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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 oligosyndactyly. Courtens *et al.* reported an infant with oligosyndactyly 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, oligosyndactyly 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

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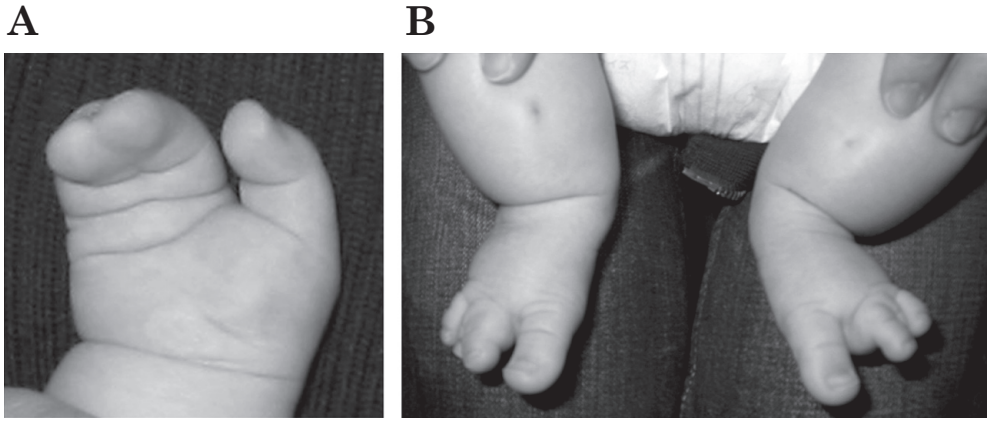

Fig. 1 Photographs of the patient at 7 mo of age. The right hand (A) and bilateral feet have oligosyndactyly (B). Bilateral lower legs have anterior bowing with associated overlying skin dimpling (B).

(Fuhrmann syndrome, MIM228930), brachydactyly-ectrodactyly with fibular aplasia or hypoplasia (fibular aplasia with ectrodactyly, MIM113310) and fibular aplasia, tibial campomelia, 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 campomelia, 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

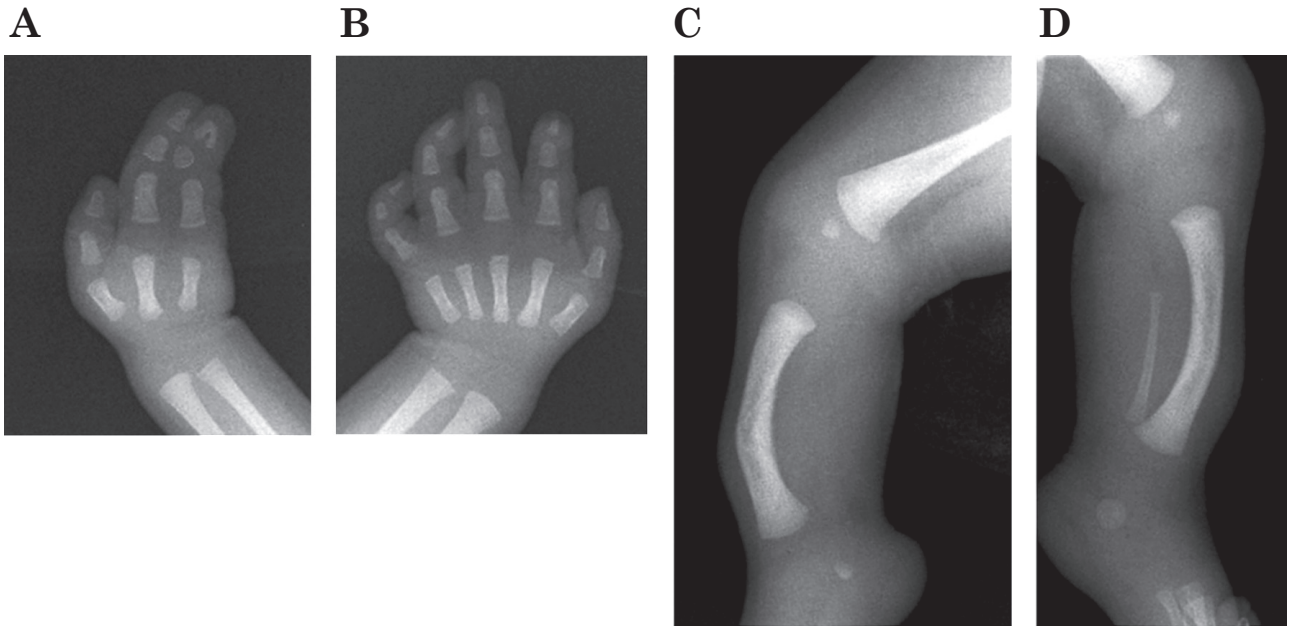

Fig. 2 A radiograph of the right hand showed the presence of only three metacarpal bones (probably IV and V are absent) and that the third distal phalange was fused with the fourth (A). The left hand was normal (B). There was a short angulated tibia with left fibular aplasia (C) and right fibular hypoplasia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

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).

