



Case Report

Prenatally Diagnosed Hereditary Chondrodysplasia Punctata in The Early Second Trimester with Fetal MRI and Postmortem Correlation

Gregor Dovjak^{1*}, Scharrer A², Bettelheim D³, Hainfellner J⁴, Kasprian G¹, Prayer D¹

¹Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria

²Clinical Institute for Pathology, Medical University of Vienna, Austria

³Department of Obstetrics and Feto-maternal Medicine, Medical University of Vienna, Austria

⁴Clinical Institute of Neurology, Medical University of Vienna, Austria

***Corresponding author:** Gregor Dovjak, Department of Biomedical Imaging and Image-guided Therapy Medical University of Vienna Waehringer Guertel 18-20, 1090 Vienna, Austria. Email: Gregor.Dovjak@meduniwien.ac.at

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Abstract

Chondrodysplasia Punctata (CDP) is a group of heterogeneous disorders with the typical radiological finding of epiphyseal stippling. We present the case of a prenatally diagnosed CDP with fetal MRI and postmortem confirmation by MRI, x-ray, autopsy and histology. Based on the phenotype, radiological and histological findings, and the fact that a maternal aunt of the fetus had presented with the same features, the diagnosis of Conradi-Hunermann syndrome was possible.

Case Report

We present the case of a 37-year-old mother (gravida 3, para 2) referred for a fetal MRI at the gestational age of 19+1 weeks. The referring first trimester ultrasound scan showed an increased nuchal translucency of 6 mm, a generalized subcutaneous edema of 5mm, a microthorax. There was a slightly increased trisomy 13 risk of 1:58. Also, the patient's sister (the aunt of the fetus) had died at the age of 8 days and had been diagnosed with a Chondrodysplasia Punctata (CDP). The MRI indication was based on the ultrasound finding of "suspect skeletal dysplasia", as even with knowledge of the family history ultrasound could not make an unequivocal diagnosis. Amniocentesis, Chorionic villus sampling, the traditional and a long-term cell culture as well as a comparative genomic hybridization array did not show any remarkable abnormalities. The fetal karyotype was 46XX and there were no microdeletions or -duplications. Also, the ultrasound examinations prior to the fetal MRI did not show any premature calcifications.

The subsequently performed 1.5 Tesla fetal Magnetic Resonance Imaging (MRI; Philips Ingenia) showed the following findings (Figure 1):

- Slightly reduced fronto-occipital diameter of the head.
- Marked neck edema and slight generalized edema.
- Flat face profile, the nasal bone could not be delineated, no retrognathia.
- Slight hypertelorism with an interocular distance of 11 mm.
- Normal brain development.
- Bell-shaped configuration of the thorax, reduced the lung volumes (80% of the expected volume).
- Ascites (5 mm prehepatic) and bulging of the abdominal wall.
- Hypointense bones (primarily the vertebrae and long bones) on Echo Planar Imaging (EPI) sequences compared to age related fetuses.
- Shortened extremities and slightly bowed long bones, club feet.

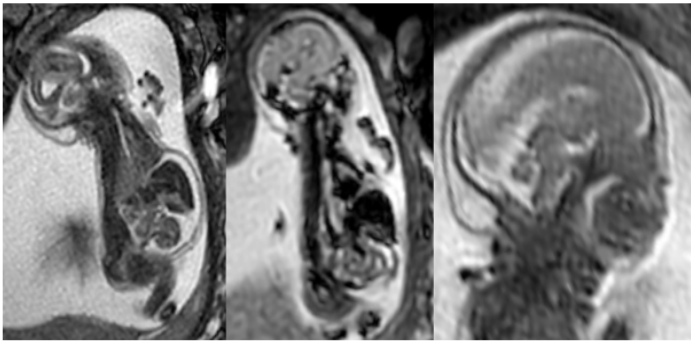


Figure 1: Sagittal fetal MRI with T2-weighted sequences on the left and right image and an Echo Planar Imaging sequence (EPI) in the middle. There is a marked ascites with protruding abdomen, a neck edema and a nasomaxillary hypoplasia best appreciated on midsagittal images. The EPI sequence shows the hypointense bone structure of the vertebral bodies.

