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Severe nasomaxillary hypoplasia (Binder phenotype) on prenatal US/MRI: an important marker for the prenatal diagnosis of chondrodysplasia punctata

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Abstract

Background—Chondrodysplasia punctata is a skeletal dysplasia caused by a diverse spectrum of etiologies, with outcomes ranging from antenatal demise to a normal life span. Prenatal detection can be challenging.

Objective—To review a series of cases of chondrodysplasia punctata associated with nasomaxillary hypoplasia, known as the Binder phenotype, and to highlight prenatal ultrasound and MRI findings, as well as postnatal MRI and radiographic findings.

Materials and methods—We retrospectively reviewed ultrasound, MRI and radiographic imaging findings in postnatally confirmed cases of chondrodysplasia punctata from 2001 to 2017. We analyzed prenatal findings and correlated them with maternal history, postnatal imaging, phenotype, genetics and outcome.

Results—We identified eight cases, all with prenatal US and six of eight with prenatal MRI between 18 weeks and 32 weeks of gestational age. Reasons for referral included midface hypoplasia in four cases; family history in one case; intrauterine growth restriction in one case; short long-bones, intrauterine growth restriction and multicystic kidney in one case; and multiple anomalies in one case. In six cases, postnatal radiographs were performed. In four cases, postnatal spine MRI imaging was performed. The diagnosis of chondrodysplasia punctata was suggested in prenatal reports in six of eight fetuses. Seven of eight fetuses had Binder phenotype with severe nasomaxillary hypoplasia. Limb length was mildly symmetrically short in four of eight cases and normal in four of eight fetuses. Two of eight fetuses had epiphyseal stippling identified prenatally by US; this was present postnatally in six neonates on radiographs. Hand and foot abnormalities of brachytelephalangy were not detected on the prenatal US or MRI but were present in six of eight

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Compliance with ethical standards

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fetuses on postnatal radiographs or physical exam. Four of eight fetuses had prenatal spine irregularity on US from subtle stippling. Six of eight had spine stippling on postnatal radiographs. One fetus had cervicothoracic kyphosis on prenatal US and MRI, and this was postnatally present in one additional neonate. One case had prenatally suspected C1 spinal stenosis with possible cord compression, and this was confirmed postnatally by MRI. There was a maternal history of systemic lupus erythematosus in two and hyperemesis gravidarum in one. Outcomes included one termination and seven survivors.

Conclusion—Chondrodysplasia punctata can be identified prenatally but findings are often subtle. The diagnosis should be considered when a fetus presents with a hypoplastic midface known as the Binder phenotype. Maternal history of lupus, or other autoimmune diseases or hyperemesis gravidarum can help support the diagnosis.

Keywords

Chondrodysplasia punctata; Fetus; Magnetic resonance imaging; Prenatal; Skeletal dysplasia; Ultrasound

Introduction

Chondrodysplasia punctata is a skeletal dysplasia with classic radiologic findings of multiple small punctate calcifications in multiple epiphyses. The clinical features identified in chondrodysplasia punctata are caused by a diverse spectrum of etiologies, syndromes, prenatal exposures and genetics resulting in varied outcomes. A relatively new comprehensive classification for chondrodysplasia punctata includes disorders of peroxisomal and lysosomal storage disorders, cholesterol biosynthesis disorders, chromosomal abnormalities and disrupted vitamin K metabolism with deficiency of the arylsulfatase E enzyme (ARSE) (Table 1) [1, 2]. Many of these disorders can be detected by amniocentesis if the diagnosis of chondrodysplasia punctata is suspected prenatally [2]. The association with autoimmune disorders such as systemic lupus erythematosus (SLE), mixed connective tissue disorders, and scleroderma was first reported approximately 25 years ago, but has not been described in the radiologic literature [3, 4].

Outcomes of infants with chondrodysplasia punctata have a wide spectrum. At the severe end of the spectrum there can be antenatal demise, postnatal lethality within the first few weeks of age, or sublethal sequelae with demise in the first 10 years of age [OMIM #302950, 215100, and 302960]. Severe developmental delays, growth failure, seizures and cataracts can occur. Milder forms, however, occur with a normal life span. The prenatal imaging diagnosis can be challenging because of the variable etiologies and prenatal findings [2, 5]. The rhizomelic form with severe proximal limb shortening and the brachytelephalangic type of chondrodysplasia punctata, with characteristic shortening of the distal phalanges, have been diagnosed prenatally. Recently, the Binder phenotype with severe hypoplasia of the nasal pyramid and midface has been associated with chondrodysplasia punctata [6]. The Binder type of nasomaxillary dysplasia consists of underdevelopment (hypoplasia) of the central segment of the face, especially of the nose and upper jaw (nasal maxillary region). This results in a distinctly abnormal short, flat nose with flattened nasal bridge, abnormally positioned nasal bone (more vertical in position than

