Binder syndrome: a phenotype rather than a definitive diagnosis?

Binder syndrome is a congenital malformation characterized by nasomaxillary hypoplasia. It can be isolated or associated with multiple etiologies, such as maternal intake of coumarin-based anticoagulants during pregnancy, systemic lupus erythematosus and some other monogenic conditions, such as Keutel syndrome or chondrodysplasia punctata (CDP)[1]. We report the case of a 24-year-old primigravida referred to our fetal medicine unit at 27 + 2 weeks' gestation, following the finding of significant fetal facial dysmorphism during a routine ultrasound examination at 23 weeks. Amniocentesis with a traditional cell culture of the amniotic fluid followed by array comparative genomic hybridization, 37 kb, revealed a normal karyotype, 46XY. The woman's medical history was unremarkable.

Ultrasound examination and fetal magnetic resonance imaging (MRI) performed in our center confirmed facial malformation suggestive of Binder phenotype, characterized by a flat nose and abnormal convexity of the maxilla (Figure 1). Other findings included abnormal epiphyseal ossification centers, short limbs and brachytelephalangy. When Binder phenotype is diagnosed prenatally, a thorough search for associated abnormalities is mandatory in order to identify correctly the etiology, of which one of the most important is CDP.

CDP is a heterogeneous group of congenital skeletal dysplasias. This condition may have a genetic cause with several different inheritance patterns and, as in our case, the clinical presentation of the X-linked recessive type (CDPX1, brachytelephalangic type) includes Binder phenotype, stippling calcifications and brachytelephalangy associated with hypoplastic nails[2]. CDPX1 is a rare condition affecting only males, due to the X-linked recessive inheritance pattern. The condition is associated with mutations either within the arylsulfatase E gene (*ARSE*) or chromosomal deletions in the region of the short arm of the X chromosome encompassing *ARSE*[3].

In the current case, the diagnosis of CDPX1 was proposed following a multidisciplinary meeting between perinatologists and geneticists. Given the variability of the clinical manifestations and no clear genotype–phenotype correlation, prenatal counseling was challenging. The couple decided to terminate the pregnancy at 28 weeks' gestation and the confirmed diagnosis of CDPX1 was available only after completion of full postmortem investigation.

Pathological examination confirmed Binder phenotype and brachytelephalangy. Multiple and abnormal calcifications of the trachea and skeleton were also found (Figure 1). Targeted genetic studies performed on the amniotic fluid detected a hemizygous mutation (c.1743G > A, p.Trp581) in *ARSE*, confirming the diagnosis of CDPX1 (Online Mendelian Inheritance in Man (OMIM) number 302950).

To date, there are only two published reports describing the prenatal diagnosis of CDPX1 based on brachytelephalangy and stippling calcifications of the femora and vertebrae[4,5]. In our case, Binder phenotype, brachytelephalangy and abnormal epiphyseal ossifications in a male fetus were identified prenatally on ultrasound examination and confirmed on fetal MRI.

In conclusion, tertiary-level conventional ultrasound can be accurate for the prenatal diagnosis of CDP due to the detection of Binder phenotype associated with abnormal epiphyseal ossification centers and hypoplasia of the distal phalanges of the hands. However, to identify the specific type of CDP, targeted genetic analysis is required.

