Received: 8 October 2023 | Revised: 5 December 2023 | Accepted: 18 December 2023 | Published online: 12 January 2024

DOI: 10.1002/ijgo.15351

Obstetrics

Prenatal ultrasound signs of Aarskog-Scott syndrome in a twin pregnancy: A case report

Emma Bertucci[1] | **Simone Giulini**[1] | **Giovanna Sighinolfi**[1] | **Martina Benuzzi**[1] | **Licia Lugli**[2]

[1]Obstetrics and Gynecology Unit, Department of Medical and Surgical Sciences for Mothers, Children and Adults, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria Policlinico, Modena, Italy

[2]Neonatal Intensive Care Unit, Women's and Children's Health Department, University Hospital of Modena, Modena, Italy

Correspondence
Emma Bertucci, Obstetrics and Gynecology Unit, Department of Medical and Surgical Sciences for Mothers, Children and Adults, University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria Policlinico, via del Pozzo 71, Modena, 41125 Emilia Romagna, Italy.
Email: emma.bertucci@unimore.it

KEYWORDS
Aarskog-Scott syndrome, genetic diagnosis, prenatal diagnosis, twin pregnancy

Aarskog-Scott syndrome is a rare X-linked developmental disorder (that could phenotypically overlap with other syndromes) characterized by a variety of structural anomalies that involve mainly the face, distal extremities, and external genitalia.[1] Aarskog-related signs include short-statured individuals with craniofacial anomalies such as hypertelorism, short nose, ptosis, and genital dysmorphism such as shawl scrotum and cryptorchidism.[2]

We describe below the case of a dichorionic-diamniotic twin pregnancy obtained by an in vitro fertilization procedure (intracytoplasmic sperm injection plus embryo transfer) with the prenatal finding of shortened fetal long bones. Aarskog-Scott syndrome was diagnosed at birth.

The patient in the case was a 33-year-old Caucasian woman, gravida 1, para 0. The patient and her husband were heterozygote carriers for cystic fibrosis. Genetic counseling was provided to the couple. The pregnancy was achieved after intracytoplasmic sperm injection plus embryo transfer for severe oligo-astheno-teratozoospermia. A 5AA blastocyst was transferred. The patient's personal and family histories were unremarkable. At 7^{+1} weeks of pregnancy two gestational chambers, two yolk sacs, and two embryos with cardiac activity were found, with crown-rump lengths of 11 and 10 mm, respectively. The fetal DNA test (11^{+6} weeks) showed low risk; it was performed at the couple's request. The nuchal translucency was 2.50 mm (above the 95th centile) for both fetuses and was performed at 11^{+0} weeks of pregnancy. The morphologic ultrasound (16^{+2} and 21 weeks) was found to be normal. The early ultrasound was performed at the request of the couple, the other was the fetal anatomy scan of the second trimester. An invasive prenatal diagnosis for cystic fibrosis mutations was offered but the couple declined. At 26^{+1} weeks of pregnancy, biometry of the femur and humerus was reported to be on the 5th centile for both fetuses, following the growth curves (Figure 1).

At 30^{+2} weeks of pregnancy the third-trimester scan was normal, but the femoral length was below the 3rd centile (Figure 2).

It was explained to the couple that long bone biometrics could indicate skeletal abnormalities in the third trimester if growth stopped. Fetal biometry at 34^{+6} weeks reported that the femur lengths and head circumferences were below the 5th centile, which followed the curves. A neonatology consultation was also performed.

At 37^{+0} weeks of pregnancy the femur lengths were below the 3rd centile but head and abdominal circumferences were normal (Figure 3). The couple was told that further diagnostic tests would need to be performed in the postnatal period. At 37^{+4} weeks, the patient was admitted to our unit with maternal hypertension, low platelets, and proteinuria. This was preeclampsia with HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. The patient had signed the consent for vaginal birth; the office ultrasound had seen both fetuses in the cephalic position. The 24-h proteinuria was found to be 347 mg. At 37^{+6} weeks, medical induction of labor was started using vaginal and oral prostaglandins. Oxytocin was started as soon as dilatation was 6 cm.

