Case Report

A Japanese Male Patient with ‘Fibular Aplasia, Tibial Campomelia and Oligodactyly’: An Additional Case Report

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Abstract. We report a male infant with FATCO syndrome, an acronym for fibular aplasia, tibial campomelia, and oligodactyly. Courtens et al. reported an infant with oligodactyly of the left hand, complete absence of the right fibula, bowing of the right tibia, and absence of the right fifth metatarsal and phalanges. They noted 5 patients with similar clinical features, and proposed the FATCO syndrome. Our patient had a left-sided cleft lip, cleft palate, oligodactyly of the right hand and bilateral feet, and bilateral anterior bowing of the limbs associated with overlying skin dimpling. Radiographs showed a short angulated tibia with left fibular aplasia and right fibular hypoplasia. We consider our case the 6th patient with FATCO syndrome, and the cleft lip and palate, not reported in the previous 5 patients, may allow us to further understand the development of the extremities and facies.

Key words: FATCO syndrome, tibial campomelia, cleft palate

Introduction

Unilateral or bilateral fibular aplasia is a rare malformation, although the fibula is the most common long bone associated with a congenital absence (1, 2). Most cases of fibular aplasia are isolated and sporadic events, which implies that the majority is caused by nongenetic and teratogenic insults. However, fibular aplasia can be a part of a malformation syndrome when associated with focal deficiency of the proximal femur and distal digital and/or toe anomalies. In addition, fibular aplasia is sometimes associated with shortness or deformity of the extremities as well as growth retardation (3).

In the Online Mendelian Inheritance in Man (OMIM) database, malformation syndromes that have fibular aplasia are categorized into 18 entities, which include orofaciodigital syndrome X (MIM165590), fibular aplasia or hypoplasia, femoral bowing and poly-, syn- and oligodactyly
(Fuhrmann syndrome, MIM228930), brachydactyly-ectrodactyly with fibular aplasia or hypoplasia (fibular aplasia with ectrodactyly, MIM113310) and fibular aplasia, tibial camptomelia, and oligosyndactyly syndrome (FATCO syndrome, MIM246570). The latter two conditions seem to be similar and do not show facial anomalies. On the other hand, the clinical features in orofaciodigital syndrome X include oral and facial anomalies such as telecanthus, a flat nasal bridge, retrognathia and cleft palate (4).

As hand and foot malformations, split-hand/foot malformation (SHFM) is common and has a birth prevalence of 1 in 18,000 (5, 6). SHFM is genetically heterogeneous, and five loci have been mapped (7, 8). When SHFM coexists with long bone deficiency, it is called split-hand/foot malformation with long bone deficiency (SHFLD) (8). In SHFLD, the tibia is often missing, but the fibula is rarely involved.

Here, we report a male infant with malformations consisting of fibular aplasia, tibial camptomelia, oligodactyly and cleft lip and palate and discuss the diagnosis of our patient.

Case Report

The boy was born at term (38 3/7 wk) and was the first child of non-consanguineous parents, aged 33 (father) and 32 (mother). Delivery was by cesarean section due to breech position. His birth weight was 2,400 g (−1.5 SD), length was 45.1 cm (−1.9 SD), and head circumference was 32.5 cm (−0.6 SD). His apgar scores were 8 and 9 at 1 and 5 min, respectively. No medication had been taken during the perinatal period. On examination at birth, he was noted to have a left-sided cleft lip, cleft palate, oligosyndactyly of the right hand (Fig. 1A) and bilateral feet (Fig. 1B), and bilateral anterior bowing of the limbs associated with overlying skin dimpling (Fig. 1B). He did not show joint contractures or nail hypoplasia. He had no abnormal findings for the heart, brain, and abdominal organs on ultrasound examination. His weight gain was good, and he reached 3,655 g (−1.0 SD) at the age of one month. Radiographs showed a short angulated tibia with left fibular aplasia (Fig. 2C) and right fibular hypoplasia (Fig. 2D). The right hand had only three metacarpal bones (probably IV and V are absent), and the third distal phalange was fused with the fourth (Fig. 2A). The left hand was normal clinically and
radiographically (Fig. 2B). Both femurs were straight. A single toe was missing from both feet (Fig. 1B).