normal) and an overall flattened midface known as an arhinoid face. The nasal septum is abnormally short and the nostrils have a half-moon, comma-like or triangular shape. Frontal sinuses are frequently absent. The Binder phenotype occurs in all the varying diagnoses described in Table 1. It is suspected that some cases of the Binder phenotype that are or were previously thought to be isolated, with some cases undiagnosed until the teenage years, are in fact cases of undiagnosed milder forms of chondrodysplasia punctata. Because there is loss of the epiphyseal stippling over time, the diagnosis is never considered. In some cases of chondrodysplasia punctata associated with maternal autoimmune disease such as SLE, Binder phenotype has been detected either pre- or postnatally [1, 3, 4].

The purpose of our study was to review a series of chondrodysplasia punctata cases with prenatal imaging to highlight findings by prenatal ultrasound and MRI, particularly nasomaxillary hypoplasia (Binder phenotype), because it has become evident that Binder phenotype might be highly associated with chondrodysplasia punctata. An awareness of the association might assist in the challenging prenatal diagnosis of chondrodysplasia punctata in view of the multiple etiologies and outcomes. In addition, nasomaxillary hypoplasia might be associated with significant postnatal distress, and prenatal imaging could help in delivery management.

Materials and methods

We conducted a retrospective review of prenatal ultrasound (US) and MRI imaging performed at our referral fetal center with postnatally proven chondrodysplasia punctata from 2001 to 2017. We identified cases from the department radiology report search program (Montage Search and Analytics; Montage Healthcare Solutions, Philadelphia, PA) by searching prenatal and postnatal radiology reports. Studies were performed by three pediatric radiologists with extensive fetal imaging expertise (E.I.R., 9 years, A.R.B., 16 years, D.I.B., 26 years). Author A.R.B. performed a retrospective review of reports and images.

Prenatal US examinations were performed with a Voluson E10 or a LOGIQ E9 (GE Healthcare Ultrasound, Milwaukee, WI) or an IU22 (Philips Healthcare, Bothell, WA) unit. MRI was performed on a Discovery 450 1.5-T or Optima 450W 1.5-T unit (GE Healthcare, Milwaukee, WI); MRI sequences included a combination of 3- to 4-mm half-Fourier single-shot fast spin echo with T2-weighting (T2-W SSFSE) in three planes, steady-state free precession (SSFP), and T1-weighted fast spoiled gradient echo breath-hold (T1-W GRE; coronal and/or sagittal planes). Prenatal MRI studies were performed at our fetal center on the same day as the US examinations.

We reviewed images for features of chondrodysplasia punctata including abnormal fetal profile, abnormal limb length, spinal kyphosis or stenosis, stippled epiphyses, irregular/stippled spine, and abnormalities of the hands and feet. We measured frontonasal angles. We analyzed reports to determine which features of chondrodysplasia punctata were detected prospectively. We also correlated maternal history, postnatal imaging, phenotype and genetics, and outcome with prenatal findings when available.

The study complied with the Health Insurance Portability and Accountability Act and was approved by the institutional review board, which waived patient informed consent for the purposes of this study.

Results

We identified eight cases of chondrodysplasia punctata with postnatal confirmation. The most common referral was for midface hypoplasia, possible arhinia or absent, short or flat nasal bone in four cases (cases 1, 2, 3, 7). Other reasons for referral included intrauterine growth restriction (case 4), short long-bones with unilateral multicystic kidney and intrauterine growth restriction (case 6), sibling with chondrodysplasia punctata (case 5) and multiple anomalies including a cystic hygroma, Dandy-Walker malformation and ventricular septal defect (case 8). In two cases, pregnancy-associated plasma protein A level was low.

All eight cases had prenatal US at our referral fetal center, five with 3-D volumes; six of eight also had fetal MRI. Case 5 was referred for a screening US only because of having a sibling with chondrodysplasia punctata. Case 6 was referred for US to further assess renal anomalies. One case had three sonograms and one case had two sonograms at our center for follow-up assessment.

