Case Report

Femoral-facial syndrome: Report of 2 fetal cases

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ABSTRACT

Femoral-facial syndrome (FFS) is a congenital disorder, characterized by facial dysmorphism and femoral hypoplasia. We describe the prenatal ultrasound and autopsy findings of FFS in 2 female fetuses born to diabetic mothers. Prenatal ultrasound showed micrognathia, low-set dysplastic ears and very short femora. Autopsy also demonstrated cleft palate, hypoplastic genitalia and visceral malformations including interventricular communication and posthemorrhagic hydrocephalus. Histologic study showed hyperplasia of the islets of Langerhans and femoral cartilage abnormalities. The growth plate displayed poor columnar organization of the growth plate with small zones of chondrocyte hypertrophy. Our case reports and the previously published cases of FFS allow discussing the variable expression of this challenging condition, its strong association with maternal diabetes mellitus and the main differential diagnoses.

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Introduction

Femoral-facial syndrome (FFS), initially called “femoral hypoplasia-unusual facies syndrome,” is an uncommon well-defined congenital entity (OMIM 194780). It was first described in literature in the early 1960s, but it was later delineated as a distinctive entity by Daentl et al [1]. Subsequently, several case reports of different ethnic groups have been published describing the same disorder [2–15]. To the best of our knowledge, there have been fewer than 70 reported cases in the literature. The phenotype mainly comprises hypoplasia or aplasia of femora and characteristic facial features which include long philtrum, thin upper lip, micrognathia, and low-set or dysplastic ears. Other frequent findings are short broad-tipped nose, upsloping palpebral fissures, cleft palate, and talipes equinovarus. A wide spectrum of other inconsistent malformations is observed, especially involving the skeleton, the genitourinary tract and the central nervous system (CNS) [6,7,10,12–14,16]. The etiopathogenesis is still a subject of controversy. A strong association between this condition and maternal diabetes is well documented [2,6,8,12–15]. Indeed, about 38% of affected infants are born to patients with diabetes. Moreover, FFS shares similarities with caudal regression syndrome (CRS), another condition commonly associated with maternal diabetes [2,15]. Genetic factors have been evoked as a basis for
increased susceptibility or Mendelian inheritance since this disease is found to cluster in some families [9,17]. However, no specific gene mutations have so far been identified. Recently, a study reports a de novo complex rearrangement of chromosome 2q37.2 in an affected girl [18]. Further genetic studies are required to investigate the genomic basis of this challenging condition.

In this report, we describe the in utero presentation of severe FFS in 2 female fetuses born to diabetic mothers. We also define the spectrum of associated malformations and discuss the etiology as well as the differential diagnosis with similar disorders.

Case reports

Case 1

A 39-year-old women, gravida 3, para 3, was referred to our department at 23 weeks' gestation (WG) because of an abnormal ultrasound which detected short femora and facial dysmorphism at 18 WG. She had 1 live infant from the first pregnancy. She had no knowledge of any malformations or genetic disorder in her family. She had a history of diet-controlled type 2 diabetes mellitus and antiphospholipid syndrome which resulted in a stillbirth in the early third trimester of the second pregnancy. Fetal autopsy was not performed. According to the gynecologist, the stillborn fetus did not have any of the characteristic features of FFS. The patient started treatment with heparin and prednisone during her third pregnancy and continued to follow her diet to maintain control of her diabetes. Repeated ultrasound confirmed the faciofemoral anomalies (Fig. 1). After counseling, the parents opted for termination of pregnancy which was carried out at 24 WG. Cytogenetic analyses were not performed. Maternal glycohemoglobin (HbA1c) performed 10 days after delivery was 6.8% (normal ranges 4%-5.6%), which was indicative of unbalanced diabetes. Complete fetal examination was achieved. The 24-week-old female fetus weighed 611.9 g which was within normal ranges for the gestational age. She manifested characteristic dysmorphic craniofacial features including relative macrocrania, hypertelorism, Pierre Robin sequence, short nose with broad tip and hypoplastic alae nasi, long filtrum, thin lips, small mouth, low-set and posteriorly rotated ears, and low implantation of hair. She also presented with short neck, major labia hypoplasia and limbs anomalies including rhizomelic micromelia predominating on lower limbs, malposition of the extremities (camptodactyly, overlapping toes), and nail hypoplasia (Fig. 2). A cutaneous sacral dimple was noted without spinal dysraphism. Skeletal radiographs showed Sprengel deformity, short humeri, extremely hypoplastic femora, hypoplastic fibulas, hypoplastic pelvic bones with narrow and vertical iliac wings, short sacrum and ossification of the astragalus which normally occur at 28 WG (Fig. 3).

