CEOG Clinical and Experimental Obstetrics & Gynecology

Case Report

Prenatal diagnosis of femoral hypoplasia-unusual facies syndrome associated to sacral hemivertebra

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Summary

Femoral hypoplasia-unusual facies syndrome (FH-UFS), also known as femoral-facial syndrome, is an extremely rare condition. The diagnostic criteria for this entity include: femoral hypoplasia in association with facial dysmorphism. Its pathogenesis is unknown. However, it has been associated with insulin-dependent diabetes mellitus during pregnancy. The present is a case of a pregnant woman with type-2 diabetes mellitus with a 17-year disease course without associated complications. The first-trimester screening ultrasound study revealed a female fetus with micrognathia and low-set ears. On week 22+4 of pregnancy, ultrasound showed a fetus with micrognathia, bilateral femoral agenesis, and hemivertebra at the S3-S4 level associated with a skin defect at the same level.

Key words: Micrognathia; Femoral agenesis; Diabetes mellitus.

Introduction

Femoral hypoplasia-unusual facies syndrome (FH-UFS), is also known as femoral-facial syndrome. The main findings are micrognathia associated with femoral agenesis or hypoplasia of different degrees. Its pathogenesis is unknown. The prenatal diagnosis is possible also in the first trimester of pregnancy. It has been associated with insulin-dependent diabetes mellitus during pregnancy, where early ultrasound scan diagnosis would be beneficial given its prognosis.

Case Report

A 39-year-old woman, with a previous miscarriage, was referred to the present unit at 12 weeks of gestation for fetal micrognathia. She had type-2 diabetes with a 17-year disease course and obesity with a body mass index of 32. The family history was unremarkable. Pregnancy was achieved spontaneously without preconceptional care. On week 9 of her pregnancy, her blood level of glycosylated hemoglobin was 11.6% (HBA1c) in laboratory tests was assessed on week 9 of pregnancy. The first-trimester screening ultrasound study revealed a female fetus with marked micrognathia and low-set ears (Figure 1A); the nuchal translucency was 1.5 mm and other anatomical findings were unremarkable. Laboratory results showed βhCG level of 0.3 MoM and PAPP-A level of 0.5 MoM. A chorionic villous sample was performed and the study showed a normal fetal karyotype, 46 XX.

The patient failed to attend pregnancy control visits and ultrasound studies planned for weeks 16 and 20-22. She returned on week 22+4 of pregnancy for an ultrasound study, which showed severe fetal micrognathia (Figures 1B, C) and right femur agenesis. The left femur was difficult to examine, although it seemed to be hypoplasic (13 mm); the remaining of the long bones were normal (Figures 2A and B).

Feet were normal, except for both fifth toes, which was in a wrong position towards the external side. A sacral hemivertebra was observed at the S3-S4 level, associated with a skin defect at that level, without neural tube defects (Figures 2C-E). All other anatomical findings were normal. Femoral hypoplasia-unusual facies syndrome was diagnosed. The patient decided to proceed with legal termination of pregnancy. Fetal postmortem anatomopathological and X-ray studies confirmed agenesis of the right femur and severe hypoplasia of the left femur, presence of only three sacral vertebrae including one hemivertebra in the S2-S3 segment, micrognathia, low-set ears, and a sacral bone profusion, which appeared like a truncated spine associated with partial caudal regression syndrome (Figure 3).

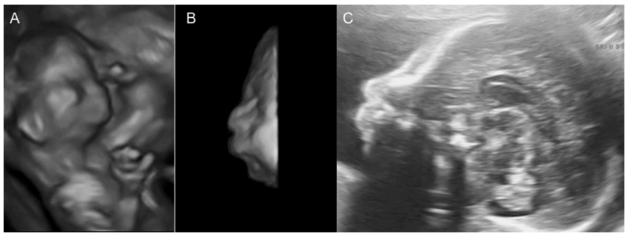

Figure 1. — Micrognathia. A: 3D reconstruction of the micrognatia and the low set ears in the first trimester. B and C: Micrognathia at 22 weeks.