Six had postnatal or autopsy radiographs available for review; four of six also had postnatal MRI spine imaging and three of six also had CT spine imaging to further assess cervical kyphosis, possible stenosis and poor mineralization of the cervical vertebrae. Gestational ages at the time of imaging at our center ranged from 18 weeks 3 days to 32 weeks. There were four males and four females.

Amniotic fluid volumes were normal in five, high normal in two and mildly increased in one case with amniotic fluid index of 25.

The diagnosis of chondrodysplasia punctata was prospectively raised in six of eight cases. The diagnosis was not suggested in case 6, without the associated Binder phenotype, and in case 2, one of our earlier cases with Binder phenotype.

Final diagnoses included six brachytelephalangi chondrodysplasia punctata cases, two cases with abnormal arylsulfatase E enzyme gene sequencing, and one case with unknown etiology (Table 2). Of the six with brachytelephalangi chondrodysplasia punctata, two mothers had autoimmune disease (case 1 with SLE, case 6 with SLE, Sjogren syndrome and hypothyroidism), while one had hyperemesis gravidarum with negative arylsulfatase E enzyme gene sequencing and no deletion/duplication detected (case 7). In Case 8, the pregnancy was terminated with autopsy radiographs confirming chondrodysplasia punctata, normal karyotype and microarray, and normal whole exome sequencing.

Prenatal facial findings

The most striking presentation prenatally was nasomaxillary hypoplasia (Binder phenotype) in seven of eight cases (tables 2 and 3). This was well seen by US and by MRI when performed. Findings were noted both on retrospective and prospective reviews with small verticalized nasal bone (flattened with increased frontonasal angle) and with flat or concave

facial profile (Figs. 1, 2, 3 and 4). Frontonasal angles measured retrospectively by US were increased, with verticalized nasal bones in seven of eight ranging from 135–162° (normal value mean 126°±7° from 14 weeks to 39 weeks of gestational age) [7, 8]. Of the seven fetuses with nasomaxillary hypoplasia, fluid-filled nostrils were identified in five of seven by US, excluding arhinia (Fig. 5).

Three-dimensional analysis of the face was helpful in three fetuses, confirming the presence of nostrils and contributing to an increase in parental understanding of the facial anomaly.

All six fetuses with an MRI demonstrated a concave facial profile from retraction of the maxilla. Five of six fetuses showed lack of fluid in the anterior nasopharynx (Figs. 2, 3 and 4). The MRI documented small fluid-filled nostrils in 4 of 6 fetuses on coronal images of the face, ruling out arhinia (Fig. 5). Thin 2-mm coronal images were most useful for nostril evaluation (Fig. 5).

MRI was superior to US in demonstrating a square upper jaw alveolar ridge (five fetuses on MRI versus two fetuses on US; Fig. 6).

Binder phenotype was predictive of a component of respiratory distress, present in five of six live cases with nasomaxillary hypoplasia and absent in the case with a normal profile.

Prenatal airway and trachea

The posterior nasopharynx, hypopharynx, trachea and lungs appeared normal in the six fetuses with prenatal MRI.

Long-bone length and contour

The fetus in case 6, with a normal midface had mildly shortened limbs without bowing or fractures, was at 5% on fetal biometry charts (Table 4). The maternal history of SLE, hypothyroidism and Sjogren antibodies was the clue to this fetus having chondrodysplasia punctata.

Among the seven fetuses with midface hypoplasia, bone length was normal in four fetuses and mildly symmetrically short in three fetuses, all of whom were in the 5th percentile on fetal biometry charts.

Stippled epiphyses

Two fetuses had epiphyseal stippling identified prenatally by US, one of which did not have postnatal radiographs for confirmation (Table 4). In six cases, postnatal/autopsy radiographs demonstrated epiphyseal stippling most conspicuous in the hands and feet, with either minimal or no stippling of long-bone epiphyses (Figs. 7 and 8). MRI was not helpful in identifying stippling.

Hands and feet

Abnormalities of the hands and feet were not appreciated on the prenatal US/MRI either prospectively or retrospectively (Table 4). Four neonates were diagnosed as brachytelephalangic chondrodysplasia punctata by postnatal radiographs that showed small

triangular distal phalanges of fingers and toes with scattered hypoplastic/broad phalanges, metacarpals and metatarsals (Fig. 8). In case 5, the neonate was diagnosed clinically by physical exam by the geneticist recognizing terminal phalangeal hypoplasia with short broad nails.