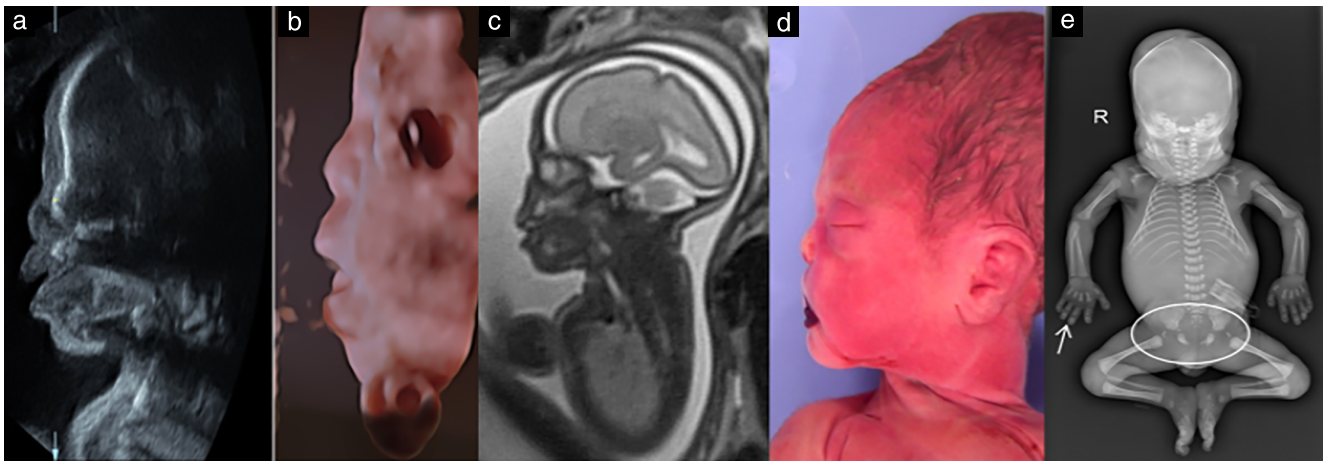

Figure 1 Facial profile of fetus with X-linked recessive chondrodysplasia punctata, as seen on two- (a) and three- (b) dimensional ultrasound, magnetic resonance imaging (c) and postmortem examination (d), showing flat nasofrontal angle and verticalized nasal bones typical of Binder phenotype. (e) Postmortem X-ray of same fetus, showing skeletal anomalies of chondrodysplasia punctata, including hyperechoic focal calcifications (puncta) on femoral epiphyses (encircled area) and brachytelephalangy (hypoplasia of distal phalanges of hands) (arrow). R, right.

Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.

E. Mazzone[1,2]*, T. Cos Sanchez[1], N. Persico[3], M. M. Cannie[4] and J. Jani[1]
[1]*Department of Obstetrics and Gynecology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium;*
[2]*Department of Medicine and Surgery, Unit of Surgical Sciences, Obstetrics and Gynecology, University of Parma, Parma, Italy;*
[3]*Department of Obstetrics and Gynaecology 'L. Mangiagalli', Fondazione IRCCS, Ca Granda Ospedale Maggiore Policlinico, Milan, Italy;*
[4]*Department of Radiology, University Hospital Brugmann, Université Libre de Bruxelles, Brussels, Belgium*
**Correspondence.*
(e-mail: eleonora.mazzone@gmail.com)
DOI: 10.1002/uog.19198

References

1. Keppler-Noreuil KM, Wenzel TJ. Binder phenotype: associated findings and etiologic mechanisms. *J Craniofac Surg* 2010; **21**: 1339–1345.
2. Eash DD, Weaver DD, Brunetti-Pierri N. Cervical spine stenosis and possible vitamin K deficiency embryopathy in an unusual case of chondrodysplasia punctata and an update classification system. *Am J Med Genet A* 2003; **122A**: 70–75.
3. Sheffield LJ, Osborn AH, Hutchison WM, Sillence DO, Forrest SM, White SJ, Dahl HH. Segregation of mutations in arylsulphatase E and correlation with the clinical presentation of chondrodysplasia punctata. *J Med Genet* 1998; **35**: 1004–1008.
4. Benaicha A, Dommergues M, Jouannic JM, Jacquette A, Alexandre M, Le Merrer M, Ducou Le Pointe H, Garel C. Prenatal diagnosis of brachytelephalangic chondrodysplasia punctata: case report. *Ultrasound Obstet Gynecol* 2009; **34**: 724–726.
5. Boulet S, Dieterich K, Althuser M, Nugues F, Durand C, Charra C, Schaal JP, Jouk PS. Brachytelephalangic chondrodysplasia punctata: prenatal diagnosis and postnatal outcome. *Fetal Diagn Ther* 2010; **28**: 186–190.

Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.