Revised manuscript accepted for publication October 3, 2017

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 1, 2019
doi: 10.12891/ceog4329.2019

7847050 Canada Inc.
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Published: 10 February 2019

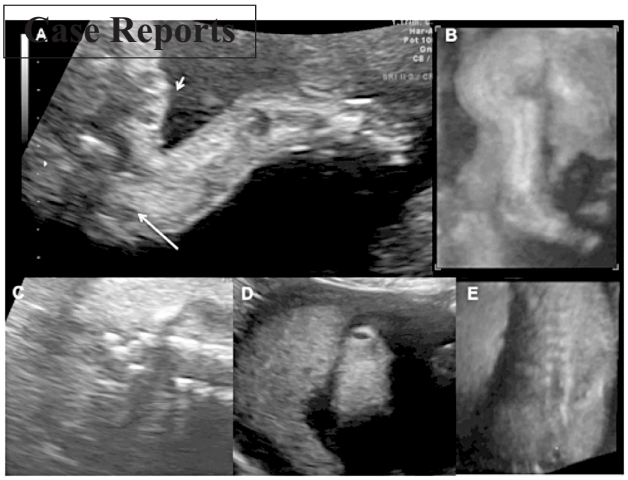

Figure 2. — A: 22 weeks, fetal pelvis with female external genitalia (short arrow) and no visualization of bilateral fetal femur (long arrow). B: 3D reconstruction of the fetal limbs, bilateral absent of thighs, and both femurs. C: Sacral hemivertebra. D, E: sacral skin defect and 3D reconstruction.

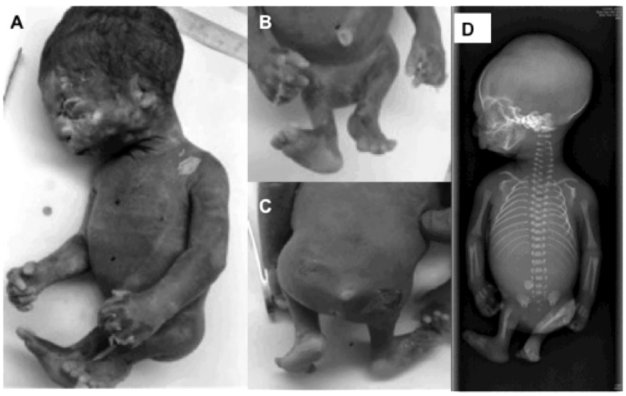

Figure 3. — Postnatal findings. The fetus presented micrognathia, thin upper lip, short nose with broad tip, upstanding palpebral fissures (A), absent thigh (B), skin defect with a bone protrusion (C). Fetal X-ray: micrognathia and absent bilateral femurs, sacral hemivertebra with only three sacral vertebrae.

Table 2. — *FH-UFS associated abnormalities.*

Craniofacial	Micrognathia
	Facial fissure
	Small nose with a wide tip
	Long philtrum
	Thin upper lip
	Upslanting palpebral fissures
	Hypertelorism
	Glossoptosis
	Low set ears
	Short neck
Skeleton	Dysgenesis of the sacrum
	Humeroradial synostosis
	Absence or hypomorphism of tibia or fibula
	Syndactyly
	Polydactyly
	Talipes
	Club-feet
	Overriding toes
	Hemivertebra
	Axilar and inguinal pterygium
CNS	Hydrocephalus
	Ventriculomegaly
	Partial agenesis of corpus callosum
	Defects in neuronal migration
	Heterotopy
Genitourinary	Renal dysplasia
	Renal agenesis
	Multicystic kidney
	Anomalies of the collector system
	Pelvic kidneys
	Cryptorchidsm
	Hypoplasia of labia or penis
	Absent uterus and vagina
	Macropenis
Other	Certain cardiovascular anomalies

Discussion

FH-UFS (OMIM 134780), also known as femoral-facial syndrome, is an extremely rare entity[1].

Its main characteristics are: micrognathia associated with unilateral or bilateral femoral hypoplasia or aplasia of different degrees. This deficiency occurs in 0.1–0.2/10,000 births with the bilateral form corresponding to only 10–15% of cases [2].

Is a rare anomaly syndrome of unknown etiology, although it is known to be associated with maternal type 1 diabetes mellitus [3]. Insulin dependent diabetic mothers are known to have two- to three-fold higher risk of congenital anomalies than the general population [4, 5].

In most cases of FH-UFS, the type of inheritance is sporadic, although cases of family background have been described with dominant autosomal inheritance [6, 7]. Recently, the duplication 22q37.2 has been proposed as a genetic cause for the femur phenotype in a girl affected by FH-USFS, but only one case is reported in the literature [8]. Other contributing factors described are exposure to drugs (thalidomide), viral infections, radiation, and focal ischemia or trauma [1, 2] as well as severe fetal constraint secondary to oligohydramnios [9].