Spine

Four fetuses (cases 2, 3, 7 and 8) were prospectively thought to have spine abnormalities, with irregularity, narrowing and possible segmentation anomalies on the prenatal US (cases 2, 3, 7, 8) and cervical narrowing in case 7 on MRI (Table 5, Fig. 9). Postnatal radiographs indicated that these changes were actually a manifestation of spinal stippling of the vertebral bodies, posterior elements, costovertebral junctions and disc spaces, most commonly at the levels of the cervical and sacral spine. Two additional fetuses without prenatal detection of spine stippling had stippling noted postnatally in the cervical and sacral regions (cases 1 and 6).

Cervicothoracic kyphosis was identified prenatally in one case (case 2) by US and MRI and confirmed postnatally on radiographs, postnatal MRI and CT (Fig. 9). Cervicothoracic kyphosis was not identified prenatally in case 1 but was observed on postnatal radiographs and postnatal MRI.

Cervical kyphosis was detected prenatally in case 7 and confirmed postnatally on MRI and CT. Cervical stenosis at the C1 level was suggested prenatally and cervical stenosis with cord compression with cord atrophy was confirmed on the postnatal MRI and CT at the C1-C2 level.

Abnormal vertebral development of the cervical spine with poorly ossified vertebral bodies was a feature in five of six neonates with postnatal radiographs also demonstrating cervical spine stippling. Retrospective assessment of the cervical spine on the prenatal MRI suggests this finding might be appreciated with a lack of dark and light signal of the alternating vertebral bodies and disc spaces (Fig. 9).

Clinical outcome

Seven infants survived, four with mild respiratory distress at birth and one with severe distress requiring intubation. Four of the five infants with lack of fluid in the anterior nasopharynx prenatally had respiratory distress at birth, with two requiring nasal dilatation for stenosis of the nostrils. Two infants had unilateral profound hearing loss, and four had feeding difficulties (tables 2 and 3). There was one termination at 20 weeks of gestation.

Discussion

Chondrodysplasia punctata is a complex skeletal dysplasia with diverse underlying etiologies, variable forms of genetic inheritance, including X-linked recessive, X-linked dominant and autosomal recessive, and variable degrees of severity and outcome (Table 1). Prenatal detection of chondrodysplasia punctata has been described but remains challenging, with prenatal counseling being problematic because of the difficulty in confirming the diagnosis and the wide spectrum of outcomes.

The distinctive facial appearance of maxillary dysostosis consisting of severe hypoplasia of the nasal pyramid and midface can be associated with chondrodysplasia punctata, providing an important clue to the diagnosis [6]. This facial appearance was described by Binder in 1962 and was initially considered a syndrome [9, 10]. Quarrell et al. [11] in 1990 suggested that the use of the term syndrome was inappropriate and recommended the term Binder phenotype. The Binder phenotype is manifest by severe midface hypoplasia resulting in a flat profile with absent or decreased nasal bridge, a verticalized nasal bone with an increased or absent frontonasal angle, and a flattened mandibular arch resulting in a square alveolar ridge [6, 9]. Postnatally, the nose is hypoplastic with flattening of the alae and nasal tip. On postnatal radiographs, there is aplasia or hypoplasia of the nasal spine with localized maxillary hypoplasia. The face can appear arhinencephaloid but the brain is normal and sense of smell is normal [12]. The flattening of the profile improves over time, becoming less noticeable by 5–8 months of age [2]. The distinctive flattening of the nose distinguishes the Binder phenotype from other causes of maxillary hypoplasia such as the acrocephalosyndactyly syndromes, which have other associated features such as shallow orbits, ocular proptosis and craniosynostosis.

Since Quarrell's description, several case reports have described prenatal 2-D and 3-D US and MRI findings, as early as 21 weeks of gestation [6, 9, 13–16]. Levailant et al. [6] in 2009 reported a series of eight fetuses with Binder profile detected with ultrasonography. Etiologies included fetal warfarin syndrome, infantile sialic acid storage, probable Keutel syndrome and five unclassifiable types of chondrodysplasia punctata. In 2015, a case of Binder phenotype was detected at 14 weeks of gestation secondary to vitamin K deficiency from hyperemesis [15]. Our case series lends further support to a strong association between nasomaxillary hypoplasia (Binder phenotype) and chondrodysplasia punctata, with the Binder phenotype present prenatally in seven of our eight cases. Our series in conjunction with the prior literature suggests that the Binder phenotype can be present in most if not all of the varying etiologies associated with chondrodysplasia punctata.

