CLINICAL CASE

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Prenatal hypophosphatasia: ultrasound findings and diagnosis

Hipofosfatasia prenatal hallazgos ecográficos y diagnósticos

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ABSTRACT

Hypophosphatasia is a skeletal dysplasia caused by mutations in the ALPL gene that impair bone mineralization. The nonspecific nature of ultrasound findings and their overlap with other skeletal dysplasias make prenatal diagnosis challenging. We report the case of a 37-year-old pregnant woman at 20 weeks' gestation with ultrasound findings suggestive of severe skeletal dysplasia with suspected lethality. Amniocentesis showed a normal prenatal karyotype. A cesarean section was performed at 38 weeks, resulting in a live newborn with micromelia and a hypoplastic thorax. Postnatal studies revealed decreased alkaline phosphatase levels, and genetic testing identified a homozygous c.892G>A p.(Glu298Lys) mutation in the ALPL gene, confirming the diagnosis of prenatal hypophosphatasia.

Keywords: Hypophosphatasia; Prenatal Diagnosis; Ultrasonography, Prenatal; Osteochondrodysplasias.

RESUMEN

La hipofosfatasia es una displasia ósea causada por mutaciones en el gen ALPL que afectan la mineralización ósea. La inespecificidad de los hallazgos ecográficos y su superposición con otras displasias óseas dificultan el diagnóstico prenatal. Se presenta el caso de una gestante de 37 años con embarazo de 20 semanas y hallazgos ecográficos sugestivos de displasia ósea severa con sospecha de letalidad. Se realizó amniocentesis con cariotipo prenatal normal. Se realizó cesárea a las 38 semanas, obteniéndose un recién nacido vivo con micromelia y tórax hipoplásico. Los estudios postnatales evidenciaron fosfatasa alcalina disminuida y el análisis genético confirmó una mutación homocigota c.892G>A p.(Glu298Lys) en el gen ALPL, estableciendo el diagnóstico de hipofosfatasia prenatal.

Palabras clave: Hipofosfatasia; Diagnóstico Prenatal; Ultrasonografía Prenatal; Displasias Óseas.

Introduction

Bone dysplasias represent a heterogeneous group of genetic disorders that impair the development of osteochondral tissue and are classified into more than 400 subtypes[(1)]. Within this group is hypophosphatasia (HPP), an inherited metabolic disorder caused by mutations in the ALPL gene that result in decreased activity of tissue-nonspecific alkaline phosphatase (TNAP).

Deficiency of this enzyme leads to the accumulation of inorganic pyrophosphate (PPi), an inhibitor of bone mineralization, which interferes with proper bone formation and contributes to its musculoskeletal and systemic manifestations[(2)].

HPP presents a broad clinical spectrum ranging from severe prenatal forms to mild phenotypes diagnosed in adulthood. It can result from de novo mutations or from autosomal dominant or recessive inheritance of the ALPL gene. The perinatal form is rare and is estimated to occur in one in every 100,000 to 300,000 live births[(3)]. The prognosis depends on the severity of the disease and the respiratory compromise associated with pulmonary hypoplasia.

The objective of this article is to present the clinical case of a fetus with severe bone dysplasia, with ultrasound findings suggestive of

lethality and a postnatal diagnosis of prenatal hypophosphatasia, describing the ultrasound findings and the diagnostic process to contribute to the existing literature on this rare condition.

Clinical case

A 37-year-old primigravida at 20 weeks' gestation was referred to the Central Military Hospital in Bogotá, Colombia—a referral center for maternal-fetal medicine—for a detailed anatomical ultrasound following a previous finding of short long bones on an ultrasound performed at 18 weeks. Neither the patient nor her partner had a personal or family history of genetic disorders or consanguinity. No first-trimester ultrasound was available, and the prenatal tests performed during the first trimester were within normal limits. On physical examination, the patient was asymptomatic upon admission, with vital signs within normal limits. The gynecological and obstetric examination revealed no pathological findings, with a pregnant uterus, uterine height consistent with gestational age, and a single live fetus in cephalic presentation.

