

Four FATCO syndrome cases: clinical, autopsy and placental features with literature review update

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ABSTRACT

Fibular Aplasia-Tibial Campomelia-Oligosyndactyly, or FATCO, is a rare syndromic condition reported in 18 cases so far, from which only 3 were diagnosed at prenatal stages. In this study we report comprehensive clinical, placental and autopsy findings of four additional prenatal cases of FATCO, with the aim of further delineating this syndromic condition. Understanding this disorder at prenatal stages will allow for an earlier diagnosis through the identification of key features, thus permitting an adequate parental counselling about the pregnancy development.

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INTRODUCTION

Limb malformations in neonates occurs in approximately 1 in 1,000 [1]. Fibular aplasia is the most common malformation amongst long bone deficiency syndromes [2]. FATCO (OMIM 246570) is an extremely rare syndromic condition involving Fibular Aplasia-Tibial Campomelia-Oligosyndactyly, first designated by Courtens *et al.* (2005). Individuals with this syndrome present a remarkable shortening and anterior bowing of one or both lower limbs and oligosyndactyly of at least one foot. Frequently, involvement of upper extremities also occurs. Nevertheless, psychomotor development was always described as normal [3-11] and heart defects were rarely reported [7,11,12]. An update of the literature review describing major malformations reported so far is displayed in Supplementary data 1. Up to now, three FATCO subjects have been diagnosed at a prenatal stage [5,12,13]. From these, a single case was described where FATCO syndrome was diagnosed during ultrasound examination and where parents decided to continue with their pregnancy [5]. In the other two reports, skeletal dysplasia was identified during ultrasound imaging but FATCO syndrome was only diagnosed during fetal autopsy [12,13]. Further cases are

needed in order to have a comprehensive understanding of this disorder prenatally, allowing parents to make an informed decision about their pregnancy development. In the present study, we report four unrelated cases of FATCO syndrome, of which three of them were diagnosed during fetal autopsy and one diagnosed during ultrasound examination. Prenatal, autopsy and placental findings are detailed in full for a comprehensive FATCO diagnosis.

All the cases enrolled in the present study were unlinked and unidentified from their donors. Due the retrospective nature of the study, no written informed consent from patients was obtained. The Ethical Review Committees of the involved institutions approved the work and waived the need for written informed consent.

CASE REPORT

Fetus 1. Fetus 1 was a product of the first pregnancy of a non-consanguineous Caucasian healthy couple, with no reported family history of skeletal dysplasia. The mother was 34 years of age at time of pregnancy and claims to not have taken any drugs nor been exposed to radiation during pregnancy. First trimester screening revealed no ultrasound anomaly and nuchal translucency (NT) and crown to rump length (CRL) measurements at

13 weeks (w) + 1 day (d) gestational age (GA) were 1.9 mm and 68.1 mm, respectively ($>50^{\text{th}}$ percentile, $>P_{50}$). Standard biometric measurements were appropriate for GA with free β -hCG: 1.18 MoM and PAPP-A: 0.37 MoM, and thus overall result was of reduced risk for combined prenatal screening of trisomy 21, 18 and 13. During second trimester ultrasound screening, at 21w + 6d GA, abnormal skeletal ultrasound findings were found, showing skeletal malformations on right lower limb with shortening and bowing of the tibia, fibular aplasia and Rocker-Bottom feet with only four toes (Figure 1, A1-A2). At the same GA, fetal echocardiogram was performed with normal outcome. Amniocentesis was performed at 22w of GA and revealed a normal karyotype for a male fetus (46,XY). Parents requested medical termination of pregnancy (MTP) which was granted with permission from the Prenatal Diagnosis Unit Ethics Committee. MTP was performed at 23w + 2d GA via vaginal misoprostol. X-ray analysis confirmed prenatal findings (Figure 1, B1-B2). Fetal autopsy reported a male fetus with minor cranio-facial anomalies and oligosyndactyly, with absence of the 5th toe and the 5th metatarsal, associated with fibular aplasia and tibial campomelia. Autopsy diagnosis was concluded as FATCO syndrome (Figure 1, C; Table 1).