The distinctive facial phenotype is easily recognizable on prenatal MRI as well as on US. Cases 1 and 2 were so severe that arhinia was in the differential diagnosis. MRI was useful in identifying the nostrils and demonstrating lack of fluid in the anterior nasopharynx and a square alveolar ridge. Our experience led us to more strongly consider the likely diagnosis of chondrodysplasia punctata in our most recent cases, none of which had skeletal manifestations such as shortening to consider chondrodysplasia punctata.

Recognition of the association of the Binder phenotype with chondrodysplasia punctata is particularly useful because other chondrodysplasia features might be missed by US and MRI. While the rhizomelic form of chondrodysplasia punctata has features of severe long-bone shortening and metaphyseal flaring, other forms of chondrodysplasia punctata have normal length and configuration [5]. The stippling of the epiphyses can be subtle on US and not seen on MRI. While hand and foot findings are striking postnatally, they are easily missed prenatally on US and MRI. An awareness of the timing of the appearance of the normal ultrasound prenatal ossification centers can help detect abnormal stippling (Table 6) [5, 17]. In the future, echoplanar imaging, which shows hyperintense cartilaginous epiphyses, might improve detection of stippling on MRI.

Stippling of the vertebrae can also be difficult to recognize prenatally. On US it can mimic a segmentation anomaly or a stenosis and is not well seen on MRI. Incomplete ossification of the cervical spine can also result in a pseudo or true appearance of cervical stenosis. True cervical spine stenosis with cervical cord compression and extensive spinal anomalies including non-ossification of the vertebral bodies of the cervical spine has been reported and C1-C2 cervical stenosis was seen in one of our cases on MRI at 24 weeks [1, 18]. Specifically looking for vertebral stippling on US when alert to the Binder phenotype might increase prenatal detection. Prenatal 3-D US of the spine and prenatal high-resolution CT might assist in diagnosis [19].

Cervicothoracic or cervical kyphosis can be present in chondrodysplasia punctata, as was identified prenatally on both US and MRI in cases 2 and 7 and postnatally in three cases. This distinctive feature might be a sequela of the extremely poor mineralization of the cervical spine.

The brachytelephalangic type of chondrodysplasia punctata (X-linked recessive or sporadic from de novo mutation) has classic findings in the hands and feet consisting of small triangular distal phalanges and scattered hypoplastic/ broad phalanges, metacarpals and metatarsals. These findings are difficult to detect prenatally although hypoplasia of the distal phalanges has been reported at 30 weeks of gestation in a Binder phenotype fetus [2]. In another case with the Binder phenotype and epiphyseal stippling at 30 weeks of gestation, triangular hypoplastic tufts were detected [19]. A concerted search for these findings might result in a greater detection rate. The brachytelephalangic type of chondrodysplasia punctata has an overall better prognosis, which might assist in prenatal counseling, if detected [19].

An interesting more recent association of chondrodysplasia punctata with maternal disorders such as autoimmune disease and hyperemesis, which disrupts vitamin K metabolism, can also provide important clues to the diagnosis. Two of our six cases with the brachytelephalangic type of chondrodysplasia punctata were offspring of mothers with autoimmune disease, or specifically SLE. Chitayat et al. [3] reported eight cases with maternal SLE associated with chondrodysplasia punctata, only one of which was suspected prenatally. Nasal hypoplasia, while present, was missed prenatally in all eight infants [3]. Two cases had intrauterine demise, one died at 6 months and five survived. Of the five survivors, respiratory symptoms were reported in three, including respiratory distress syndrome in one and episodes of apnea in two. Four were relatively well (two with short stature), but a 9-year-old developed autoimmune and neuropsychiatric disorders and was found to have a unilateral cataract and unilateral sensorineural hearing loss [3, 4].

The association of chondrodysplasia punctata with maternal disrupted vitamin K metabolism from hyperemesis is significant because the potential for preventing, decreasing or reversing the severity of the Binder phenotype with vitamin K supplementation has been raised [15].

Outcomes with chondrodysplasia punctata are variable, depending on the underlying etiology. Even in the milder cases with the brachytelephalangic form, potential medical complications such as sleep apnea, mixed conductive and sensorineural hearing loss, and cervical spinal stenosis/instability and feeding difficulties occur [16]. Difficulty in newborn

ventilation can also be caused by airway compression from laryngeal calcifications or by central hypoventilation from spine entrapment/cervical stenosis [2]. Respiratory distress can be mild or severe, even with patent nares, patent trachea and normal lungs, and can require tracheostomy [16]. One group of authors suggested an ear, nose and throat otolaryngologist at the delivery room might be useful to support airway control [16]. No support was needed in our cases.