A review of the literature in PubMed database for prenatally diagnosed cases with absent or hypoplasic femur and micrognathia, or characteristic facial findings of this condition was performed.

Micrognathia and shortened femur can be demonstrated by ultrasonographic imaging in early stage of pregnancy (Table 1). Thirteen cases are published prenatally and only three cases have been reported in the first trimester [10, 12, 17].

The present authors propose that it is important to perform early ultrasound imaging studies to diabetic pregnant women, due to the increased risk of fetal malformations. In

Table 1. — *Reported cases of FH-UFS with prenatal diagnosis criteria.*

Case	Reference	DM	GA (w)	Bilateral Femoral hypo/aplasia	Other bone hypo/aplasia	Facial anomalies	Other anomalies	Outcome	Postnatal findings
1	Tadmor [10](1993)	+	32	+	+	Cleft lip/palate	-		Cleft lip and palate, short thigh, short proximal arms,sloping shoulders, hypoplastic left scapula, cryptorchidism, shawl scrotum, single palmar creases
2	Baraitser[11](1994)	Ns	¿	+	-	Micrognathia	Preaxial polidactyly		Characteristic face, clef palate
3	Robinow[7] (1995)	-	25	+	-	Micrognathia	-	Term delivery	Characteristic face, clef palate, short thigs
4	Paladini[12] (2007)	-	21	+	-	Cleft lip/palate, micrognathia	Unilateral renal agenesis	TOP	Severe bilateral and asymmetric femoral hypoplasia, elongated philtrum, thin upper lip, epicanthus, unilateral renal agenesis, short neck and a pelvis with vertically orientated iliac blades
5	Paladini[12] (2007)	+	21	+	-	Micrognathia, low set ears	-	TOP	Cleft palate, mandible, elongated philtrum, thin upper lip, severe unilateral hypoplasia of the left femur, severe micrognathia and low-set ears
6	Paladini[12](2007)	-	13	+	-	Micrognathia	-	TOP	Severely hypoplastic femora, an abnormal left foot and moderate micrognathia
7	Figueroa[13] (2009)	-	21	+	-	Micrognathia	-	TOP	Severe bilateral femoral hypoplasia, micrognathia, low-set ears
8	Castro [14](2014)	+	13	+	-	Micrognathia, nasal hypoplasia, elongated philtrum, thin upper lip	-		Severe micrognathia, short nose, elongated philtrum, thin upper lip, upstanding palpebral fissure, cleft palate
9	Silvas[15] (2013)	-	14+4	+	-	-	Mild pielectasis, patellar malposition	TOP	Micrognathia, elongated philtrum, low-set ears, short neck, campodactyly, arthrogryposis, axillary and inguinal pterigium, talipes equino-varus, ectopic, hypoplasic and multicystic right kidney, ureteral dilatation.
10	Silvas[15] (2013)	-	16	+	-	Micrognathia	Umbilical cyst x2, percretta placenta previa	TOP	Bilateral femoral shortening, micrognathia, hypertelorism, low-set ears, cleft palate.
11	Nowaczyk[16](2010)	+	12	+	+	Severe micrognathia, upturned nose, prominent cheeks	Sacral segmental dysgenesis, and left humeroradial synostosis,	Term delivery	Micrognathia , narrow mouth and full cheeks, a short nose with anterverted nares and a broad tip, and a long philtrum, glossoptosis, with an U-shaped cleft soft palate,short neck. The proximal segments of both arms were short, the thighs absent, bilateral clubfeet, overriding toes, fork-like 2 - 3 toe syndactyly, symphalangism of both thumbs and overlapping fingers. Absent right femur, severe shortening of left femur, bilateral humeroradial synostosis, a fracture of the proximal right radius, 11 pairs of ribs, and a sacrum convex to the right with only 3 vertebra.
12	Nowaczyk (2010)	+	15	+			Sacral vertebrae were disorganized. Bilateral cerebral ventriculomegaly.	TOP	Small mouth with marked retrognathia and hypoplastic mandible, long philtrum, thin upper vermilion border, and bilateral low-set dysplastic ears, cleft soft palate and glossoptosis. The upper limbs showed contractures at the shoulders with pterygia across the axillae, bilateral club feet, renal hypoplasia,absent uterus and vagina with normal ovaries, bilobed lungs,and hydrocephalus, bilateral humeroradial synostosis, bilateral severe hypoplasia of the femora and disorganized sacrum.
13	Our case	+	22+4	+	-	Severe micrognathia	Low-set ears, 5th toe malposition sacral hemivertebra (S3-S4), skin defect at such level	TOP	Severe micrognathia, facial dysmorphia, short nose, elongated philtrum, thin upper lip, low set ears, 3 sacral vertebrae and hemivertebra.

