A case with proximal femoral focal deficiency (PFFD) and fibular A/hypoplasia (FA/H) associated with urogenital anomalies

Hacer Ergin[1], C. Nur Semerci[2], Mevlüt Bican[1], Füsun Düzcan[2], A. Baki Yağcı[3]
Kadri Murat Erdoğan[2], A. Çevik Tufan[4]

Departments of [1]Pediatrics, [2]Medical Biology Genetics Unit, [3]Radiology, and [4]Histology and Embryology, Pamukkale University Faculty of Medicine, Denizli, Turkey

SUMMARY: Ergin H, Semerci CN, Bican M, Düzcan F, Yağcı AB, Erdoğan KM, Tufan AÇ. A case with proximal femoral focal deficiency (PFFD) and fibular A/hypoplasia (FA/H) associated with urogenital anomalies. Turk J Pediatr 2006; 48: 380-382.

Malformations of the lower limbs are rare and heterogeneous anomalies. Some congenital anomalies involving face, gastrointestinal system, skeletal system, urogenital system, heart, lung and diaphragma associated with lower limb malformations have been described in the literature. Here, we report a case of left proximal femoral focal deficiency (PFFD) together with fibular aplasia associated with left undescended testis and hypospadias. The putative embryologic mechanisms of lower limb defects and their possible association with lower urogenital tract malformations are also discussed.

Key words: proximal femoral focal deficiency (PFFD), fibular a/hypoplasia (FA/H), urogenital anomalies, Hox genes.

Proximal femoral focal deficiency (PFFD) and fibular aplasia/hypoplasia (FAH) are considered as the main anomalies involved in congenital asymmetry of the lower limbs. PFFD is a rare anomaly, occurring with a frequency of approximately 0.2/10,000 live births. PFFD is described as an outbreak of femoral hypoplasia or aplasia, isolated or associated with fibular and/or ulnar anomalies. It is an uncommon congenital defect that involves the femur and acetabulum in varying degrees. It can either be isolated or in combination with other defects of the lower limbs including absence or hypoplasia of the patella, FAH, and absence of lateral foot rays[1-3]. In addition, some congenital anomalies involving other systems such as face, gastrointestinal system, skeletal system, urogenital system, heart, lung and diaphragma associated with lower limb malformations have also been described in the literature[4-7]. Urogenital anomalies that can be associated with PFFD are described as hypospadias, cryptorchidism, small penis, vaginal septum, double uterus, double cervix, vesico-ureteric reflux, ectopic ureteric orifices, and pelvi-ureteric obstruction.

Here, we present a male infant with PFFD/FAH associated with urogenital anomalies including hypospadias and left undescended testis and discuss the possible molecular mechanisms that may have caused these defects.

Case Report

The male infant is the first child of healthy nonconsanguineous parents. Both parents were 28 years old. Family history and pregnancy were unremarkable. There was no history of maternal diabetes or exposure to any teratogenic agent during the pregnancy. The boy was delivered spontaneously at 39 weeks of gestation. Birth weight was 3500 g (50th centile), length was 50 cm (50th-75th centile), and occipitofrontal head circumference was 34 cm (25th-50th centile). Physical examination revealed a shorter left lower limb compared to the right. There were four toes including cutaneous syndactyly between two of them and the left foot was also twisted. The right lower limb, upper limbs and face were normal (Fig. 1). Radiographic examinations showed marked hypoplasia of the proximal 3/4 portion of the left femur. The ossification of the distal

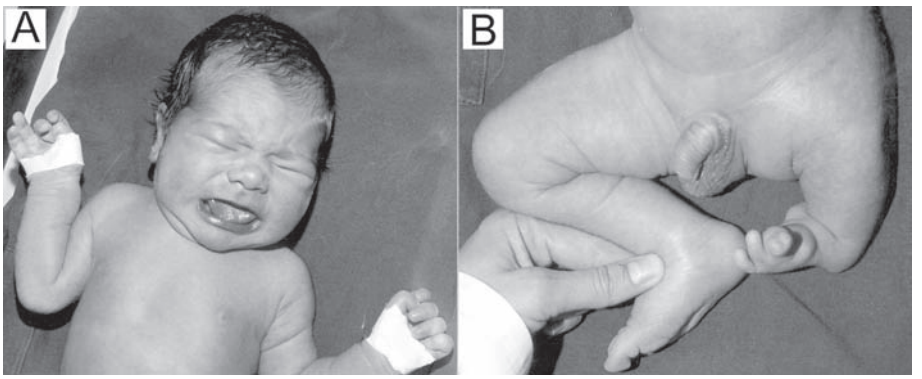

Fig. 1. Phenotype of the patient. A) Normal face, head and upper extremities. B) Normal right lower extremity and the affected left extremity.