Conclusion

Chondrodysplasia punctata results from multiple diverse etiologies and the associations with maternal SLE/mixed connective tissue disorders or hyperemesis can be important clues to the diagnosis. The outcome is variable, ranging from lethal, sublethal or mild postnatal difficulties depending on the cause of the chondrodysplasia punctata and associated cervical stenosis and spinal compression. Prenatal findings can be subtle, with normal-length long bones or long bones that are mildly shortened. Stippling and hand and feet anomalies can be difficult to recognize. Hypoplastic midface is an important clue in considering chondrodysplasia punctata, spurring the search for additional US and MRI findings as well as assessment of maternal risk factors that could help confirm the diagnosis.

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Fig. 1. Normal frontonasal angle and profile in a fetus at 28 weeks 6 days of gestational age. The angle is determined by the intersection of a line drawn from the upper point of the forehead to the nasal bone and a line drawn along the nasal bone to the nasal tip

Fig. 2.

Imaging in a 23-week fetus referred for possible arhinia, case 2. **a** Sagittal US image of the fetal profile shows a flat maxilla with verticalized nasal bone (*arrow*). **b** Sagittal T2-W single-shot fast spin-echo MRI image shows flattened midface with a concave appearance (*long arrow*) and lack of fluid in the anterior nasopharynx (*short arrow*). **c** Postnatal sagittal view of the skull confirms the presence of midface hypoplasia with a verticalized nasal bone (*arrow*). **d** Clinical photograph of the infant at 8 months of age shows flattened midface

Fig. 3. Normal 32-week fetus. Axial T2-W single-shot fast spin-echo MRI shows completely fluid-filled anterior nasopharynx (*arrows*)

Fig. 4. Flattened profile with midface hypoplasia, case 8 imaged at 18 weeks 3 days of gestation. **a** Sagittal US image shows flat nose and midface. **b** Sagittal T2-W single-shot fast spin-echo MRI shows flattened nose and midface. Note the Dandy-Walker malformation in the posterior fossa. **c** Autopsy image at 20 weeks 1 day of gestation shows corresponding flattened profile with midface hypoplasia

Fig. 5. Nostril evaluation in a fetus at 30 weeks 3 days of gestation, case 3. **a** Coronal US image shows fluid-filled nostrils (*arrows*). Nostrils appear wide-spaced in this case because of upturned nostrils with short columella. **b** Coronal MR T2-W single-shot fast spin-echo image shows fluid-filled nostrils (*arrows*) in the same fetus

Fig. 6.

Alveolar ridge imaging in a fetus at 24 weeks 2 days of gestation, referred for hypoplastic nose, case 7. **a** Axial US image of the alveolar ridge suggests squared appearance (*arrows*). **b** Axial T2-W single-shot fast spin-echo (SSFSE) MR image of the alveolar ridge confirms squared appearance (*arrows*). **c** Sagittal US image shows hypoplastic nose with verticalized nasal bone (*arrow*). **d** Sagittal T2-W SSFSE MR image shows Binder phenotype with flattened midface (*black arrow*) and lack of fluid in the anterior nasopharynx, with patent

trachea (*white arrow*). **e** Axial T2-W SSFSE MR image shows a normal horseshoe configuration alveolar ridge in a 28-week fetus (*arrows*) for comparison

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Fig. 7.

Prenatal long bone and ankle ultrasound images at 23 weeks of gestation with postnatal comparison radiographs (case 2). **a** Prenatal longitudinal US image shows premature ossification in the proximal right femur (*arrow*). **b** Postnatal anteroposterior (AP) radiographic image of the pelvis shows punctate ossification in both proximal femora (*white arrow* corresponds to prenatal image **a**). Punctate ossifications are also noted in the sacrum (*black arrow*). **c** Prenatal coronal US image shows stippling in the ankle (*arrow*). **d** Postnatal AP radiograph shows stippling in the ankle (*arrows*)

Fig. 8.

Postnatal stippling in case 2. **a, b** Radiographs of the hand (**a**) and foot (**b**) show small triangular distal phalanges of fingers and toes (*short white arrow*), scattered hypoplastic/broad phalanges and metacarpals and metatarsals (*long white arrows*) and stippling (*black arrows*). These findings were not well seen prenatally

Fig. 9.

