et al22 | Kelly et al23 | Kozlowski et al24 |
|------------------------------------|------------------|-----------------|------------------|------------------|-------------------|---------------|-------------------|
| Skeletal dysplasia meeting 1993    |                  |                 |                  |                  |                   |               |                   |
| Fetal chondrodysplasia punctata    |                  |                 |                  |                  |                   |               |                   |
| Musculoskeletal exam               | Not reported     | Brachydactyly   | • Symmetrical,    | • The limbs are  | Not reported       | • Generalized  | Pectus excavatum |
|                                    |                  | with drum stick | mild limb       | slightly short   |                   | hands brachydactyly |                 |
|                                    |                  | swelling        | shortening       | short            |                   | • Short first,  |                  |
|                                    |                  |                 | • Short fingers  | • Short,        |                   | second, second  |                  |
|                                    |                  |                 | and camptodactyly| malpositioned   |                   | and fourth      |                  |
|                                    |                  |                 | fingers          | fingers          |                   | proximal       |                  |
|                                    |                  |                 | • The toes       | • Underdeveloped|                   | proximal       |                  |
|                                    |                  |                 | overlapped with  | right palmar    |                   | phalanges      |                  |
|                                    |                  |                 | hypoplastic nails| creases          |                   |               |                  |
|                                    |                  |                 | on the feet      |                  |                   |               |                  |
| Developmental history              | Normal           | Normal          | Not reported     | Not reported     | Not reported      | Not reported   | Intellectual delay |
|                                    | Normal           | development at 15 months | Not reported | Not reported | Not reported | Not reported |                  |
| 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 |                  |
| 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  | Not reported      |
|                                   |                  |                 |                  |                  |                   | Positive anti-RNP |                  |

Table 1 (Continued)

|                         | Kozlowski et al24 | Shanske et al19 | Chitayat et al19 | Chitayat et al19 | Tim-aroon et al23 | Roy et al27 |
|-------------------------|-------------------|-----------------|------------------|------------------|-------------------|-------------|
| 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       | German           | Caucasian        | Thailand          | Indian Hindu |
| Consanguinity           | Not consanguine   | Not consanguine | Not consanguine  | Not consanguine  | Not consanguine   | Not consanguine |
| Maternal disease        | SLE               | SLE diagnosed postnatailly | SLE | SLE | SLE | SLE diagnosed postnatailly |
| Medications in pregnancy| • Quinine         | • Azathioprine  | • Prednisone     | • Prednisone     | • Prednisolone    | • Fraxiparin |
|                         | • Chloroquine     | • Hydroxychloroquine| • Methyldopa    | • Methyldopa     |                  |             |
|                         | • Epanutin         | • sulfate       | • Amlodipine     |                  |                  |             |

(Continued)
Table 1 (Continued)

| Mother’s antibodies | Shanske et al29 | Kozlowskiet al24 | Chitayat et al19 | Tim-aroon et al23 | Roy et al27 |
|---------------------|-----------------|------------------|------------------|------------------|------------|
| Positive ANA        | Not reported    | Not reported     | Not reported     | Not reported     | Positive ANA |
| Positive anti-RNP   |                 |                  |                  |                  |             |
| antibodies          |                 |                  |                  |                  |             |
| Positive anti-RO    |                 |                  |                  |                  |             |
| and anti-LA         |                 |                  |                  |                  |             |
| antibodies          |                 |                  |                  |                  |             |

| Pregnancy history   | Epilepsy        | UTI              | High blood pressure | Anatomy scan showed discrepancy of 4 weeks in femoral length and 2 weeks in humeral length | Not reported          |
|---------------------|-----------------|------------------|---------------------|------------------------------------------------------------------------------------------------|----------------------|
| Not reported        |                  |                  |                     |                                                                                                 | Uneventful            |
|                     |                  |                  |                     |                                                                                                 | No exposure to infection |

| Birth weight        | 3080 g          | 2176 (25th centile) | 127 g               | Not reported                                                                                      | 2970 g (50th centile) |
|---------------------|-----------------|--------------------|---------------------|------------------------------------------------------------------------------------------------|----------------------|
| Birth HC            | 38 cm           | 33 cm (50th centile)| Not reported        | Not reported                                                                                      | 35 cm (75th centile) |
| Birth length        | 34 cm           | 42 cm (below 10th centile) | Not reported        | Not reported                                                                                      | 45 cm (10th centile) |