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

Table 1 Cases of FATCO syndrome

Reference	Sex	Lower extremities	Upper extremities	Comment
Hecht and Scott (a)	F	Tibia: anterior bowing and shortness with associated overlying soft tissue dimples Fibula: absence Femora: normal Four-ray feet	Left hand: oligosyndactyly Right hand: absence Ulnae: normal	No heart defect Mental development: normal at age 9 mo
Capece *et al.* (b)		Left tibia: bowed Left fibula: absence Femur: normal Fifth toe: absence Clubfeet	Right hand: oligosyndactyly Ulnae: normal	A fetus at 24 wk of gestation Small-for-date
Huber *et al.* (c) Case 1	M	Tibia: bowed and short with dimpling unilaterally Fibulae: absence Oligosyndactyly Femora: normal		Pelvis: normal No cardiac anomalies Neurological development: normal
Huber *et al.* (c) Case 2	M	Tibia: bowed and short with dimpling bilaterally Fibulae: absence Oligosyndactyly Femora: normal	Oligosyndactyly	Pelvis: normal No cardiac anomalies Neurological development: normal
Courtens, *et al.* (2)	M	Left lower limb: normal Right lower limb: shortening and anterior bowing at the distal third of tibia with associated overlying soft tissue dimpling Oligosyndactyly Vth ray: absence Fibula: complete absence Femora: normal	Left hand: oligosyndactyly Right hand: normal Humeri: normal Ulnae: normal Radii: normal	No facial dysmorphia No other anomalies
Our case	M	Tibia: anterior bowing and shortness associated with overlying skin dimpling Left fibular: aplasia Right fibular: hypoplasia Bilateral feet: oligosyndactyly	Right hand: oligosyndactyly Ulnae: normal Humeri: normal	A left-sided cleft lip, cleft palate

(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/Raas-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 Furmann 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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References

1. Lewin SO, Opitz JM. Fibular a/hypoplasia: review and documentation of the fibular developmental field. Am J Med Genet 1986; 25 (Suppl 2):215–38.
2. Courtens W, Jespers A, Harrewijn I, Puylaert D, Vanhoenacker F. Fibular aplasia, tibial campomelia, and oligosyndactyly in a male newborn infant: a case report and review of the literature. Am J Med Genet 2005;134A:321–5.
3. Stanitski DF, Stanitski CL. Fibular hemimelia: a new classification system. J Pediatr Orthop, 2003;23:30–4.
4. Figuera LE, Rivas F, Cantu JM. Oral-facial-digital syndrome with fibular aplasia: a new variant. Clin Genet 1993;44:190–2.
5. Czeizel AE, Vitéz M, Kodaj I, Lenz W. An epidemiological study of isolated split hand/foot in Hungary, 1975–1984. J Med Genet 1993;30:593–6.
6. Elliott AM, Evans JA, Chudley AE. Split hand foot malformation (SHFM). Clin Genet 2005; 68:501–5.
7. Naveed M, Nath SK, Gaines M, Al-Ali MT, Al-Khaja N, Hutchings D, *et al.* Genomewide linkage scan for split-hand/foot malformation with long-bone deficiency in a large Arab family identifies two novel susceptibility loci on chromosomes 1q42.2–q43 and 6q14.1. Am J Hum Genet 2007;80:105–11.
8. Babbs C, Heller R, Everman DB, Crocker M, Twigg SRF, Schwartz CE, *et al.* A new focus for hand/foot malformation with long bone deficiency (SHFLD) at 2q14.2 identified from a chromosome translocation. Hum Genet 2007;122:191–9.
9. Woods CG, Stricker S, Seemann P, Stern R, Cox J, Sherridan E, *et al.* Mutations in WNT7A cause a range of limb malformations, including Fuhrmann syndrome and Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome. Am J Hum Genet 2006;79:402–8.
10. Evans JA, Martin HR, Greenberg CR. Fibular Aplasia With Ectrodactyly. Am J Med Genet 2002;113;52–8.
11. Pfeiffer RA, Stoss H, Voight HJ, Wundisch GF. Absence of fibula and ulna with oligodactyly, contractures, right-angle bowing of femora, abnormal facial morphology, cleft lip/palate and brain malformation in two sibs: a possibly new lethal syndrome. Am J Med Genet 1988;29:901–8.
12. Kumar D, DugganMB, Mueller RF, Karbani G. Familial aplasia/hypoplasia of pelvis, femur, fibula, and ulna with abnormal digits in an inbred Pakistani Muslim family: a possible new manifestations of the syndromes of Fuhrmann, Al-Awadi, and Raas-Rothschild. Am J Med Genet 1997;70:107–13.
13. Duijf PHG, Bokhoven HV, Brunner HG. Pathgeneisis split-hand/split-foot malformation. Ham Mol Genet 2003;12:R51–60.
14. Vega H, Waisfisz Q, Gordillo M, Sakai N, Yanagihara I, Yamada M, *et al.* Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. Nat Genet 2005;37:468–70.