Spinal findings in case 2 at 23 weeks of gestation. **a** Sagittal US image shows accentuated cervicothoracic kyphosis (*short arrow*) and ill-defined cervical vertebrae (*long arrow*) that raised the question of segmentation anomalies. **b** Sagittal prenatal MR fast imaging employing steady-state acquisition (FIESTA) image confirms cervicothoracic kyphosis and poorly visualized cervical vertebral bodies (*arrow*). Note the alternating dark and light signal pattern in the rest of the spine. **c** Postnatal cervical radiograph confirms cervicothoracic kyphosis and flattened, poorly ossified cervical vertebrae with punctate calcifications. **d** Sagittal T1-W postnatal MR image confirms the cervicothoracic kyphosis and poorly ossified vertebral bodies in both the cervical (*long arrow*) and sacral spine (*short arrow*). **e** Axial US of the fetal thoracic spine shows extra ossification anterior to the three segments of the thoracic spinal arch (*arrow*). **f** Retrospective analysis of the sagittal US image of the fetal sacral spine shows extra bony foci consistent with stippling. **g** Postnatal spine lateral radiograph shows stippling anterior to the lumbar vertebral bodies (*short arrows*) and in the sacrum (*long arrow*). The sacrum is also poorly mineralized

Table 1

Diverse etiologies of chondrodysplasia punctata

Peroxisomal and lysosomal storage diseases	Cholesterol biosynthesis disorders	Chromosomal abnormalities	Disrupted vitamin K metabolism-arylsulfatase E enzyme
Rhizomelic chondrodysplasia punctata, autosomal recessive	<i>CPDX2</i> (Conradi-Hünermann), X-linked dominant	Trisomy 13	Autoimmune disease-SLE, MCTD, scleroderma
Zellweger syndrome	Greenberg dysplasia	Trisomy 21	Exposure-warfarin, phenytoin, alcohol, rubella
GM1 gangliosidosis, I cell, galactosialidosis	Smith-Lemli-Opitz	Turner syndrome	Maternal Vitamin K deficiency-malabsorption, celiac disease, hyperemesis
			Brachytelephalangic <i>CDPX1</i> -X-linked recessive, Keutel syndrome

GM1 monosialotetrahexosylganglioside, *MCTD* mixed connective tissue disease, *SLE* systemic lupus erythematosus

Table 2

Case summary

Case	Gestational age at first referral	Imaging	Gender	Maternal history	Prenatal binder phenotype	Final type of chondrodysplasia punctata	Type of prenatal imaging		Other anomalies	Clinical outcome
							US	MR		
1	21 W 5D		F	SLE	+	Brachytelephalangic	+	+	–	Survival, feeding difficulties
2	23 W		F	None pertinent	+	Brachytelephalangic, <i>ARSE</i> gene without a pathological variant	+ 3-D	+	–	Survival
3	30 W 3D		M	None pertinent	+	Likely brachytelephalangic, <i>ARSE</i> gene with a pathological variant	+	+	Small thorax	Survival, slow weight gain, unilateral hearing loss
4	19 W 1D		F	Low PAPP-A, IUGR, prior lymphoma	+	<i>ARSE</i> gene with a pathological variant, X-linked recessive	+ 3-D	+	–	Survival, SGA, feeding difficulties
5	19 W 4D		M	Previous male child with chondrodysplasia punctata, X-linked	+	Brachytelephalangic, X-linked recessive	+ 3-D	–	–	Survival, SGA, unilateral hearing loss, immature speech, narrow palate
6	26 W		M	SLE, hypothyroidism, Sjogren syndrome, low PAPP-A, IUGR	–	Brachytelephalangic, <i>ARSE</i> gene without a pathological variant	+	–	Multicystic dysplastic kidney, UPJ obstruction, IUGR	Survival, feeding difficulties, mild facial dysmorphism, delayed visual development, neonatal lupus
7	4 W 2D		M	Sickle cell trait, hyperemesis gravidarum	+	Brachytelephalangic, <i>ARSE</i> gene without a pathological variant	+ 3-D	+		Survival, feeding difficulties
8	18 W 3D		F	None pertinent	+	Unknown-whole exome sequencing negative	+ 3-D	+	Dandy-Walker malformation, mild hydrocephalus, VSD, persistent right umbilical vein, two lobed lungs	Termination

