

Case Report

THE FEMUR-FIBULA-ULNA (FFU) COMPLEX: DOES IT NEED GENETIC COUNSELING ?

Femur-Fibula-Ulna (FFU) kompleksi: Genetik danışmanlık gerekir mi ?

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ABSTRACT

The femur-fibula-ulna (FFU) complex is a rare sporadic syndrome. The etiology is unknown. Familial occurrence is very rare. In a case the genetic components is unclear, it is rather difficult to give genetic counseling. In this report we discuss how we evaluate this syndrome from a genetic counselor's window and genetic counseling for this patient should be based on which principle.

Key words: femur-fibular-ulna (FFU) complex, genetic counseling

ÖZET

Femur-Fibula-Ulna (FFU) kompleksi nadir görülen bir sporadik sendromdur. Etiyolojisi bilinmeyen hastalık çok nadiren ailevi geçiş gösterir. Genetik nedenlerin net olarak bilinmediği olgularda genetik danışmanlık daha zor olabilmektedir. Burada, bu sendromun nasıl değerlendirileceğini bir genetik danışmanın bakış açısından tartışarak "Bu hastaya hangi temellere dayanarak genetik danışma verilmelidir ?" sorusunu yanıtlamaya çalışacağız.

INTRODUCTION

The Femur-Fibula-Ulna (FFU) complex (OMIM #228200) is a rare, mostly sporadic limb deficiency syndrome. Its prevalence has been estimated about 1 in 100.000 live births[1]. Males are effected nearly twice than females. Limb malformations in the FFU complex are usually unilateral (1). FFU consists highly variable combinations of congenital anomalies of femur, fibula, and/or ulna, which can appear along with finger/toe anomalies at the ulnar/fibular side. The typical defect of the femur can be designated as PFFD (proximal focal femoral deficiency). Upper limb defects, a defect of ulna or ulnar ray, amelia of one arm, hypoplasia of the humerus, and humero-radial synostosis. are usually a major component of this syndrome. Also, the lower limbs are less often affected than the upper limbs. The lower limb deficiency may be located on the asymmetrical side of the upper limb defect. The right side upper limb is preferentially involved (2). In this report we discuss how we evaluate this syndrome from a genetic counselor's window and genetic counseling for this patient should be based on which principle.

CASE REPORT

A 22-year-old girl who has upper and lower limb malformations applied to our clinic for genetic counseling. External examination revealed bilateral

amelia, severe right lower limb hypoplasia with rhizomesomelic shortening. There was scoliosis on the back and pes cavus deformity of the right foot. Right foot 1th and 2th fingers were quite discreted. 3th, 4th and 5th fingers were shorter and 4th finger was on the 3th finger. There was partial cutaneous syndactyly of fingers 4 and 5. The patient had a sacral dermal sinus. Other physical examination findings were normal except for hirsutism on the medial femoral regions (Figure1).

We learned that she was born 3500 grams by spontaneous vaginal delivery at a hospital without uneventful gestation period and any birth injuries.

Perinatal history was normal except for influenza infection in the first months of pregnancy. The parents were normal, healthy and non-consanguineous. No other family members were known to have similar phenotype in the pedigree analysis.

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Figure 1. Physical appearance of the patient

Electrocardiographic examination of the patient and other laboratory findings were normal. Chromosome analysis showed a normal 46,XX karyotype.

Radiographic findings; rotoscoliosis on thoracal vertebral (Figure 2-A), shallow fossa acetabuli on the right, proximal right femur dislocated toward to iliac bone, incomplete development and deformed appearance of right femur and tibia (Figure 2-B), highly rudimental right fibula (Figure 2-C) and pes cavus deformity on the right with bifid appearance of the 3th metatarsal, 4 pcs metatarsal and 6 pcs phalanks (Figure 2-D). The left hemipelvis and left femur appear normal.



Figure 2. X-rays of the patient

DISCUSSION

Genetic counseling is a vital part of the field of medical genetics. Genetic counselors provide information and support to families affected by or at risk of a genetic disorder. They serve as a central resource of information about genetic disorders but sometimes you may need to give genetic counseling for non-genetic diseases. This patient's mother came to us with some questions in her mind: when my daughter got married, what is the risk of occurrence of this condition in her children? What is the risk of my son's children for this condition? etc. FFU is not considered a hereditary condition, but the mother wanted to learn genetic risks? In this case, what does a genetic counselor do?

In FFU, there isn't an evidence from parent to child transmission. Familial recurrence may be due to chance. It does not seem to be associated with consanguinity or a paternal age effect (3,4). Patients have been reported in all populations without geographic or ethnic predominance. Few cases observed in monozygotic twins have been discordant (5). There is no evidence for specific environmental causes.

There are some similarities between the FFU complex and focal dermal hypoplasia. The FFU complex shows a degree of asymmetry similar to the high degree of asymmetry of limb defects seen in the X-linked dominant focal dermal hypoplasia (OMIM #305600) (6). Focal dermal hypoplasia or the Goltz syndrome is usually sporadic and occurs mainly in primarily females while FFU in males. But all FFU cases are sporadic so this complex is certainly not due to a dominant X-linked inheritance. Some authors support early somatic mutation as a cause of FFU, but this is has not yet been proven (3,5,7). So, in my opinion, our case can be evaluated as a child with congenital malformations and genetic counseling should be based on this principle.

In the context of congenital malformations genetic counseling is essential. Although the high incidence of congenital malformations in miscarriages, stillborns and liveborns, the mechanism underlying those diseases are still poorly understood. In the absence of well established cause, genetic counseling becomes quite difficult. Only a strong family history of congenital anomalies may provide valuable information concerning risk determination. In most cases, no family history is reported with an identified unique case. If the malformation is part of a more complex syndrome the chances to find a diagnosis increases. Otherwise, when an isolated malformation is described the likelihood of finding the cause is drastically reduced.

When considering isolated congenital malformations, in an important proportion of cases, it is suggested that effect of genetic factors be considered as in multifactorial model (8). Congenital malformations usually occur in the setting of multiple congenital anomalies, including dysmorphic facial

features, or in association with different organ malformations, growth abnormalities and developmental defects (9). When multiple congenital anomalies are identified, it is usually possible to not recognize a known syndrome. In those cases, screening new methodologies such as exome sequencing (WES), array-CGH or MLPA are useful to diagnose the cause.

As a conclusion, congenital malformations, particularly the sporadic ones, are highly heterogeneous disorders due to the huge amount of genetic and epigenetic mechanisms involved in their etiopathogenesis. Genetic counseling may sometimes be required in the absence of known genetic causes.

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