The parents were not consanguine, and conception was spontaneous. There was no maternal alcohol or drug intake during and before pregnancy. She had two previous unremarkable pregnancies and her medical history was clean except for a hand surgery due to de Quervain syndrome and adnexitis a decade prior to the current pregnancy. After counselling the mother did not wish to continue with the pregnancy in gestational week 21+1. The abortion was performed with mifepristone and misoprostol.

A 3 Tesla postmortem MRI (Siemens Magnetom Vida) was performed 17 days after the fetal MRI and confirmed prenatal findings. The findings of the nasomaxillary hypoplasia in combination with the hypointense stippling calcifications in the epiphyses were even more prominent than on prenatal imaging. Retrospectively the epiphyseal calcifications could also be delineated on the fetal MRI. A postmortem babygram confirmed the shortened and slightly bowed proximal long bones, the bell shaped microthorax and the big protruding abdomen with ascites (Figure 2). In all epiphyses were stippling ossification centres. They were most prominent in the proximal long bones, the vertebral bodies, ribs and adjacent to the iliac wings. The vertebral bodies were decreased in height, whereas the intervertebral space was irregularly wide.

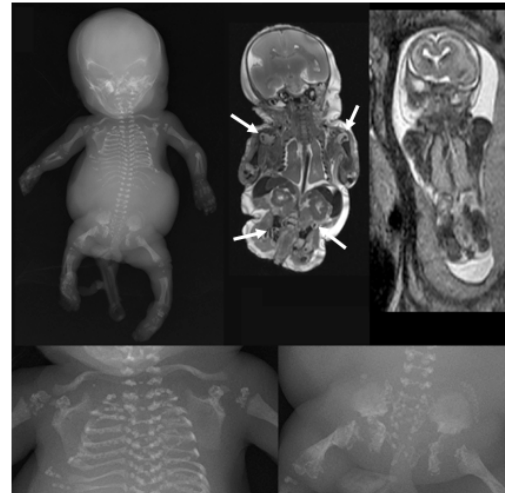


Figure 2: Comparison of the postmortem babygram (left and bottom) with the coronal postmortem MRI (middle; constructive interference in steady state sequence) and the coronal T2-weighted fetal MRI (right). Note that in all images the stippling calcifications can be delineated in the epiphyses of the long bones. On the postmortem MRI they represent the hypointense spots in the otherwise hyperintense cartilage (arrows). On the fetal MRI they could only be delineated retrospectively.

In the autopsy the fetus had a length of 18 cm and a birth weight of 330g (Figure 3). The described findings of the imaging modalities could be confirmed. Additionally, a relative microstomia and irregular bone-cartilage borders of the ribs were found. A dedicated brain dissection showed no remarkable findings. The histological specimen of the large joints showed intermittent vascularized connective tissue areas with ossification / calcification. Also, there were extended areas of calcification compatible with the diagnosis of CDP (Figure 4). The mother's sister (born in 1985 and died at the age of 8 days) had an analogous phenotype as described above and showed similar findings on the x-ray and histologic specimen (images not retrievable), therefore the diagnosis of CDP was made. Also, the skin showed hyperkeratosis. There were no signs of intrauterine infection and the chromosomal analysis showed a normal female chromosome set 46XX. The child died after a long attack of apnea with an unsuccessful resuscitation.

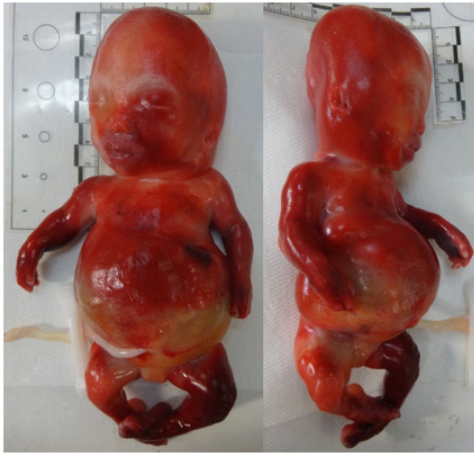


Figure 3: Postmortem situs prior to autopsy. The fetus shows a microthorax, a prominent abdomen and shortened long bones. Also, there is a reduced fronto-occipital diameter and a nasomaxillary hypoplasia consistent with the Binder phenotype.