At 38^{+1} weeks the first infant was delivered vaginally with Apgar scores of 8 and 9 at 1 and 5 min, respectively. Birth weight was 2640 g (9th centile), length was 48 cm (10th centile), and head circumference was 33 cm (17th centile).

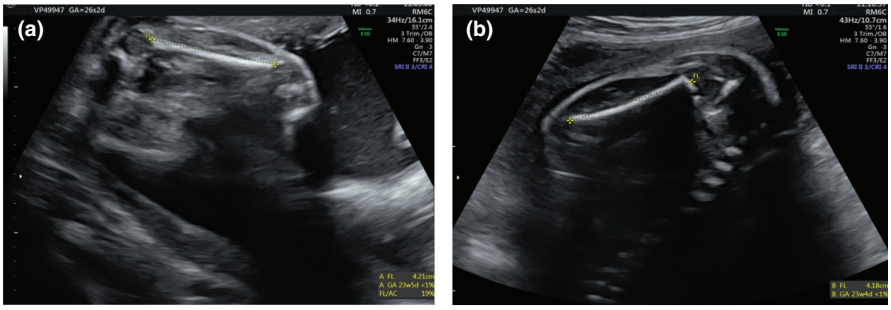

FIGURE 1 (a) Femoral length at 26^{+1} weeks of gestation of fetus 1. (b) Femoral length at 26^{+1} weeks of gestation of fetus 2 on the 5th centile.

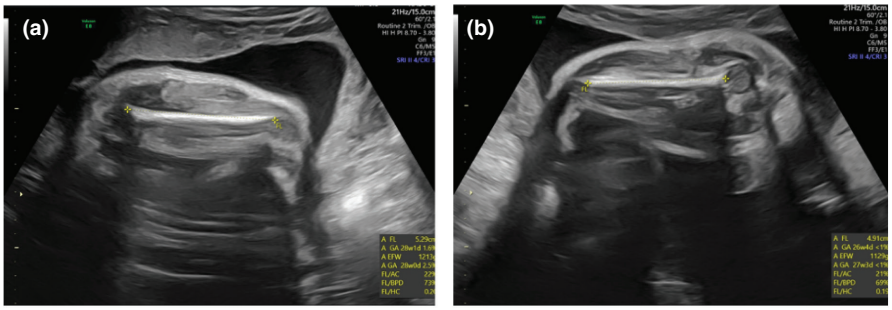

FIGURE 2 (a) Femoral length at 30^{+2} weeks of gestation of fetus 1. (b) Femoral length at 30^{+2} weeks of gestation of fetus 2 was 47 cm (10th centile).