Fetus 2. Pregnant was referred to the Centre at 20w+3d GA due to suspected anomalies on the lower left limb of the fetus. Fetus 2 was the first pregnancy of Caucasian healthy parents. Family history of skeletal dysplasia, drug intake or exposure to radiation during pregnancy was denied. Mother was 33 years old at time of current pregnancy. Combined first trimester screening test was performed at 11w + 4d of GA with standard results with NT: 1.3 mm and CRL: 48.4 mm (P_{50}); free β -hCG: 0.69 MoM and PAPP-A: 1.20 MoM and, therefore, result was concluded as reduced risk for trisomy 21, 18 and 13. An ultrasound at 17w + 2d GA lead to suspicion of an anomaly present on the lower left limb. No heart defects were found by fetal echocardiogram. Amniocentesis was performed and chromosomal analysis revealed a male fetus with normal karyotype (46,XY). Alpha-fetoprotein was measured in the amniotic fluid and levels (1.1 MoM) were within reference values for GA.

At 20w + 3d GA, ultrasonography showed normal right lower limb (tibia/fibula complex 16/18 mm) and left lower limb with skeletal anomaly: single bone with a remarkable shortening (10 mm), overlying soft tissue dimpling (Figure 1, D) and clubfoot. MTP was requested by the parents and performed with permission from the Prenatal Diagnosis Unit Ethics Committee, via vaginal misoprostol. Fetal X-Ray confirmed fibular aplasia and tibial campomelia (Figure 1, E1-E2). Besides the latter two features, fetal autopsy also reported bilateral oligosyndactyly (3-ray feet), indicating FATCO syndrome as diagnosis (Figure 1, F).

Fetus 3. Pregnant was referred to the Centre at 23w+2d GA due to suspected anomalies on the lower right limb. Fetus 3 was the second pregnancy of Caucasian healthy parents. Family history of skeletal dysplasia, drug intake or exposure to radiation during pregnancy was denied. Mother was 24 years old at time of current pregnancy. Combined first trimester screening test was performed at 11w + 4d of GA with standard results with NT: 1.3 mm and CRL: 48.3 mm. Alpha-fetoprotein was measured in the amniotic fluid and levels (1.1 MoM) were within reference values for GA. Result was concluded as reduced risk for trisomy 21, 18 and 13. No heart defects were found by fetal echocardiogram. Amniocentesis was performed and chromosomal analysis revealed a female fetus with normal karyotype (46,XX).

At 20w + 4d GA, ultrasonography showed normal left lower limb (tibia/fibula complex 16/18 mm) and right lower limb with skeletal anomaly: remarkable short femur and fibular aplasia and tibial campomelia (Figure 1, G). MTP was requested by the parents and performed at 23w + 2d with permission from the Prenatal Diagnosis Unit Ethics Committee, via vaginal misoprostol. Fetal X-Ray confirmed fibular aplasia and tibial campomelia (Figure 1, H1-H2). Besides the latter two features, fetal autopsy also reported a typical overlying soft tissue dimpling and bilateral oligosyndactyly (3-ray feet), indicating FATCO syndrome as diagnosis (Figure 1, I). Esophageal atresia with tracheal fistula were also identified without others anomalies.

Fetus 4. Fetus 4 was a product of the second pregnancy of a non-consanguineous Caucasian couple, with no reported family history of skeletal dysplasia. The mother was 38 years old at time of pregnancy and also presented previous arterial hypertension with taking 2.5 mg of bisoprolol per day until 9w of GA. A first trimester pregnancy-induced gestational diabetes are also diagnosed. Family history of skeletal dysplasia or exposure to radiation during the pregnancy was denied. No heart defects were found by fetal echocardiogram. Combined first trimester screening test was performed at 11w of GA with standard results of NT: 1.7mm and, therefore, result was concluded as reduced risk for trisomy 21, 18 and 13. Due to a poor ultrasound window suspicion rudimentary right leg and feet are noted. Amniocentesis was performed and array CGH study revealed a male fetus with a normal karyotype (46,XY). Second trimester echography screening at 21w+3d of GA showed a major defect in left leg, with fibular agenesis, tibial campomelia and rudimentary feet (ultrasound data not available). MTP was requested by the parents, which was granted with permission from the Prenatal Diagnosis Unit Ethics Committee, and it was performed via vaginal misoprostol at 21w+5d of GA. Fetal X-Ray confirmed fibular aplasia (unilateral) and tibial campomelia and it also revealed hypoplasia of the tarsal bones and oligosyndactyly (Figure 1, J1-J2). Fetal autopsy further reported shortening of right lower limb consistent with FATCO syndrome as diagnosis (Figure 1, K).

