A Turkish Female Twin Sister Patient with Fibular Aplasia, Congenital Tibia Pseudoarthrosis, Oligosyndactyly, and Negative *WNT7A* Gene Mutation

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Abstract

We report a rare limb defect named as fibular aplasia, tibial campomelia, and oligosyndactyly (FATCO) syndrome in a female monozygotic twin with a normal twin sister, presented with anterior tibia pseudarthrosis, oligosyndactyly, and pes equinovarus. Radiographic examination displayed the absence of left fibulae, anterolateral pseudarthrosis of left tibia, and the absence of some metatarsus and phalangeal bones. Our case report is the first to report that only one of the identical twins was affected by FATCO syndrome, which is a significant finding because the pathogenicity of FATCO syndrome is yet to be identified, and this clinical case may provide a new insight for discovering the etiology of FATCO syndrome.

Keywords

- FATCO
- fibular aplasia
- oligosyndactyly

Introduction

Fibular aplasia, tibial campomelia, and oligosyndactyly (FATCO) syndrome (OMIM no. 246570) is an extremely rare syndrome and first described in 1981 by Hecht and Scott.¹ Patients with FATCO syndrome showed shortening and anterior bowing of the lower limb at the distal third of the tibia with soft tissue dimpling on the same area, oligodactyly of the foot, and oligosyndactyly of the hand. The etiology of this syndrome is currently unknown. The syndrome is usually sporadic, but X-linked, autosomal recessive, and dominant inheritances have been previously reported.² A few genes have been searched for FATCO (*WNT7A*, *TP63*, and *WNT10B*), but any specific mutation for this syndrome was detected.^{2–4} On the other hand, mutations in *WNT7A* have been shown to cause Fuhrmann syndrome (OMIM no. 228930) and the Al-Awadi/Raas-Rothschild syndrome (OMIM no. 276820), which are other rare limb malformations characterized by various degrees of limb aplasia or hypoplasia and joint dysplasia.⁵

In this report, we documented a rare congenital limb deficiency comprising features of FATCO syndrome.

Case Report

An 8-month-old female infant was referred for genetic evaluation by the orthopedic department because of evident extremity abnormalities. She was one of monozygotic twin sisters; her twin sister was apparently healthy, and they have two healthy elder brothers. Her parents were unrelated and her family history was unremarkable (►Fig. 1). The patient was born at full term by elective cesarean section, with birth weight of 1.8 kg. The pregnancy and delivery were uneventful. The mother had no history of chronic illness or use of tobacco, drugs, alcohol, or exposure to radiation during pregnancy. When our patient was born, her mother was 37 years old and her father was 26 years old.

On physical examination of 8 months of age, she was 62 cm and 6.8 kg and her head circumference was 40.5 cm.

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Fig. 1 Pedigree of our case's family (our case: III:4).

On clinical examination, there was a regenerated anterolateral pseudarthrosis of left tibia with a bowing at the distal third of it, associated with soft tissue dimpling over the apex of the deformity. There was oligodactyly on left foot which has four fingers (►Figs. 2 and 3), while the right foot was normal. In her upper extremities, the right hand had five fingers with a bigger third finger than the other fingers (►Fig. 4); the left hand had duplication of the fourth finger's distal phalanx (►Fig. 5). The rest of the upper extremities was normal. Her external genitalia were normal. She had neither facial dysmorphism nor other external anomalies.

Radiographic examination revealed a complete absence of the left fibula and anterior bowing of the left tibia (►Fig. 6).

Fig. 2 Our patient's right and left leg comparison and the tibia pseudoarthrosis.

Fig. 3 Our patient's left foot with four fingers.

The radiograph of the left foot showed four metatarsal bones and four fingers. The radiograph of the right foot showed four metatarsi with a duplication of the third metatarsus and five fingers (►Fig. 7). The radiographic examination also showed that the right hand's fourth metacarpal bone was extremely hypoplastic (►Fig. 8). The X-ray additionally showed that the left hand had five metacarpi and fingers, but fourth finger's distal phalanx was duplicated (►Fig. 9). Humeri, ulnae, radii, spine, skull, or pelvis were otherwise all normal.