Internal examination showed increased subcutaneous fat, thymic hyperplasia, cardiovascular anomalies (posterior interventricular communication, persistence of the left superior vein cava), hepatomegaly, and kidney asymmetry with mild renal hypotrophy. The neuropathologic examination was normal.

Histologic study showed increased islets of Langerhans and cystic dilation of few renal cortical tubes. The femoral bone exhibited features of cartilage dysplasia. Growth plate showed poor columnar organization of the growth plate and small zones of chondrocyte hypertrophy (Fig. 4).

The placenta was hypoplasic (116.2 g, normal ranges 220-235 g). Histologic examination revealed anomalies which were consistent with chronic uteroplacental insufficiency, including diffuse villous hypotrophy, congestive and hypermature villi, and discrete syncytial clusters.

Case 2

A 35-year-old gravida 2 para 1 with a history of unexplained spontaneous miscarriage at 10 WG was referred to our department at 23 WG because of an abnormal ultrasound which revealed short femora. She had a history of insulin-dependent gestational diabetes mellitus. Repeated ultrasonographic examination showed a female fetus with severe micrognathia associated with very short and angular femora. Prenatal cytogenetic analyses were not performed. The couple underwent
Fig. 2 – Case 1. (a, b): Characteristic dysmorphic cranio-facial features with short neck, short and bowed lower limbs with malposition of the extremities. Note the severe micrognathia and low-set and posteriorly rotated ears in (b).

Fig. 3 – Case 1. (a, b): Skeletal radiographs demonstrate bilateral extreme hypoplasia of the femora, hypoplastic fibulas, narrow and vertical iliac wings, and short sacrum. Note the Sprengel deformity in (a).
counseling and decided to terminate the pregnancy which
was carried out at 23.5 WG. The fetus weighed 650 g which
was within normal ranges for gestational age. Macroscopic ex-
amination showed characteristic dysmorphic facial features
including hypertelorism, upslanting palpebral fissures, short
broad-tipped nose, thin lips, bifid uvula, severe microretrog-
nathia and microtic dysplastic ears. The lower limbs were
very short and bowed and the external genitalia were very hy-
poplastic (Fig. 5). Radiological examination revealed severely
hypoplastic femora with tapered upper ends, short humeri,
vertical orientation of hypoplastic pelvic bones, and sacral
hemivertebrae (Fig. 6). Internal examination showed unicor-
nate uterus, cerebral intraventricular, and posterior fossa
hemorrhage with dilatation of the lateral and third ventricles.
Histologic examination demonstrated hypertrophy and hy-
perplasia of the islets of Langerhans (Fig. 7a). Femoral growth
plate displayed very short columns of proliferating and hy-
pertrophic chondrocytes with haphazardly arranged chondro-
cytes (Fig. 7b).

The placenta was not received.

Discussion

The variability of the clinical expression and severity of FFS is
emphasized in the literature. The fetal phenotype described
in this report fit well with the severe end of the clinical spec-
trum of FFS. The case 1 presented with Pierre Robin sequence,
extreme shortening of the femora that was clearly demon-
strated at 18 WG, short sacrum, genitourinary, and cardio-
vascular abnormalities. In addition to the characteristic facial
dysmorphism, femoral hypoplasia, sacral hemivertebrae, and
severe hypoplastic external genitalia, the case 2 had unicor-
nate uterus and posthemorrhagic hydrocephalus which have
not been previously reported. In both cases the femoral growth
plate exhibited significant abnormalities. The growth plate
displayed poor columnar organization of the growth plate
with small zones of chondrocyte hypertrophy.