A detailed prenatal ultrasound revealed a fetal head with mild dolichocephaly, a cephalic index of 73%, preserved bone mineralization of the cranial vault, and brain development within normal parameters. Thoracic assessment showed a chest circumference at the 25th percentile during the second trimester, decreasing to a value below the 5th percentile in the third trimester. The fetal heart showed no structural abnormalities, with a cardiac circumference-to-thoracic circumference ratio greater than 0.6 in the third trimester. Micromelia was evident in the extremities, with dysplastic long bones (femur, tibia, fibula, humerus, ulna, and radius), with lengths below the 1st percentile and angulation of the femur, humerus, and tibia. Bone echogenicity was preserved, with no evidence of hypomineralization. The hands and feet showed no malformations, and fetal movements were within normal limits. Given the ultrasound findings suggesting a diagnosis of severe bone dysplasia with ultrasound criteria indicative of lethality, the differential diagnoses considered were osteogenesis imperfecta type II, thanatophoric dysplasia, and achondrogenesis. An invasive test for aneuploidies using G-banding karyotyping was indicated; the fetus was found to be euploid 46,XX. The absence of hypomineralization, coupled with the unavailability of a prenatal panel for bone dysplasias, made it difficult to establish a specific

Figure 1. Prenatal ultrasound: micromelia is evident, with dysplastic long bones (femur, tibia, fibula, humerus, ulna, and radius) that are shortened and bowed (white arrow on the femur, humerus, and tibia); bone echogenicity is preserved.

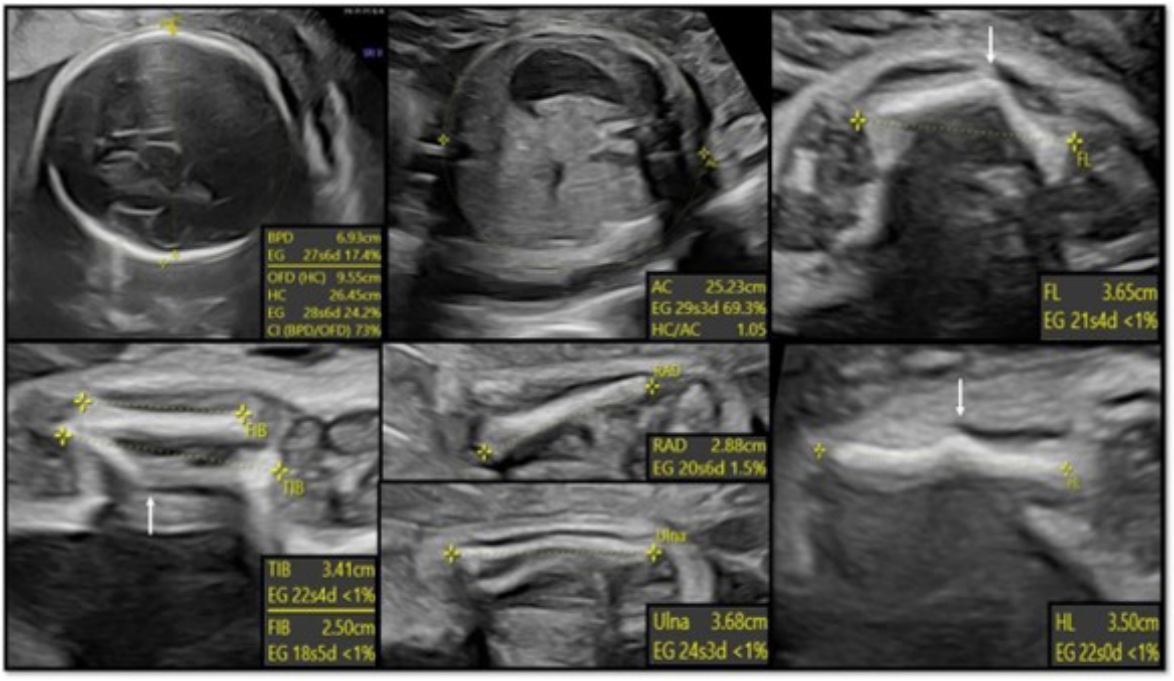
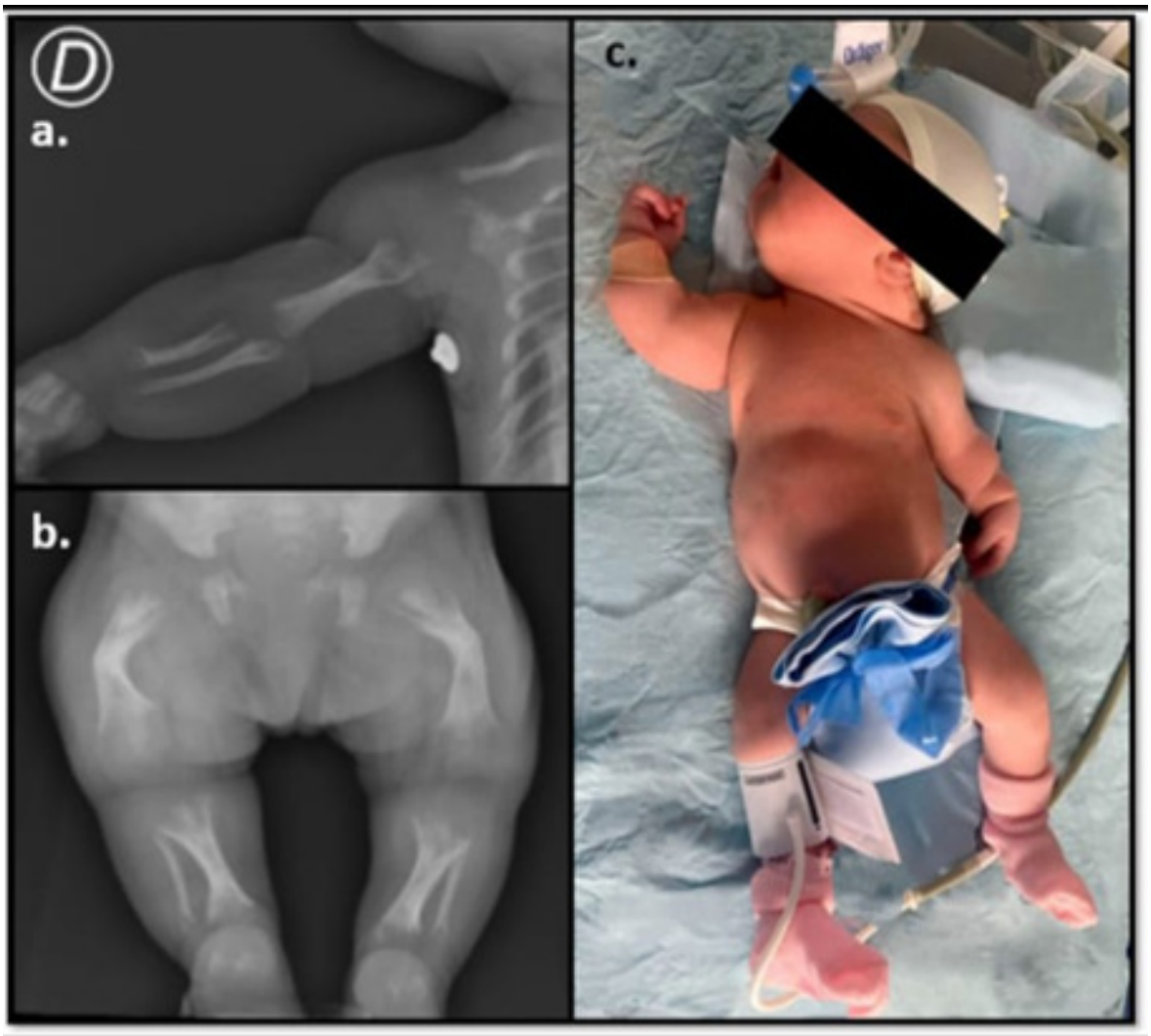