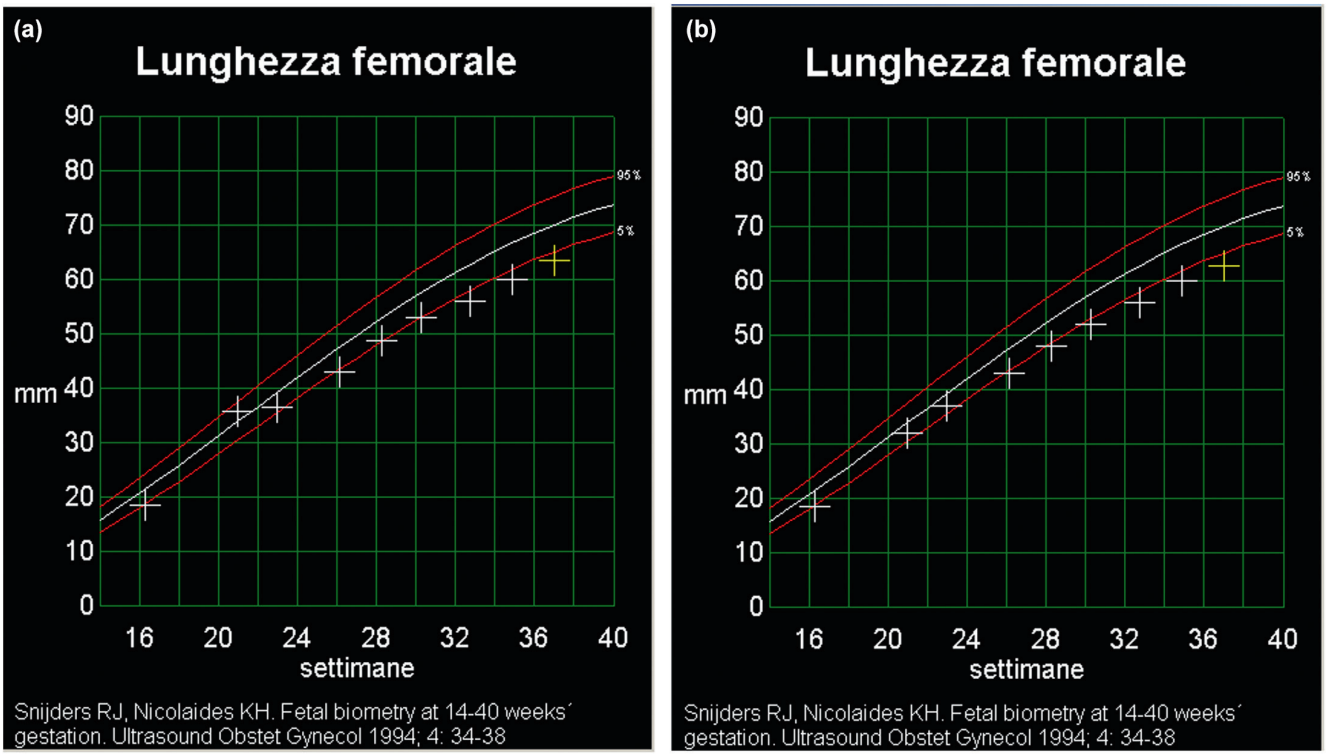

FIGURE 3 Femoral length curves of (a) fetus 1 and (b) fetus 2.

The second fetus was delivered 7 min after the birth of the first by vacuum extraction due to fetal bradycardia with Apgar scores of 5 and 9 at 1 and 5 min, respectively. Birth weight was 2500 g (5th centile), length was 47 cm (10th centile), and head circumference was 31 cm (1st centile).

Both siblings presented peculiar dysmorphic features (Figure 4), and direct sequencing of the *FGD1* gene confirmed the diagnosis. The novel variant (found in the mother) *FGD1* c.1327 C>T (Arg442Cys) was found in both siblings, confirming the diagnosis. Multiple ligation-dependent probe amplification *FGD1* analysis excluded duplication or deletion of the gene.

The siblings were followed up and at 6 months of age presented a typical Aarskog-Scott dysmorphic sign, normal neurodevelopment