The results of the laboratory tests were normal: thyroid-stimulating hormone: 4.79 mIU/L (0.53–5.4), T4: 1.39 ng/dL (0.93–1.7), parathyroid hormone: 15.0 ng/L (15–65), E₂: 25.68 ng/L (12.5–166), follicle-stimulating hormone: 9.94 IU/L (3.5–12.5), luteinizing hormone: <0.100 IU/L (2.4–12.6). An echocardiographic examination showed a 6.5 mm secundum type atrial septal defect in the hearth. Hearing and vision tests were normal. Abdominal ultrasound was normal.

A postnatal peripheral blood (from lymphocyte) karyotype analysis showed 46, XX (a normal female karyotype). Based on these clinical findings, other syndromes were

Fig. 4 Our patient's right hand with five fingers and bigger third finger.

Fig. 5 Our patient's left hand with fourth finger distal phalanx duplication.

Fig. 6 Our patient's left leg X-ray. Absent of left fibula and anterolateral tibial bowing with a normal femur.

Fig. 7 Our patient's left and right feet X-ray. Four metatarsus and four fingers on left foot, four metatarsus with third metatarsal bone duplication, and five fingers on the right foot.

Fig. 8 Our patient's right-hand X-ray. Fourth metacarpal bone was extremely hypoplastic.

needed to be ruled out. Based on current database, *WNT7A* gene is associated with other syndromes, which are similar to FATCO (such as Fuhrmann). The sequencing analysis of the coding regions of the *WNT7A* gene and exon–intron boundaries was performed and the result was normal (Illumina MiSeq analysis platform was used for his purpose and the data was analyzed by Integrative Genomic Viewer [IGV]). To confirm that there is no overlap with another disorder, for instance, neurofibromatosis (which is responsible for 40–80% of congenital anterolateral tibia pseudoarthrosis⁶), *NF1* gene sequencing analysis of coding regions and exon–intron boundaries was performed. It also revealed a normal result (the next generation sequencing [NGS] raw data were uploaded to sequence platform of Genomize and then the

Fig. 9 Our patient's left-hand X-ray. Five metacarpus and fingers but fourth finger distal phalanx was duplicated.

data was analyzed by IGV). Meanwhile, a chimerism analysis was performed, which confirmed the monozygosity of the twins.

Discussion

In this report, we described the malformations: fibular aplasia, oligosyndactyly, tibial campomelia that matched with the triad of FATCO syndrome (OMIM #246570).

The name FATCO was proposed by Courten's et al⁷ in 2005 to describe a rare syndrome, first described by Hecht and Scott in 1981, that is composed of fibular aplasia, tibial campomelia, and oligosyndactyly. This disease shows a wide range of variability in terms of clinical presentation and its exact inheritance still unknown. In addition, there are no consistent associations with environmental exposures. To date, nearly 15 patients with FATCO syndrome have been reported. Interestingly, our patient was a female as Ebtesam M. Abdalla and

Table 1 Cases of FATCO syndrome

Case	Gender	Upper extremities	Lower extremities	Additional findings	Ref.
1	M		Oligosyndactyly of the left foot Short angulated left leg Fibular aplasia of the left leg A short-angulated tibia		3
2	M	Left hand: oligosyndactyly Right hand: normal Ulnae: normal Radii: normal	Left lower limb: normal Right lower limb: anterior bowing and shortness with associated overlying soft tissue dimples Oligosyndactyly Vth ray: absence	No facial dysmorphism No other anomalies	7
3	F	Totally normal	Tibia: bilateral shortening and anterior bowing at the distal third of the tibia, skin dimpling Both fibula: absence oligosyndactyly of both feet	No other external anomalies	6
4	F	Left hand: oligosyndactyly Right hand: absence Ulnae: normal	Tibia: anterior bowing and shortness with associated overlying soft tissue dimples Fibula: absence Femora: normal Four-ray feet	No heart defect Mental development normal	16
5	M	Right hand: oligosyndactyly Ulnae: normal	Left tibia: bowed Left fibula: absence Femur: normal Fifth toe: absence Clubfeet	A fetus at 24 week Small-for-date	17
6	M		Tibia: bowing and shortness with dimples unilaterally Fibulae: absence Oligosyndactyly Femora: normal	Pelvis: normal No cardiac anomaly Neurological development: normal	18
7	M	oligosyndactyly	Tibia: bowing and shortness with dimples bilaterally Fibulae: absence Oligosyndactyly Femora: normal oligosyndactyly of both feet	Pelvis: normal No cardiac anomaly Neurological development: normal	18
8	M	Right hand: oligosyndactyly Ulnae: normal Humeri: normal	Tibia: anterior bowing and shortness with associated overlying soft tissue dimples Left fibula: aplasia Right fibula: hypoplasia Bilateral feet: oligosyndactyly	A left-sided cleft lip palate	4