Figure 2: X-ray of the extremities in newborns: a. Widening and lack of ossification of the metaphyses and proximal epiphyses of the humerus, radius, and ulna; decreased bone density. b. Widening and absence of ossification of the metaphyses and proximal epiphyses of the femur, tibia, and fibula; curvature of the mid-shaft of the femur (white arrows); decreased bone density. c. Phenotypic manifestations of a newborn with prenatal hypophosphatasia.



diagnosis during gestation. Complementary ultrasound studies included fetal echocardiography, which was normal; third-trimester neurosonography, showing adequate ossification of the skull and normal ultrasound-detected neurodevelopment of the central nervous system.

Given the suspicion of skeletal dysplasia, multidisciplinary counseling was provided to the patient and her family, including evaluations by psychiatry, psychology, and social work, with a discussion of the fetal prognosis and management options in accordance with current legislation. The pregnancy continued with maternal-fetal medicine follow-up through serial obstetric ultrasounds and assessment of fetal well-being during the third trimester, which was performed using a biophysical profile and serial fetoplacental Doppler studies, with no evidence of changes in the fetal hemodynamic pattern. At 38 weeks, the patient went into labor with regular uterine contractions, and a cesarean section was performed at the mother's request, resulting in the delivery of a live female newborn weighing 3,205 g, measuring 47 cm in length, and with an APGAR score of 8/9/9.

After birth, the newborn required hospitalization in the neonatal intensive care unit with noninvasive ventilatory support due to respiratory distress; a physical examination revealed a prominent forehead, an arched pal-

ate, and shortened limbs. Radiological studies showed decreased bone density, widening of the metaphyses and proximal epiphyses of the long bones, and bowing of the femurs. Laboratory tests revealed decreased levels of alkaline phosphatase. Genetic testing using an NGS panel for skeletal dysplasias identified a homozygous pathogenic variant c.892G>A p.(Glu298Lys) in the ALPL gene, confirming the diagnosis of perinatal hypophosphatasia. During hospitalization, the patient received multidisciplinary care, including evaluations by neonatology, pediatrics, and genetics, as well as support services from the neonatal intensive care unit NICU, followed by discharge and outpatient follow-up.