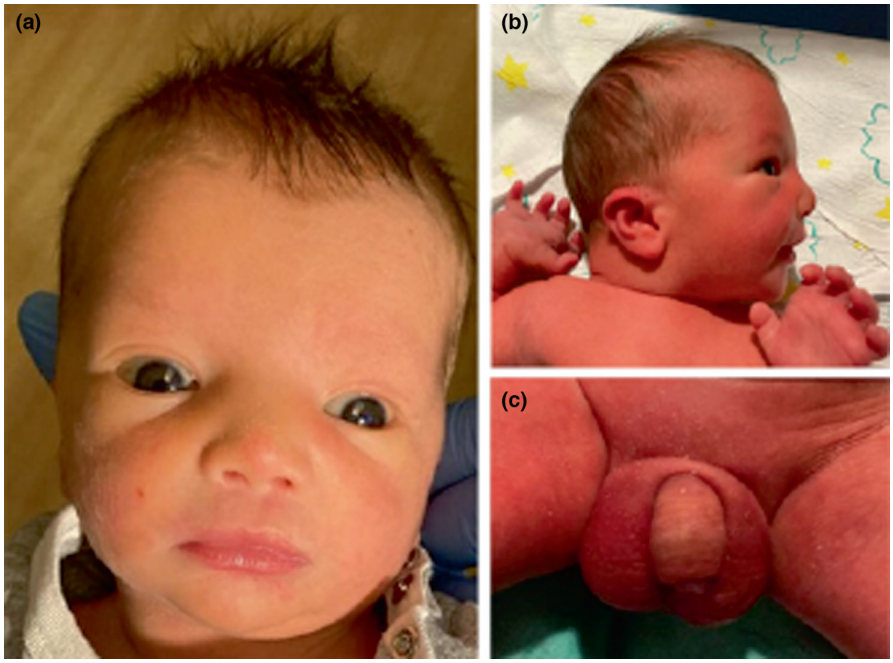

FIGURE 4 (a) First newborn with widow's peak, high forehead, hypertelorism, and large and depressed nasal bridge. (b) Profile view of the second newborn showing a flat midface and a preauricular pit. (c) Shawl scrotum.

but growth retardation: the first sibling had weight 6.6 kg (3rd centile), length 62 cm (<3rd centile), and head circumference 41 cm (3rd centile); the second had weight 6.25 kg (<3rd centile), length 63 cm (<3rd centile), and head circumference 41 cm (3rd centile). A written informed consent was signed by the mother for publication of the manuscript and for the picture. The ethical committee of our department was informed about the publication and written informed consent was obtained, in accordance with the 2021 Regional Guidelines.

A healthy fetus may have a short femur (femoral length below the 5th centile), but a short femur can be associated with skeletal and chromosomal abnormalities: in these cases karyotyping should be offered.[3]

When the short femur length appears in the third trimester, the first suspected diagnosis is achondroplasia. The most common malformations associated with a short femur are urogenital malformations, followed by cardiovascular, musculoskeletal, and cerebro/cephalic abnormalities.[4]

In this case, the syndrome, due to a novel variant c.1327 C>T *FGD1*, was inherited from the mother. The variant affects the functional protein domain, leading to the substitution of a highly conserved amino acid (arginine was substituted by cysteine).

This ultrasound finding has already been analyzed by Hubaishi et al. in 2017,[5] where an increased upper-to-lower segment ratio was found. The key point was the family history (negative in our case). So, the prospective diagnosis of Aarskog-Scott syndrome in the absence of a family history is unlikely to be achieved in utero but it could be mentioned as a possibility.

AUTHOR CONTRIBUTIONS

EB acquired data, designed and drafted the manuscript, critically reviewed the manuscript for important intellectual content, approved the final version to be published, and agreed to be responsible for all aspects of the work. GS, SG, LL, and MB contributed to the design and draft of the manuscript. They also agree to be responsible for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Emma Bertucci https://orcid.org/0000-0003-2020-9111

REFERENCES

1. Pérez-Coria M, Lugo-Trampe JJ, Zamudio-Osuna M, et al. Identification of novel mutations in Mexican patients with Aarskog-Scott syndrome. *Mol Genet Genomic Med*. 2015;3(3):197-202.
2. Zanetti Drumond V, Sousa Salgado L, Sousa Salgado C, et al. The prevalence of clinical features in patients with Aarskog-Scott syndrome and assessment of genotype-phenotype correlation: a systematic review. *Genet Res (Camb)*. 2021;2021:6652957.
3. Liu J, Huang L, He Z, Lin S, Wang Y, Luo Y. Clinical value of genetic analysis in prenatal diagnosis of short femur. *Mol Genet Genomic Med*. 2019;7(11):e978.
4. Friebe-Hoffmann U, Dobravsky L, Friedl TWP, et al. The femur too short? 1373 Fetuses with short femur during second-trimester screening. *Arch Gynecol Obstet*. 2022;306(4):1037-1044.
5. Hubaishi N, Cherifi F, Taka MK, Ashoor AB, Paladini D. Aarskog–Scott syndrome – prenatal ultrasound diagnosis in a case with positive family history. 2017;10:187-190.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.