DM: diabetes mellitus. GA (w): gestational age (weeks).

Table 3. — *FH-UFS Differential diagnosis*.

Findings	Femoral hypoplasia unusual fascies syndrome	ACRO syndrome- anophtalmia, opthalmo acromelic syndrome, syndactily syndrome, Waardenburg type extremity defects	Focal femoral dysplasia	Caudal regression syndrome	Femur, Tibia, Fibula syndrome	Campomelic Dysplasia
Femur	Femoral hypoplasia or aplasia, generally asymmetrical Variable degree of shortening	Hypoplasia	Femoral shortening classified in 5 types: Type I, simple femoral hypoplasia Type II, short femur with angled dyaphisis Type III, short femur with coxa vara Type IV, absence or defect of proximal femur Type V, rudimentary or absent femur	Femoral hypoplasia	Variable degree of shortening Generally unilateral	Symmetrical shortening Moderate to severe bowing
Other long bones	Humeroradial dysostosis Absence or hypomorphism of tibia or fibula	Tibia and fibula hypoplasia		Talipes	Tibia	Tibia bowing more marked than femoral bowing. Hypoplasic fibula
Face	Micrognathia Facial fissure Small nose with a wide tip Long philtrum Thin upper lip Upslanting palpebral fissure	Cleft lip, cleft palate	Normal	-	Normal	Micrognatia Facial fissure
Scapula	Hypoplasic sometimes	-	-	-	-	Hypoplasic scapula
Genito-urinary	Renal dysplasia Renal agenesis Multicystic kidney Anomalies of the collector system Pelvic kidneys Cryptorchidsm Hypoplasia of labia or penis Macropenis	No	No	Renal agenesis Horseshoe kidney		Ambiguous genitalia XY sex reversal
Other	Syndactyly Polydactyly Talipes Dysgenesis of the sacrum Central nervous system and cardiac abnormalities	Unilateral or bilateral anophthalmia, syndactyly, brachyidactyly Metacarpal/metatarsal fusion Carpal/Tarsal bone fusion Clinodactyly of the fifth finger Widely separated nipples	Inguinal and umbilical hernias	Sacral and lumbar vertebrae dysgenesis, pelvic anomalies, club-feet, joint contractures		Occasional ventriculomegaly Cardiac anomalies Talipes
Prognosis	Limb mobility limitation, speech and feeding impairment due to facial alterations	Important orthopedic problems Blindness	Types I, II and III have few repercussions but require surgical procedures for coxa or vara correction, or lenght discrepancy in unilateral affected cases. Types IV and V require much more complex procedures with prosthetics and arthrodesis.			Lethal
Genetics	-	Autosomal recessive	-	-	-	Autosomal recessive SOX-0 de novo mutation

the present case, even when micrognathia was found in the first-trimester ultrasound study, femoral hypoplasia was not detected that early.

Prenatal diagnosis is possible but generally, only the femoral defect is detected and most cases are diagnosed postnatally [17-29].

The associated facial dysmorphism include: micrognathia, cleft lip and cleft palate, small nose with a broad tip, long philtrum, thin upper lip, and upslanting palpebral fissures. Other associated are detailed in Table 2. This is the third reported case of prenatal finding of a hemivertebra associated with this syndrome.

The use of 3D ultrasound imaging could enhance the diagnostic capacity of ultrasonography for minor facial dimorphisms such as epicanthus, short nose with a wide tip, pronounced lip philtrum or thin upper lip.

Differential diagnosis include: anophthalmia syndrome, focal femoral dysplasia, femur-tibia-fibula syndrome, caudal regression syndrome, campomelic dysplasia kypomelic dysplasia, and Antley Bixler syndrome and are detailed in Table 3.

Acknowledgments

The authors thank Marta Pakovich for the contribution of the pictures. Pathology Department of the Complejo Hospitalario Universitario Insular Materno Infantil de Canarias.

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