The key features of the FFS are bilateral femoral hypopla-
sia and facial dysmorphism. Early definition of the minimal
diagnostic criteria for FFS is motivated by the need to distin-
guish this condition from other confusing entities. Thus, ac-
cording to Johnson et al [6], the characteristic features con-
sist of significant femoral hypoplasia and presence of at least
2 of 4 dysmorphic facial traits: upslanting eyes, hypoplastic
alae nasii with broad nasal tip, long philtrum with thin up-
per lip, and small mouth and mandible. Nevertheless, when
examining the published cases, the facial dysmorphism ap-
pears to be very variable, ranging from evident Pierre Robin
sequence with dysplastic ears (similarly to our case 1) to more
subtle features such as upslanting palpebral fissures, short
broad-tipped nose, long philtrum, thin lips, cleft palate, and
micrognathia (similarly to our case 2) [4,7,13]. In addition,
the typical facial features can be missing [5]. But, the more con-
stant feature is micrognathia (75% of cases). As it is underlined
by Maisels and Stiwiell [3], almost in all affected infants, the
cleft only involves the secondary palate. Unilateral or bilat-
eral cleft lip and palate is observed in only 4 published cases
[6,11,13,19].

The femoral hypoplasia is reported to be usually sym-
metrical in female patients, as in our cases, and asymmet-
rical in males, without any plausible explanation [1,5–7,13].
The femoral involvement can be unilateral and of a vari-
able degree, ranging from femoral agenesis to mild hypoplasia
[6,7,13,14].

FFS shows an extreme phenotypic variability as a wide
spectrum of other inconstant malformations that involve all
the systems. They include skeletal anomalies, especially ver-
tebrosegmentation defects, pelvic dysplasia, aplasia or hy-
poplasia of the fibulae, humeroradial synostosis, and Spre-
gel deformity. The pelvic abnormalities are more evident and
detailed in living children and adult patients, encompassing
hypoplastic and vertical orientation of iliac bones and ischi-
axis, undeveloped acetabulae, and large obturator foramina
[5]. The involvement of the long bones and extremities are
generally associated with severe femoral and pelvic dysplasia.
It is of particular interest that preaxial polydactyly and syn-
dactyly, which represent unusual anomalies, are documented
in only 7 and 6 reported cases, respectively [2,8,12,19]. Other
reported malformations are consistent of genitourinary, car-
diovascular, and CNS defects [2,6,7,12,13]. The genitourinary

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abnormalities are the most frequent visceral malformations, accounting for 53% of cases. It is also noteworthy that severe CNS malformations have been reported in infants with FFS born to diabetic or nondiabetic mothers, including microcephaly, neuronal migration defects, agenesis of the corpus callosum, ventriculomegaly, and neural tube defects such as encephalocele and spina bifida [10,12]. It is clear that these CNS defects may be a part of the spectrum of the FFS abnormalities. In our case reports, we only noted a posthemorrhagic hydrocephalus in 1 case despite the severity of the fetal phenotype. As documented in our cases, respiratory and gastrointestinal malformations are observed less frequently in this condition. It is important to note that there have been no available microarray data in these reports.

FFS is included in the “Limb hypoplasia-reduction defects group” (group 39) according to the classification of genetic skeletal disorders, 2015 revision [20]. We observed in our cases significant abnormalities in femoral growth plate. The chondrocytic dysplasia seemed to be generalized as the other long bones, especially humeri, were also short on X-ray. This could be supported by histologic evaluation of other cartilage sites, which was unfortunately not performed in our study. Therefore, an important question raised by this study is why the femurs are most severely affected?

Prenatal diagnosis suspicion of FFS is easy by ultrasound since the major abnormalities can be detected in utero in either late first or early second trimester, especially in the setting of maternal diabetes [13,14]. The 2 major signs, which can lead to the consideration of FFS, are the extremely shortened or absent femora and the severe micrognathia. The 3D ultrasound may assist in the depiction of facial dysmorphic features during the second. Prenatal ultrasound was not performed until second trimester in our cases (18-23 WG), at which severe femoral hypoplasia was detected. The diagnosis may occasionally be detected during the first trimester of pregnancy, earlier than 14 WG [13,14]. The early prenatal diagnosis is challenging because the fetal facial features cannot be reliably evaluated before 18 WG. However, despite these limitations, micrognathia can be apparent [13]. Early diagnosis is of extremely great importance as it allows providing parents with the necessary information about the evolution and prognosis of this syndrome. Despite the absence of intellectual disability, the orthopedic handicap may be a significant source of parental anxiety regardless of the presence of other malformations.