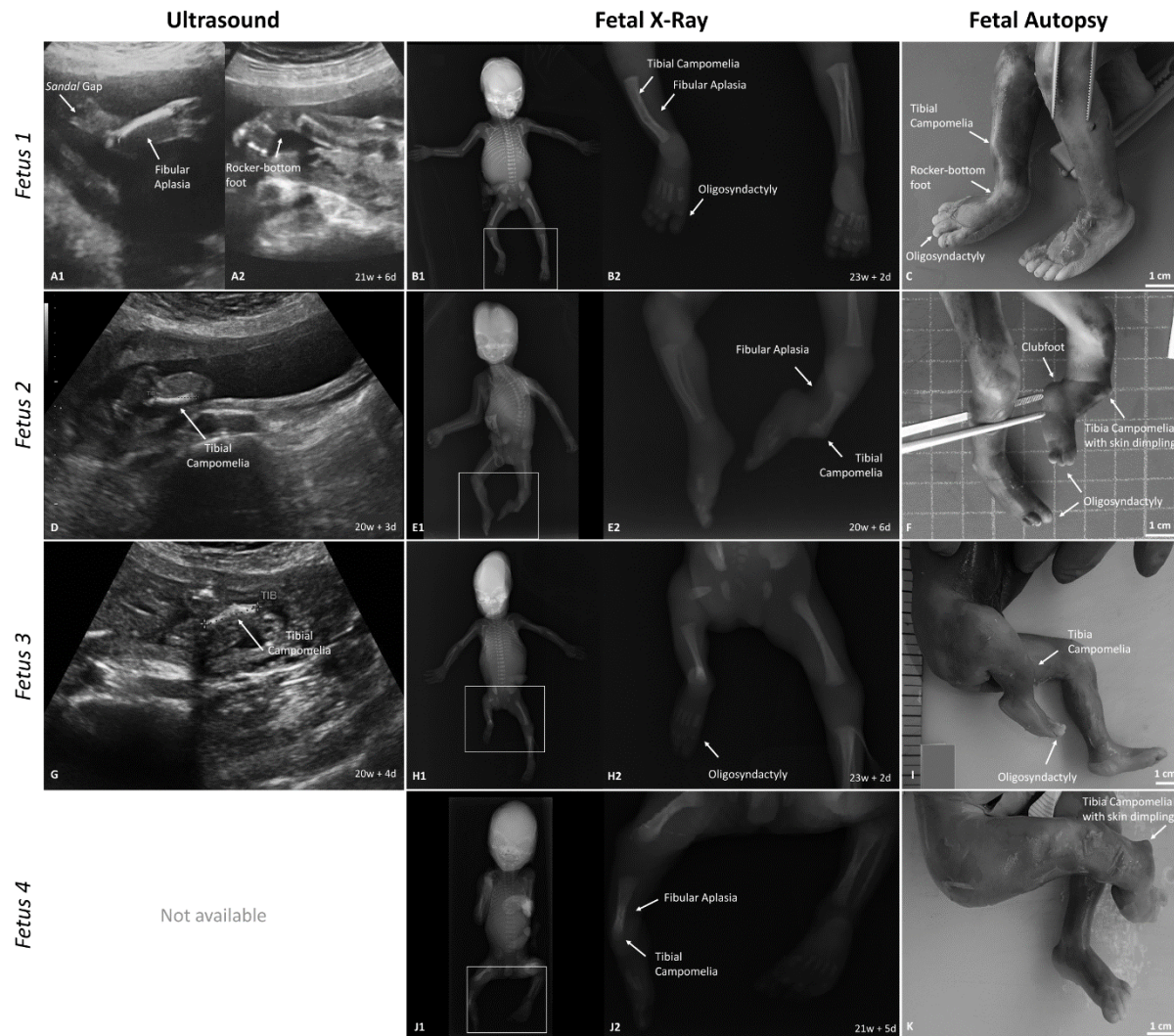


Figure 1. Image documentation of ultrasound (A1-A2, D and G), fetal X-Ray (B1-B2, E1-E2, H1-H2 and J1-J2) and fetal autopsy features (C, F, I and K) of the four fetuses presented in this study, demonstrating key features of FATCO syndrome, such as fibular aplasia, tibial campomelia and oligosyndactyly. Ultrasound imaging of the right lower limb of fetus 4 demonstrating key features of FATCO was not available.

Clinical detect anomalies and detailed autopsy description of all four fetuses and correspondent placental units are described in Table 1.

Table 1. Clinical indications and detailed macro and microscopic examination during fetal autopsy and placental study of fetuses with FATCO syndrome. (GA) gestational age.

	<i>Fetus 1</i>	<i>Fetus 2</i>	<i>Fetus 3</i>	<i>Fetus 4</i>
MEDICAL TERMINATION OF PREGNANCY (MTP)				
Gestational Age (GA)	23w + 2d	20w + 6d	23w + 2d	21w + 5d
Medical Information	Skeletal malformation of the right lower limb (Rocker-Bottom feet) leading to a shortening and bowing of the tibia, fibular aplasia, 4 toes	Absence of fibula in left lower limb	Right lower limb with short femur, short and bowed tibia, fibular aplasia and axial deviation of the foot	Right lower limb with fibular aplasia, short tibia and undeveloped right foot
Karyotype	46,XY	46,XY	46,XX	46,XY
FAMILY HISTORY				
		Arterial Hypertension		Gestational diabetes; pregnancy-induced hypertension
FETAL AUTOPSY				
Macroscopic Examination				
Fetal gender (GA)	Male (GA 23 weeks)	Male (GA 21 weeks)	Female (GA 23 weeks)	Male (GA 21 ⁺ weeks)
Biometric parameters	Normal	Lower	Normal	Normal
Body weight (total, g)	Normal – 480	Normal – 330	Normal – 490	Higher – 495 (normal = 389 ± 72)
Internal organs (weight, g)	Normal	Normal	Normal, except:	Normal, except:

			. Heart: Lower – 2 (normal = 3.81 ± 0.96) . Liver: Lower – 15.1 (normal = 24.3 ± 6.5)	. Cerebrum: Higher – 78.9 (normal = 54.6 ± 10.4)
Growth and bone maturity	Normal	Normal	Normal	Normal
Visceral maturity	Normal	Normal	Normal	Normal
Thoracic circumference (TC, cm)	Normal	Lower – 24.6 (normal = 26)	Normal	Higher – 16.6 (normal = 15.2)
Cranio-caudal length (CCL, cm)	Normal	Lower – 16.5 (normal = 18)	Normal	Higher – 20.3 (normal = 18.4 – 19.8)
Occipital Frontal Circumference (OFC, cm)	Normal	Lower – 18.2 (normal = 18.5 – 21.1)	Normal	Higher – 20.1 (normal = 18.5 – 19.8)
Femur length (cm)	Normal – 3.5 (P ₅₀)	Normal – 3.27 (P ₅₀)	Short – 1.12 (<P ₅₀)	Normal – 3.66 (P ₅₀)
Biparietal diameter (BPD, cm)	Normal	Lower – 4.5 (normal = 4.8 – 5.7)	Lower – 5.13 (<P ₁₀)	Normal – 5.02 (P ₅₀)
Foot length (cm)	Normal	Lower – 3.1 (normal = 3.3 – 3.8)	Normal	Higher – 4.1 (normal = 3.72 – 3.91)
Transverse cerebellar diameter (TCD, cm)	Normal	Normal – 2.1 (normal = 1.9 – 2.0)	Normal – 2.3 (normal = 2.2–2.8)	Normal – 2.3 (normal = 1.9 – 2.4)
Brain-liver weight relationship (g)	Normal – 3.8 : 1	Higher – 4.9 : 1	Higher – 4.8 : 1	Normal – 3.6 : 1
Development anomalies				
Cranio-facial dysmorphisms	Infra-orbital grooves		Micrognathia	
	Micrognathia (moderated)			
Cerebrum	Normal	Normal	Normal	Normal
Upper limbs	Ulnar deviation of the hands	Normal	Normal	Arachnodactyly
Lower limbs	Asymmetric limbs (shorter right)	Asymmetric and distinct limbs (shorter left)	Asymmetric limbs (rhizomelic shortening)	Asymmetric and distinct limbs (shorter right)
	Rocker-Bottom feet	Skin dimpling on left leg	Skin dimpling and spiculated on right leg	Skin dimpling on right leg
	Absence of the 5 th toe on right foot (oligosyndactyly)	Bilateral oligosyndactyly: absence of the 4 th and 5 th toes	Oligosyndactyly	Oligosyndactyly
Fetal X-Ray	Bilateral <i>Sandal Gap</i>	Left clubfoot	Right tight with short femur	Right lower limb shortening
	Dysplasia of the 5 th finger of both hands	Left convex thoracic scoliosis; 11 ribs to the left	Rizomelic	
	Right lower limb with shortened.	Agenesis of left fibula and short and angulated tibia; hypoplasia of the tarsal bones	Shortening of right lower limb.	Fibular agenesis, tibial campomelia.
	Absence of fibula and angulated tibia and absence of fibula, of the 5 th metatarsal bone and 5 th toe		Fibular agenesis, tibia campomelia.	Absence of 5 th and 4 th toes
External Genitalia	Normal	Big phallus	Normal	Normal
Cardio-pulmonary system	<i>Situs solitus</i> , levocardia, levoapex persistence of fetal circulation. Bifurcated cardiac apex due to the left ventricle	<i>Situs solitus</i> , levocardia, levoapex persistence of fetal circulation	<i>Situs solitus</i> , levocardia, levoapex persistence of fetal circulation	<i>Situs solitus</i> , levocardia, levoapex, persistence of fetal circulation
Microscopic Examination				
Lung	Ectasia of the lymphatic lobular septum. Without pulmonary hypoplasia	Without pulmonary hypoplasia	Without pulmonary hypoplasia	Without pulmonary hypoplasia
Fetal Autopsy Report/Diagnosis	Male fetus with 23 ws GA. Lower right limb localized developmental skeletal anomalies with fibular aplasia and tibial campomelia, and oligosyndactyly without other anomalies supporting the diagnosis of FATCO syndrome.	Male fetus with 21 ws GA, intrauterine growth restriction (IUGR). Lower left limb localized developmental skeletal anomalies with fibular aplasia and tibial campomelia; bilateral oligosyndactyly, without other anomalies, supporting the diagnosis of FATCO syndrome.	Female fetus with 23 ⁺ ws GA. Lower right limb localized developmental skeletal anomalies with fibular aplasia and tibial campomelia, oligosyndactyly. Short right femur, esophageal atresia with tracheoesophageal fistula without lung anomalies, supporting the diagnosis of FATCO syndrome.	Macerated male fetus with 21 ⁺ ws GA. Right lower limbs developmental skeletal anomalies with fibular aplasia, tibial campomelia and oligosyndactyly supporting the diagnosis of FATCO syndrome.

PLACENTAL STUDY**Macroscopic Examination**

Appearance	Single and complete	Single and complete	Single and complete	Single and complete
Weight (g)	107	103	177	108
Size (cm)	10x9x2	11x10x1.5	12x9x1.7	11x8x0.5
Membranes	Normal	Normal	Normal	Normal
Umbilical Cord	3 vessels and marginal insertion	3 vessels and central insertion	2 vessels and velamentous insertion	3 vessels and central insertion
Size (length x diameter) (cm)	18x1	25x1	15x1	31x1.2
Fetal surface vessels	Eccentric	Radial	Peripheral	Radial