Abbreviation: **FATCO**, fibular aplasia, tibial campomelia, and oligosyndactyly.

Ahmed A. El-Beheiry's patient,⁶ although there is a male predominance in this syndrome. Furthermore, in this report, we described a monozygotic twin sister with FATCO syndrome. As far as we know, no monozygotic twin sibling with FATCO syndrome has been reported until now. This report can help us to find the origin of this disease because the other healthy twin sister does not have any malformation. As we know that monozygotic twin siblings have the same DNA sequence, one can say that FATCO syndrome does not only occur due to a DNA sequence mutation but also by other mechanisms. Until now, monozygotic twins were called "genetically identical"; however, genetic and epigenetic differences within monozygotic twin pairs have been reported.⁸ One of the genetic mechanisms that may cause monozygotic twin discordance is postzygotic gene mutations.⁹ Therefore, twin sisters in this report may show different phenotypes. Molecular mechanisms such as skewed X-inactivation, newly acquired epigenetic differences, and mosaicism for chromosomal aberrations may also result in phenotypic discordance for monogenic disorders in monozygotic twins.¹⁰ Discordance for malformations in a monozygotic twin pair may also reflect environmental origins. The intrauterine environment is not necessarily equal for both monozygotic twins because of the number of cells allocated to each twin, the timing of the twinning process, and the vascular distribution from the placenta all differ.⁸

The reported phenotypic features of patients with FATCO syndrome illustrate that this syndrome represents a wide range of clinical variability of limb malformations, which may reflect its underlying genetic heterogeneity. All patients described before have had lower limb involvement but only two-third of these patients have upper limb involvement^{1,2,7} (→ **Table 1**). In our case, both upper limbs were affected. Because of the unknown genetic baseline of FATCO and a negative *WNT7A* gene analysis, we wanted to eliminate overlap with other similar conditions as the cause of congenital anterolateral tibial pseudarthrosis. Although the exact *pathogenesis of the syndrome* still remains unclear, the connection between Neurofibromatosis and congenital anterolateral tibial pseudarthrosis is well known.¹¹ Neurofibromatosis type I is a relatively common genetic syndrome that can lead to congenital anterolateral tibial pseudarthrosis,¹² and it is associated with a particular previously defined gene mutation. It is commonly considered in the differential diagnosis when anterolateral tibial bowing is detected in a child because this is an associated feature that can progress to pseudarthrosis and a high risk of fracture.^{12,13} As a result, we performed *NF1* gene sequencing analysis of coding regions and exon-intron boundaries. Similar to *WNT7A* gene result, the *NF1* gene sequencing analysis of coding regions and exon-intron boundaries was normal. Osteofibrous dysplasia, which is another cause of congenital pseudoarthrosis,¹⁴ was excluded because of the absence of any specific radiological sign; also in our patient, there is an absent fibula too. Another condition in the differential diagnosis of congenital pseudarthrosis is congenital anterolateral tibial bowing and polydactyly syndrome¹⁵; however, in our case, there were no signs of this syndrome, so we exclude that disease.

In conclusion, our patient had a healthy female twin sister, which is the most important and interesting point in our

report. The absence of any report of twin sister with FATCO syndrome may help us to determine the cause of FATCO syndrome. Discordant phenotypes of monozygotic twin sisters in this report may be the result of other genetic mechanisms such as postzygotic gene mutations, environmental factors, or amount of blood flow. Nevertheless, all these information may give an opinion about the mechanism of this disease.

Conflict of Interest

None declared.

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