| Birth weight        | 2176 (25th centile) | 127 g               | Not reported        | Not reported                                                                                      | 2970 g (50th centile) |
| Birth HC            | 33 cm (50th centile)| Not reported        | Not reported        | Not reported                                                                                      | 35 cm (75th centile) |
| Birth length        | 42 cm (below 10th centile) | Not reported | Not reported | Not reported                                                                                      | 45 cm (10th centile) |

| Pattern of stippling| Stippling at: | Vertebral bodies | Carpal bones and phalanges | The shoulders and hips | The elbows and knees | All of the tarsal bones and phalanges | Multiple stippled epiphyses |
|---------------------|----------------|------------------|---------------------------|------------------------|----------------------|--------------------------------------|---------------------------|
| Stippling at:       | Epiphyses of the knees | Vertebral bodies | Carpal bones and phalanges | The shoulders and hips | The elbows and knees | All of the tarsal bones and phalanges | Multiple stippled epiphyses |
|                     | Tarsal regions | Vertebral column | Sacral ossification centers |                        |                      |                                      |                           |

| Vertebral body defects | Hypoplasia and dysplasia of vertebral bodies | Decreased ossification | Small vertebrae with vertical clefts | Nor reported | Not reported |
|------------------------|---------------------------------------------|------------------------|--------------------------------------|--------------|--------------|
|                       |                                             |                        |                                      |              |              |
|                       |                                             |                        |                                      |              |              |

| Pattern of stippling | Vertebral bodies | Carpal bones and phalanges | The shoulders and hips | The elbows and knees | All of the tarsal bones and phalanges | Multiple stippled epiphyses |
|---------------------|------------------|---------------------------|------------------------|----------------------|--------------------------------------|---------------------------|
|                     | Epiphyses of the knees | Vertebral bodies | Carpal bones and phalanges | The shoulders and hips | The elbows and knees | All of the tarsal bones and phalanges | Multiple stippled epiphyses |
|                     | Tarsal regions | Vertebral column | Sacral ossification centers |                        |                      |                                      |                           |

| Vertebral body defects | Hypoplasia and dysplasia of vertebral bodies | Decreased ossification | Small vertebrae with vertical clefts | Nor reported | Not reported |
|------------------------|---------------------------------------------|------------------------|--------------------------------------|--------------|--------------|
|                       |                                             |                        |                                      |              |              |
|                       |                                             |                        |                                      |              |              |

Table 1 (Continued)
Fetal chondrodysplasia punctata

Roy et al.\textsuperscript{26} Tim-aroon et al.\textsuperscript{26} Chitayat et al.\textsuperscript{19} Chitayat et al.\textsuperscript{19} Shanske et al.\textsuperscript{25} Kozlowski et al.\textsuperscript{24}

- Rhizomelic shortening of extremities
- Metaphyseal flaring in humerus and femur

**Other radiologic findings**

- Asymmetric femur length
- 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

- Increased density at the bases of the third distal phalanges
- Rhizomelic shortening of extremities

**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

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*Table 1 (Continued)*
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)

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)

Not reported Height and weight below third centile

Chromosomal analysis
• Normal plasmalogen
• Normal VLCFA
• Normal phytanic acid

Not reported Normal total plasma lipids

Not reported Normal plasmalogen level

Not done Metabolic work up

Positive anti-Ro and anti-La antibodies
Positive anti-RNP antibodies
Positive ANA antibodies

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, but there is still no consensus regarding the disease definitions, classification, criteria or the relationship with other autoimmune conditions. 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. 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.

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 reported the first and the only case of a child with CDP 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;21,23 however, peroxisomal disorders were ruled out biochemically in one of the three cases only.21 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 developmental 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 Toriello32 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 CDP, 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 |
|--------------------------------------------------|-------------------------------------------------|-------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Gestational age** | 36 weeks | 34 weeks | 32 weeks | 32 weeks | 34 weeks | 37 weeks |
| **Gender** | Male | Male | Female | Female | Female | Male |
| **Paternal ethnic origin** | Caucasian | Liberian | Not reported | African-American | Not reported | Not reported |
| **Consanguinity** | Not consanguineous | Not consanguineous | Not consanguineous | Not consanguineous | Not consanguineous | Not consanguineous |
| **Maternal disease** | MCTD | MCTD | MCTD | MCTD | MCTD | MCTD |
| **Medications in pregnancy** | Prednisone | Amiodipine | Fexofenadine hydrochloride | Acetazolamide | Methylprednisolone | Not reported |
| **Mother’s antibodies** | Positive ANA | Positive ANA | Positive ANA | Positive ANA | Positive ANA | Positive ANA |
| **Pregnancy history** | Skin rash and arthralgia in the third trimester | Maternal flare up at 22 weeks’ gestation | A fetal ultrasound at 20 weeks’ gestation showed abnormalities | Not reported | Not reported | Not reported |
| **Birth weight** | 2080 g (third centile) | 584 g | Not reported | 1700 g (50th centile) | 1.32 kg (10th centile) | 1980 g (10th–50th centile) |
| **Birth HC** | Not reported | Not reported | Not reported | 30 cm (25th centile) | 29.5 cm (25th centile) | 33 cm (50th–90th centile) |
| **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) |
| **Pattern of stippling** | Stippling at: Proximal humeri, Proximal femoral heads, Vertebral bodies | Stippling: Uninhibited, Cervical and thoracic vertebrae, Proximal femurs and Taluses | Stippling at: Feet, Hips, Vertebral body, Greater trochanter bilaterally, The base of distal phalanges | Stippling at: Tarsal bones, Sacrum, Vertebral body, Stepped metacarpals and calcanei bones, Stepped 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 femora |