Chorion	Without gross anomalies	Without gross anomalies	Without gross anomalies	Hydrops
Microscopic Examination				
Placental maturity	Normal	Normal	Hypermaturity	Immature villi
Villi				
Hofbauer cells	Vacuolated Hofbauer cells	Vacuolated Hofbauer cells		
Hydropsia	Absent	Absent	Absent	Present
Vessels	Thrombosis	Normal	Normal	Decreased
Ischemia	Increased fibrin deposits	-	Increased tertiary villi	-
	Extravillous trophoblast hyperplasia	-	Extravillous trophoblast hyperplasia	
Infection	-	-	-	Acute chorioamnionitis stage 1 grade 1
Placental Report	Low weight. Fetal vessels thrombo-inflammatory events. Atypical vacuolated Hofbauer cells. Umbilical cord marginal insertion.	Atypical vacuolated Hofbauer cells.	Placentomegaly. Umbilical cord velamentous insertion.	Mesenchymal dysplasia Acute chorioamnionitis without fetal answer

DISCUSSION

Including the four fetuses described in the present study, there are now 22 cases of FATCO syndrome reported to date [3-16] (Supplementary data 1). All authors consistently report the main features characteristic of FATCO syndrome in at least one lower limb, namely, fibular aplasia/hypoplasia, tibial campomelia and oligosyndactyly of the feet. Frequently, one or both upper limbs are also involved [3,5,7,9-11,13]. Psychomotor development was always described as normal in live FATCO syndrome individuals [3-11]. Interestingly, out of 21 cases in which patient gender was reported, only 3 females were described (male to female ratio, 18:3), thus being clearly biased towards male preponderance. One of the female cases reported had a diseased half-sibling male, from the mother side, with severe symptoms also involving upper and lower extremities: absent hands, absent left leg and absent right foot, such as observed in phocomelia features [11]. Additionally, another author reported that the mother of a patient diagnosed at 11 years of age (patient 3, [7]), presented bilateral partial skin syndactyly of toes 2-3, extending to the proximal interphalangeal joints. These two examples suggest that this disorder possibly has an X-linked inheritance with variable penetrance, which is also in agreement with a suggestion from Bieganski and colleagues [7]. An interesting feature noted from literature review on prenatal diagnosed FATCO cases was that nuchal translucency (NT) measurements, between week 12 and 13, were slightly increased with 3.6 mm for both fetuses [5,12]. Fetal NT thickness above 3.5 mm (>P₉₉), between week 11 and 14, is known to be involved in congenital cardiac defects, chromosomal abnormalities and fetal malformations, including skeletal dysplasia, deformations, disruptions and genetic syndromes [17]. In the present study, all four fetuses had standard NT measurements, with percentile above 50.

Therefore, even though it is very important to take note of NT measurements, our evidence cannot support that FATCO syndrome might be related with increased NT. Nevertheless, within reported FATCO cases, increase in NT measurement has been described in association with a membranous ventricular septal defect [12]. Also,

Bieganski et al., (2012) noted that FATCO patient 1 was born with the same membranous ventricular septal defect, even though no NT value between week 11-14 was reported [7]. Furthermore, in patient 1 of Hecht and Scott (1981), a congenital cyanotic heart defect has been reported which later was identified as the cause of death at day 11 [11]. If this disorder is found to be X-linked, it would explain the severity in the male patient reported by Hecht and Scott (1981) (patient 1) in relation to his female half-sib (patient 2)[11]. Nevertheless, to this date, the etiology of FATCO syndrome remains unknown and because clinical symptoms show some degree of heterogeneity, it is very likely that many other patients were misdiagnosed and not reported.

CONCLUSION

FATCO syndrome must be considered in prenatal diagnosis, by the presence of fibular aplasia, tibial campomelia and oligosyndactyly. Shorter and asymmetric limbs can translate into a single dysplastic bone. The current study further delineates FATCO syndrome at a prenatal stage and supports that correct diagnosis during early prenatal stages is of utmost importance for adequate parental counselling on the current pregnancy and its recurrence risk for future pregnancies.

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CONFLICT OF INTEREST DISCLOSURE

Authors have no conflict of interest to declare.

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