He underwent surgery to repair the left unilateral cleft lip at 3 mo of age and had an uneventful postoperative course. Laboratory examinations and karyotype analysis were normal. A follow-up visit at 10 mo of age showed a healthy child with psychomotor development appropriate for his age; head control was achieved at 4 mo, and he sat up at 8 mo.

After obtaining informed consent from the parents, genomic DNA of the patient was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (QIAGEN K.K., Tokyo, Japan). Analysis of the WNT7A gene was performed by Dr. A Superti-Furga (University of Freiburg, Germany) as shown previously (9).

**Fig. 2** A radiograph of the right hand showed the presence of only three metacarpal bones (probably IV and V are absent) and that the third distal phalange was fused with the fourth (A). The left hand was normal (B). There was a short angulated tibia with left fibular aplasia (C) and right fibular hypoplasia (D).

**Discussion**

The present case has features of FATCO syndrome, which consists of fibular aplasia, tibial campomelia and oligosyndactyly. Courtens et al. reported a case along with 4 previously reported patients as FATCO syndrome (2) (Table 1). No further cases have been reported; we now describe a 6th patient. Though both female and male patients with this syndrome have been reported, the inheritance of the syndrome remains uncertain due to lack of information concerning familial transmission. The similarities and differences between FATCO syndrome and fibular aplasia with ectrodactyly have been discussed previously by Evans et al. (10). They argue that FATCO syndrome should be included in fibular aplasia with ectrodactyly because it also has fibular aplasia, tibial campomelia, and oligosyndactyly. The missing digits in our patient seemed to be postaxial, but could be central, as pointed out in cases of fibular aplasia with
| Reference         | Sex | Lower extremities                                      | Upper extremities                | Comment                          |
|-------------------|-----|-------------------------------------------------------|----------------------------------|----------------------------------|
| Hecht and Scott (a) | F   | Tibia: anterior bowing and shortness with associated overlying soft tissue dimples | Left hand: oligosyndactyly       | No heart defect                  |
|                   |     | Fibula: absence                                       | Right hand: absence              | Mental development: normal at age 9 mo |
|                   |     | Femora: normal                                         | Ulnae: normal                    |                                  |
|                   |     | Four-ray feet                                          |                                  |                                  |
| Capece et al. (b) |     | Left tibia: bowed                                      | Right hand: oligosyndactyly      | A fetus at 24 wk of gestation    |
|                   |     | Left fibula: absence                                   | Ulnae: normal                    | Small-for-date                   |
|                   |     | Femur: normal                                          |                                  |                                  |
|                   |     | Fifth toe: absence                                     |                                  |                                  |
| Huber et al. (c)  | M   | Tibia: bowed and short with dimpling unilaterally      | Oligosyndactyly                  | Pelvis: normal                   |
| Case 1            |     | Fibulae: absence                                       |                                  | No cardiac anomalies             |
|                   |     | Oligosyndactyly                                        |                                  | Neurological development: normal |
|                   |     | Femora: normal                                         |                                  |                                  |
| Huber et al. (c)  | M   | Tibia: bowed and short with dimpling bilaterally       |                                   |                                  |
| Case 2            |     | Fibulae: absence                                       | Oligosyndactyly                  |                                  |
|                   |     | Oligosyndactyly                                        |                                  |                                  |
|                   |     | Femora: normal                                         |                                  |                                  |
| Courtens, et al. (2) | M | Left lower limb: normal                               | Left hand: oligosyndactyly       | No facial dysmoria               |
|                   |     | Right lower limb: shortening and anterior bowing at the distal third of tibia with associated overlying soft tissue dimpling | Right hand: normal               | No other anomalies               |
|                   |     | Oligosyndactyly                                        | Humeri: normal                   |                                  |
|                   |     | Vth ray: absence                                       | Ulnae: normal                    |                                  |
|                   |     | Fibula: complete absence                               | Radii: normal                    |                                  |
|                   |     | Femora: normal                                         |                                  |                                  |
| Our case          | M   | Tibia: anterior bowing and shortness associated with overlying skin dimpling | Right hand: oligosyndactyly      | A left-sided cleft lip, cleft palate |
|                   |     | Left fibular: aplasia                                  | Ulnae: normal                    |                                  |
|                   |     | Right fibular: hypoplasia                              | Humeri: normal                   |                                  |
|                   |     | Bilateral feet: oligosyndactyly                        |                                  |                                  |