ARSE arylsulfatase E gene sequencing and deletion/duplication testing, *D* days, *IUGR* intrauterine growth restriction, *F* female, *M* male, *PAPP-A* pregnancy associated plasma protein A, *SGA* small for gestational age, *SLE* systemic lupus erythematosus, *UPJ* ureteropelvic junction, *VSD* ventricular septal defect, *W* weeks

Table 3

Prenatal facial findings of chondrodysplasia punctata with postnatal outcome

Case	Binder phenotype	Nasofrontal angle in degrees US	Lack of fluid in anterior nasopharynx MR	Square alveolar ridge		Fluid-filled nostrils		Respiratory distress at birth	Stenotic nostrils postnatal
				US	MR	US	MR		
1	+	143	+	NS	+	+	+	None	None
2	+	162	+	+	+	NS	NS	Severe, bulb suction, intubation 3 days	Steroid nasal drops, congested but patent
3	+	147	+	NS	+	+	+	Mild, BiPAP changed to high flow nasal cannula-Ox for 14 days	Nasal dilation, steroid nasal drops, apnea monitor
4	+	159	+	NS	+	NS	NS	Mild-room air day 2	None
5	+	152	NA	-	NA	+	NA	Mild-CPAP	None
6	-	127	NA	NS	NA	+	NA	None	None
7	+	135	+	+	+	+	+	Transient tachypnea and nasal congestion	Stenotic right nares-required dilatation
8	+	144	-	NS	-	+	+	Termination	Termination

CPAP continuous positive airway pressure, NA not applicable, NS not seen, BiPAP bilevel positive airway pressure

Table 4

Skeletal findings of chondrodysplasia punctata

Case	Prenatal bone length biometry percentile	Prenatal epiphyseal stippling	Postnatal epiphyseal stippling	Prenatal abnormal hands/feet	Postnatal abnormal hands/feet
1	50th	–	Hands/feet	–	+
2	5th	–	Proximal femora, hands/feet	–	+
3	5th	–	Thumbs/feet	–	Minimal shortening distal phalanges
4	5th	–	No radiographs	–	Syndactyly right 4th and 5th toes
5	24th	Knee	No radiographs	–	Clinical terminal phalangeal hypoplasia
6	5th	–	Distal femora, feet	–	+
7	50th	Proximal femur, proximal tibia, tarsus	Early ossification shoulders, hips, knees, elbows, wrist; stippled hands/feet	Possible	+
8	28th–48th	–	Proximal humeri, caudal to acetabulae, feet	–	Not well seen

Table 5

Prenatal spine findings with postnatal outcome

Case	Prenatal irregularity or spine stippling on US	Postnatal spine stippling	Prenatal cervicothoracic kyphosis US and/or MR	Postnatal cervicothoracic kyphosis spine radiograph	Prenatal MR cervical cord compression	Postnatal cervical cord compression	Postnatal MRI spine	Postnatal CT spine
1	-	Cervical, sacral	-	Present with poor cervical mineralization	-	-	Cervicothoracic kyphosis, poor cervical mineralization	None
2	+	Cervical, lumbar, sacral	+	Present with poor cervical mineralization	-	-	Cervicothoracic kyphosis, poor cervical mineralization, C1-C2 and C7-T1 narrowing	At 2 years of age C7-T1 narrowing, cervicothoracic kyphosis, cervical vertebral hypoplasia
3	+	Cervical, thoracic, lumbar, sacral	-	Poor cervical mineralization	-	-	None	No cervical compression, poor cervical mineralization
4	-	No radiographs	-	No radiographs	-	-	None	None
5	-	No radiographs	-	No radiographs	N/A	-	None	None
6	-	Cervical, sacral	-	No kyphosis but poor cervical mineralization	N/A	-	No stenosis	None
7	+	Cervical, sacral	Cervical kyphosis	Upper cervical kyphosis with poor cervical mineralization	Upper cervical stenosis	Upper cervical with cord atrophy at C1-C2	Cord atrophy at C1-C2	Upper cervical kyphotic deformity with secondary cervical stenosis
8	+	Lumbar, sacral	-	No kyphosis but poor cervical mineralization	-	unknown	None	None

N/A not applicable

Table 6

Prenatal timing of ossification of epiphyseal centers-gestational age

Calcaneus and talus	24–26 weeks
Distal femoral epiphysis	32 weeks
Proximal tibial epiphysis	36 weeks
Proximal humeral epiphysis	Near term
First coccyx segment	After term
Proximal femoral epiphysis	After term