femoral epiphysis was behind the expected level according to the gestational age. The left tibia was hypoplastic and the left fibula was absent. The foot radiographs revealed only one hypoplastic talar bone, four metatarsal bones and three phalanges on the left. No skeletal abnormality was observed on the right lower extremity (Fig. 2). There was no pathology on chest roentgenograms and abdominal ultrasonography. Routine laboratory tests and ophthalmological examination were also normal. Peripheral blood chromosomal analysis showed normal male karyotype (46,XY). The physical examination of the parents including their limbs was normal.

Discussion

Proximal femoral focal deficiency is a rare malformation of the lower limbs that involves the femur and acetabulum in varying degrees. It may occur with or without fibular hemimelia and can be unilateral or bilateral in presentation[8]. FAH covers a spectrum of malformations including variable degrees of FAH, shortening of the tibia and femur, genu valgum and lateral femoral condyle hypoplasia, knee ligament laxity, tibial bowing, ball and socket ankle joint, tarsal coalitions and missing lateral rays of the foot[9]. In the case presented, anomalies on the left side included hypoplasia of the proximal femur, fibular aplasia, tibial hypoplasia, aplasia of the distal femoral epiphyses, talar aplasia and oligosyndactyly. Some additional features and malformations have been defined associated with congenital limb deficiency including facial, gastrointestinal, urogenital, cardiac, and diaphragmatic anomalies[4-6]. In our patient, left undescended testis and hypospadias were present in addition to limb malformations.

It has long been suggested that the basis of such anomalies may involve an alteration of limb "developmental fields", i.e., tibial and

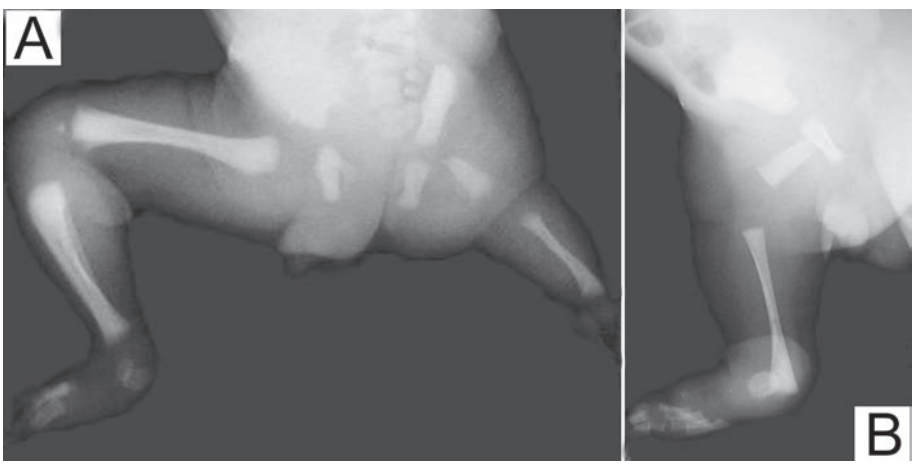

Fig. 2. Radiographic images of the lower extremities and pelvis. A) Normal right lower extremity and pelvis. B) Affected left extremity.

fibular fields[10]. However, a specific genetic cause, such as mutations involving a specific gene family, etc., has not been elaborated yet. One such affected putative gene family may be the Hox gene family involved in skeletogenesis both axial and appendicular, as well as in other systems such as the urogenital system[11].