(Continued)
| Costa et al\(^9\) Skeletal dysplasia meeting 1993 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\(^{19}\) | Schulz et al\(^{19}\) |
|---|---|---|---|---|---|
| **Vertebral body defects** | Coronal clefs | Not reported | Not reported | Vertical clefs of T3, T6 and T8 vertebral bodies | Not reported | Knee dysplasia | Asymmetric vertebrae | Clefts at multiple levels | Platyspondyly | Clefts at multiple levels |
| Other radiologic findings | Not reported | Hypoplasia of the distal phalanges | Hypoplasia of the distal phalanges | Short first, second and fourth distal phalanx bilaterally | Not reported | Short second proximal phalanx bilaterally | Short proximal and middle phalanges of the second digits |
| Facial features | Upturned nares | Nasal hypoplasia | Large anterior and posterior fontanelles | Nasal hypoplasia | Prominent eyes | Flat nasal bridge | Midface hypoplasia | Flat nasal bridge |
| | Retrognathia | Malar hypoplasia | Flattened nasal bridge | Large anterior fontanelle | Displaced inner canthi | Flat nasal bridge | | |
| | Long philtrum | | Short nose | Long philtrum | Nasal hypoplasia | Nasal hypoplasia | | |
| | Hyoplastic nose | | | Small ears | Small unilateral cortical cataract | | | |
| **Skin rash** | Not reported | Not reported | Not reported | None | Not reported | Not reported | | |
| **Musculoskeletal exam** | Narrow chest | Radially deviated index fingers | Radial deviation of the distal phalanges | Hypoplasia of the distal phalanges | 4 limbs rhizomelia | Bowed humerus | Broad phalanges | Short second metacarpals and first metatarsals | Pectus excavatum |
| | Hip contractures | Short proximal phalanges | Bilateral shortened first toes | Clinodactyly of the second fingers | | | | |
| | Hyperextended left knee | | Prominent thorax | Hypoplastic finger and toenails | | | | |
| | Overlapping fingers | | Prominent thorax | Mild rhizomelic shortening of the humeri | | | | |
| | Club feet | | | Normal | | | | |
| **Developmental history** | Developmental delay | Not reported | Not reported | Normal | Normal development | Normal motor development | Normal development | | |

(Continued)
### Table 2 (Continued)

| Costa et al16 | Chitayat et al19 | Chitayat et al19 | Curry et al David Smith meeting 199314 | Curry et al David Smith meeting 199314 | Schulz et al30 | Schulz et al30 |
|--------------|-----------------|-----------------|---------------------------------------|---------------------------------------|---------------|---------------|
| Growth parameters | Not reported | Not reported | At 7 weeks: | At age 7–10 years: | Normal | At 18 months: | Not reported |
|                        |                |                | • Length on 10th–25th centile | • Height 118 cm (10th centile) |                | • Weight on 10th centile |               |
|                        |                |                | • Weight on 50th–75th centile | • Weight 34 kg (95th centile) |                | • Height on third centile |               |
|                        |                |                | • HC on 90th centile |                  |                |                           |               |
| 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 |                           |               |
| Antibodies level      | Not reported | Not reported | Not reported | Not reported |                            | • Positive ANA | Not done |
|                        |                |                |                        |                        | • Positive anti-Ro |                        |               |
|                        |                |                |                        |                        | • Positive anti-RNP |                        |               |
|                        |                |                |                        |                        | • Positive anticardiolipin antibodies |                        |               |

**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 from 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 calcification activities of MGP.39

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.40

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 MCTD30 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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