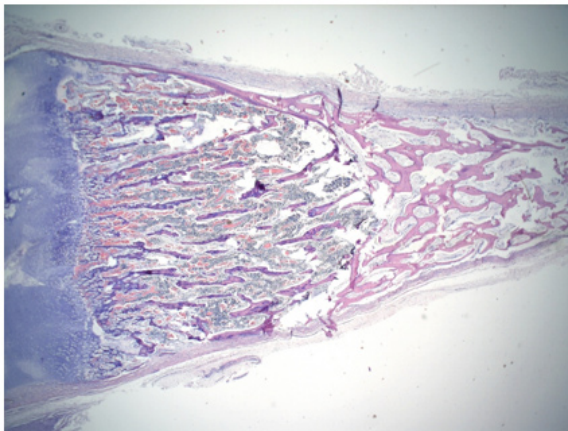


Figure 4: Histological specimen of the fetal femur. There are areas of calcifications within the otherwise normal cartilage.

Discussion

CDP is a group of heterogeneous disorders with the radiological finding of epiphyseal stippling. The etiologies can be divided in three major groups: inborn errors of metabolism (including peroxisomal dysfunction, cholesterol synthesis and mucopolysaccharidosis among others), disruption of Vitamin K metabolism (for example maternal warfarin intake or maternal vitamin deficiency) and chromosomal abnormalities as for example trisomy 18 and 21 (see extensive review by Irving et al.) [1]. In the group of genetic etiologies are de novo mutations and a multitude of gene mutations with different inheritance patterns. Since CDP is a diverse group of disorders, also life expectancy and quality widely vary between the different entities. The phenotype

and radiologic findings are sometimes similar, although they show a different genotype [2]. The typical postnatal phenotypical and radiological findings have been described in several studies [3, 4]. On the contrary there are only few reports of prenatal diagnosis by ultrasound [5].

We report a prenatally detected case of a CDP with typical epiphyseal stippling, shortened long bones, a microthorax and ascites. The present nasomaxillary hypoplasia is also called Binder phenotype which is known to be associated with CDP [6, 7]. The hypointense bone signal in fetal MRI, especially on the Echo Planar Imaging (EPI) sequences, is an indicator for (in this case premature) calcification. The epiphyseal calcifications were only detectable retrospectively in the fetal MRI, as the contrast between the cartilage and calcification was distinctly lower compared to postmortem imaging. After a literature research, the described changes were radiologically and morphologically compatible with CDP of the type CDPX2, also known as Conradi-Hunermann syndrome [1]. This is a rare x-linked dominant syndrome with a mutation in the emopamil-binding-protein, involved in the cholesterol pathway [8, 9]. As the mother's sister had similar findings, the non-affected mother should therefore be a carrier of this x-linked dominant disease.

This is one of the first presentations of a CDP prenatally in fetal MRI with characteristic findings in prenatal and postmortem imaging. Although we lack an exact genetic testing, the typical phenotype, radiologic presentation and inheritance pattern are indicative of Conradi-Hunermann syndrome. The differential diagnosis are other subtypes of CDP. The family history provided the context to specifically look for stippling calcifications which led to specific review of the epiphyses in MRI. In conclusion fetal MRI is a useful tool to assess characteristic findings associated with Chondrodysplasia punctata.

Disclosure of Interests

The authors have no financial, personal, political, intellectual or religious interests to disclose.

Contribution to Authorship

Each author contributed equally to the manuscript. Dovjak G. wrote the manuscript and prepared the figures. Scharrer A. and Hainfellner J. performed the autopsy and pathological workup of the fetus. Bettelheim D. did the prenatal ultrasonography and evaluated the maternal data. Kasprian G. and Prayer D. did the reporting and helped in the formation of the manuscript.

Details of Patient's Consent

Prior to fetal MR examinations all patients (that we include in studies or case reports) sign an informed consent waiver that their anonymized data may be used for teaching purposes and studies as well as possible publications.

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