Five paralogous gene families, Hox 9-13, from Hox A and Hox D gene groups, come together in a co-linearly (HoxA-9 to HoxA-13 and HoxD-9 to HoxD-13) and play important roles in limb skeletal development. The paralogous groups that are represented with a smaller number, such as HoxA-9/HoxD-9 or HoxA-10/HoxD-10, start their patterning function during limb development earlier and in a more proximally localized area compared to those that are represented with a higher number, such as HoxA-12/HoxD-12 or HoxA-13/HoxD-13. This allows the patterning of each different skeletal area by another paralogous group of HoxA/HoxD genes. However, there are some structures where the functions of two consecutive paralogous groups overlap. Thus, they can compensate for each other's function up to a very significant degree, so that if a mutation blocks the function of one of these paralogous genes, the other continues to function to pattern the same skeletal structure (i.e. HoxA-9 can compensate for HoxD-9 to pattern the humerus) (Fig. 3).

In our case, mutation(s) involving the Hox gene clusters may be a part of the genetic causes of the defects seen in this child[11]. Genetic studies have shown that the severity of the phenotype correlates with the increasing number of mutated alleles. These types of mutations are rare and usually sporadic due to the effect of teratogenic agents during the period of activation of these genes in the process of axial and appendicular skeletogenesis[1,3,11]. Cases with familial history, on the other hand, are extremely rare.

The knowledge of involvement of Hox genes in developmental processes other than skeletogenesis, i.e., in the urogenital system and others, is supportive of our hypothesis for this case[3,11,12]. Thus, it is our belief that there is quite a lot of genetic information available to start to evaluate involvement of candidate gene mutations in such malformations like PFFD and FAH, and Hox gene clusters may be a good candidate to start this approach.

REFERENCES

1. Hamanishi C. Congenital short femur. Clinical, genetic, and epidemiological comparison of the naturally occurring condition with that caused by thalidomide. J Bone Joint Surg Br 1980; 62: 307-320.
2. Sorge G, Ardito S, Genuardi M, et al. Proximal femoral focal deficiency (PFFD) and fibular a/hypoplasia (FA/H): a model of a developmental field defect. Am J Med Genet 1995; 55: 427-432.
3. Ashkenazy M, Lurie S, Ben-Itzhak I, Appelman Z, Casbi B. Unilateral congenital short femur: a case report. Prenatal Diagn 1990; 10: 67-70.
4. Lipson AH. Amelia of the arms and femur/fibula deficiency with splenogonadal fusion in a child born to a consanguineous couple. Am J Med Genet 1995; 55: 265-268.
5. Verma A, Jain N, Jain K. Additional malformations in femoral hypoplasia: unusual facies syndrome. Indian J Pediatr 2002; 69: 531-532.
6. Düzcan F, Ergin H, Perçin EF, Tepeli E, Erkula G. Femoral-facial syndrome with hemifacial microsomia and hypoglossia. Clin Dysmorphol 2004; 13: 43-44.
7. Khoury NJ, Haddad MC, Hourani MH. Tibial and fibular developmental fields defects. Eur Radiol 1999; 9: 1879-1881.
8. Stormer SV. Proximal femoral focal deficiency. Orthop Nurs 1997; 16(5): 25-31.
9. Caskey PM, Lester EL. Association of fibular hemimelia and clubfoot. J Pediatr Orthop 2002; 22: 522-525.
10. Lewin SO, Opitz JM. Fibular a/hypoplasia: review and documentation of the fibular developmental field. Am J Med Genet 1986; 91: 347-356.
11. Goodman FR. Limb malformation and the human Hox genes. Am J Med Genet 2002; 112: 256-265.
12. Gilbert SF. Development of the tetrapod limb. In: Gilbert SF (ed). Developmental Biology (7th ed). Sunderland: Sinauer Associates Inc. Publishers; 2003: 523-546.

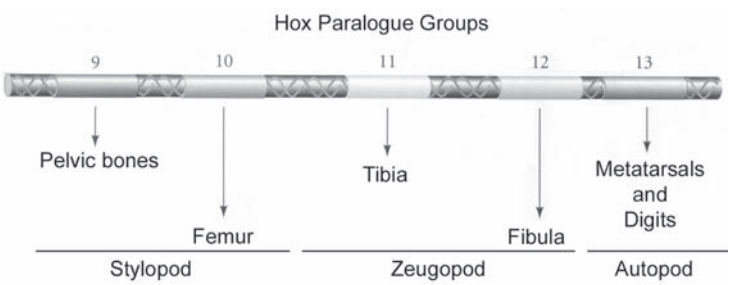

Fig. 3. Working hypothesis implicating Hox gene mutations in skeletal malformations (Adapted from Gilbert SF[12]).