Discussion

Hypophosphatasia is a rare genetic disorder caused by mutations in the ALPL gene that result in a deficiency of tissue-nonspecific alkaline phosphatase, an enzyme essential for bone mineralization[2]. This disorder leads to the accumulation of inorganic pyrophosphate and other substrates that inhibit normal bone formation[4]. More than 400 mutations in the ALPL gene have been described, which explains the wide clinical variability of the disease, ranging from severe prenatal forms to mild presentations diagnosed in adulthood[5].

Prenatal suspicion of the condition usually arises from ultrasound findings consistent with bone dysplasia, generally identified during the second or third trimester of pregnancy[5,6]. Among the most common findings are bone hypomineralization, cranial deformities, decreased chest circumference, shortening and angulation of the long bones, and, in some cases, intrauterine fractures[5,6]. However, these findings are not unique to hypophosphatasia and can be observed in multiple skeletal dysplasias, which complicates prenatal etiological characterization[7,8].

The literature on the prenatal diagnosis of hypophosphatasia is limited. Tongsong et al. described a case diagnosed in the second trimester in which ultrasound revealed severe shortening of the limbs and reduced bone ossification—findings suggestive of severe skeletal dysplasia consistent with congenital hypophosphatasia[9]. These findings are comparable to those observed in our case, where the presence of micromelia and abnormalities in the morphology of the long bones initially suggested severe skeletal dysplasia.

During the first trimester, ultrasound findings are typically nonspecific, although increased nuchal translucency has been reported in the absence of major structural anomalies[6]. Starting in the second trimester, more evident findings can be identified, such as micromelia, angulation of the long bones, and a hypoplastic thorax—the latter associated with a poor prognosis due to the risk of pulmonary hypoplasia[5,6].

Fetal skeletal dysplasias constitute a group of disorders characterized by great genetic and

Table 1. Comparative table of values indicating suspected lethal bone dysplasia and ultrasound findings in the second and third trimesters and in newborns.

Measurements	Values that determine lethal skeletal dysplasia	Ultrasound II trimester	Ultrasound III trimester
Ultrasound findings II, III trimester and newborn			
Weeks of Gestation		20 Weeks	34 Weeks
Femur length		19.9 mm, < percentile 1	44.8 mm, < percentile 1
abdominal circumference		146 mm	312 mm
Thoracic circumference		133 mm, percentile 25-50	225 mm, percentile 2.5-5
Ultrasound Markers of Lethal Bone Dysplasia			
Severe micromelia	Present	Present	Present
Poor bone mineralization	Present	Absent	Absent
Thoracic circumference	Lower percentile 5	Absent	Present
Thoracic/abdominal circumference ratio	< 0.8	0.9 Absent	0.7 Present
Cardiac/thoracic circumference ratio	> 0.6	0.50 Absent	0.64 Present
Femur length/abdominal circumference ratio	< 0.16	0.13 Present	0.14 Present
Severe polyhydramnios and/or fetal hydrops	Present	Absent	Absent

phenotypic heterogeneity[8]. In some cases, prenatal diagnosis can be confirmed through molecular testing of amniotic fluid. Popa-Todirenchi et al. reported a case in which targeted genetic analysis of amniocytes identified a pathogenic variant in the ALPL gene during pregnancy[10]; however, the availability of panels for prenatal skeletal dysplasias is limited, they are costly, and prenatal results may be delayed, which limits timely prenatal clinical decisions

The prenatal diagnosis of hypophosphatasia remains a challenge due to its phenotypic variability and the overlap of ultrasound findings with those of other skeletal dysplasias[11]. In our case, the absence of evident hypomineralization and the lack of timely access to prenatal genetic testing for bone dysplasias made specific characterization during pregnancy difficult; therefore, the definitive diagnosis was established in the postnatal period based on phenotypic findings, radiological studies, and complementary genetic testing.

Conclusion

Prenatal hypophosphatasia is a rare condition for which a diagnostic suspicion arises based on ultrasound findings of fetal bone dysplasia. However, due to the clinical variability of the disease, these findings are nonspecific and may overlap with other forms of skeletal dysplasia.

The described ultrasound findings include increased nuchal translucency in the first trimester and, beginning in the second trimester, bone hypomineralization, dysplastic bones, angulation of long bones, micromelia, and hypoplastic thorax.

Given the nonspecific nature of prenatal findings, a multidisciplinary approach is essential; this should include detailed ultrasound evaluation, genetic counseling, and planning for postnatal evaluation at referral centers to achieve an accurate etiological characterization and to properly guide perinatal management and counseling. This report contributes to the existing literature on prenatal hypophosphatasia and highlights the importance of considering this condition within the differential diagnosis of fetal skeletal dysplasias.

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