The diagnosis of FFS is easily established in neonates or fetuses after interruption of the pregnancy. The differential diagnosis of FFS is particularly discussed on the prenatal ultrasound. It involves a group of rare diseases whose characteristic features include micrognathia and femoral hypoplasia, especially skeletal dysplasias such as campomelic dysplasia, Antley-Bixler syndrome, and kyphomelic dysplasia.
In fact, these conditions are characterized by shortening and abnormal bowing of the long bones. In FFS, the femora are usually more severely affected and the other long bones are rarely involved. The CRS should also be considered in the differential diagnosis. Similarities between FFS and CRS are early pointed in literature [2,3]. There are many findings which overlap between these congenital disorders, especially the sacral and urogenital tract abnormalities, though facial anomalies are uncommon in CRS and the sacral dysgenesis is less frequently observed in FFS. Given their similarities, both conditions may represent different manifestations of the same disorder which is relevant to a common pathogenetic mechanism affecting the early skeletal morphogenesis at different times of embryogenesis [5–8]. The report of Gupta et al [15] of an infant born to diabetic mother and presenting with features of both disorders supports this hypothesis.

The etiology of this rare syndrome has remained uncertain since the first description in 1975 [1]. The scarcity, sporadic occurrence, and the phenotypic heterogeneity of this syndrome prevent phenotypic and genetic correlations. The full syndrome may represent the most severe expression of a malformation complex with isolated femoral hypoplasia as the mildest manifestation [6]. Maternal diabetes is found to be associated with approximately 40% of the previously published cases of FFS. The teratogenic effect of diabetes is raised because of the associated malformations and similarities shared by this syndrome with the CRS which has been recognized as part of the spectrum of diabetic embryopathy. Compared with the literature data, some features especially first arch syndrome, cardiovascular defects, cerebral ischemic-hemorrhagic injury, and hyperplasia of the islets of Langerhans, provide additional arguments involving maternal diabetes in FFS pathogenesis. The risk of this disease could be increased by interaction of maternal diabetes with genetic factors. In fact, the characteristic facial features in combination with bilateral femoral hypoplasia, as well as the bilateral and severe symmetrical limb defects noted in many cases argue in favor of a possible genetic predisposition [3]. Genetic involvement is early aroused by Lampert [17] who describes an affected father and daughter and suggests that FFS may be inherited as an autosomal dominant trait. The report of

**Fig. 6** – Case 2. Skeletal radiograph demonstrates bilateral severe hypoplasia of the femora, hypoplastic and vertical pelvic bones, and sacral hemivertebrae.

**Fig. 7** – Case 2. (a): Pancreatic tissue shows hypertrophy and hyperplasia of the islets of Langerhans (H&E, x40). (b): Proximal femoral epiphysis shows major growth plate abnormalities with less well-defined columns of proliferating and hypertrophic chondrocytes. Columns of hypertrophic chondrocytes are very short (H&E, x40).
Robinow et al. [9] also supports the occasional transmission of the FFS as an autosomal dominant with incomplete penetrance. However, there have been no instances of parental consanguinity, no obvious paternal age effect, no further instances of genetic transmission, and no familial history of skeletal disorders. Thus, many hypotheses are raised, stating that genetic heterogeneity and nongenetic factors are possibly involved in this syndrome [6]. It is plausible to suggest that disturbance of glucose pathways in early development, similar to other teratogens such as viral infection, perfusion failure, and drug exposure, would be a strong maternal environmental factor acting on a polygenic background. Thus, as it is pointed out by Lord and Beighton [5], FFS is a condition that underlies complex and multifactorial mechanisms rather than a syndromic entity resulting from a simple genetic mechanism. The recent report of Spielmann et al. [18] provides a powerful argument in favor of a genetic basis of FFS. Using a combination of array CGH, qPCR, and FISH, they identified a de novo deletion/duplication together encompassing more than 70 genes in terminal 2q in an affected girl born to nondiabetic mother. The size, gene content, and de novo occurrence of this chromosome abnormality provide consistent evidence of its pathogenicity. These findings corroborate the hypothesis of a polygenic background, but do not exclude a multifactorial pathogenesis. Further genetic studies are required to identify the specific involved genes and their exact role in the determination of the FFS phenotype.

In conclusion, we reported on 2 further fetuses presenting with FFS. The fetopathologic examination allowed us to especially point out the variable expression of this challenging condition and the significant abnormalities in femoral growth plate. These findings emphasize the need for etiologic investigation of FFS that shows multifactorial inheritance.

Declaration of Competing Interest

The authors declare no competing interest.

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