(a) Hecht JT, Scott CI, Jr. Limb deficiency syndrome in half-sibs. Clin Genet 1981;20:432–7. PubMed ID: 7337959
(b) Capece G, Fasolino A, Della Monica M, Lonardo F, Scarano G, Neri G. Prenatal diagnosis of femur-fibula-ulna complex by ultrasonography in a male fetus at 24 weeks of gestation. Prenatal Diag 1994;14:502–5. PubMed ID: 7937589
(c) Huber J, Volpon JB, Ramos ES. Fuhrmann syndrome: two Brazilian cases. Clin Dysmorph 2003;12:85–8. PubMed ID: 12868468
ectrodactyly syndrome. Though it remains possible that fibular aplasia with ectrodactyly encompasses FATCO syndrome, we believe that FATCO syndrome, as an independent entity, is a better diagnosis for our patient since fibular aplasia with ectrodactyly is rather heterogeneous and autosomal dominant inheritance is speculated in familial cases, although the sex ratio is biased toward males.

Interestingly, the cleft lip observed in our patient has not been described in previous cases of FATCO syndrome, and this may argue against the diagnosis. Fibular agenesis and cleft palate are components of oral-facial-digital syndrome X (4); however, absence of a facial phenotype, such as telecanthus, flat nasal bridge, and retrognathia, likely excludes oral-facial-digital syndrome X for our patient. The severe and lethal sib cases reported by Pfeiffer et al. also differ from our patient, since they exhibited absence of the fibula and ulna with oligodactyly, contractures, right-angle bowing of the femora, abnormal facial morphology, cleft lip/palate, and brain malformation (11).

FATCO syndrome differs from Fuhrmann syndrome in that it does not manifest pelvic and femur abnormalities. Moreover, no defect of the ulna and a straight femur characterizes FATCO syndrome, whereas skeletal abnormalities in Fuhrmann syndrome include aplasia/hypoplasia of the ulna, hypoplasia of the pelvis, aplasia/hypoplasia of the femur, fibular aplasia, and variable digital abnormalities, as well as absent/dysplastic nails. In the family with Fuhrmann syndrome originally described by Kumar et al. (12), Woods et al. found an A109T mutation in the WNT7A gene, which controls the dorsoventral patterning (9). Overlap has been recognized between Fuhrmann syndrome and Al-Awadi/Rass-Rothschild syndrome (MIM 276820). Accordingly, Woods et al. demonstrated a homozygous missense mutation in the WNT7A gene, R292C, in a consanguineous family in which three members had been diagnosed with Al-Awadi/Rass-Rothschild syndrome (12). In our case, absence of mutations in the WNT7A gene implies that FATCO syndrome and Fuhrmann syndrome are distinct. Fuhrmann syndrome also has similarities with femur-fibula-ulna syndrome, or FFU syndrome (MIM 228200).

Ectrodactyly is often misused as a synonym for split-hand/split foot malformation (SHFM). In contrast to the central absence of digits in SHFM, ectrodactyly points to any absence deformity of the digits (13). In FATCO syndrome and fibular aplasia with ectrodactyly, digit defects are not confined to the central rays. In addition, defects of the fibula are rarely associated with SHFM, thus, ruling out SHFLD. It is noteworthy that the association of cleft palate with SHFM is seen in ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome (EEC). We excluded EEC due to lack of skin and hair characteristics.

Severe short limbs associated with long bone defects are observed in phocomelia. The most well known disorder that shows this defect is Roberts syndrome (MIM 268300), and the responsible gene has recently been identified as the ESCO2 gene by two groups, including our group (14). The clinical features of our patient do not match this syndrome.

In conclusion, we report the 6th patient with FATCO syndrome. He had a cleft lip and palate, which have not been reported previously. Our case may allow us to further understand the development of the extremities and facies.

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