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Prenatal Diagnosis of Antley-Bixler Syndrome and POR Deficiency

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, fetus
Final Diagnosis: Antley-Bixler syndrome
Symptoms: Craniosynostosis • midface hypoplasia • femoral bowing • radiohumeral synostosis
Medication: None
Clinical Procedure: Prenatal diagnosis of severe fetal bone disease using detailed ultrasonography and computed tomography
Specialty: Obstetrics and Gynecology • Maternal-Fetal Medicine

Objective: Rare disease

Background: Prenatal diagnosis of severe bone diseases is challenging and requires complete and precise analysis of fetal anomalies to guide genetic investigation and parental counselling.

Case Report: We report a rare case of Antley-Bixler syndrome prenatally diagnosed at 26 weeks' gestation by ultrasound and computed tomography in a 28-year-old woman with a history of early termination of pregnancy for "malposition of the inferior limbs". The prenatal ultrasound scan showed severe femoral bowing and frontal bossing. Taking into account the high probability of a recurrent severe skeletal disorder, a computed tomography (*CT*) scan was proposed. *CT* findings revealed bilateral femora deformation, craniosynostosis, severe midface hypoplasia, and radiohumeral synostosis. These anomalies strongly suggested Antley-Bixler syndrome. Sequencing of the *POR* gene in the fetus and the parents revealed compound heterozygous mutations in exon 9 and intron 7, both inherited from each parent, and this finding allowed genetic counseling.

Conclusions: The first step in the proper prenatal diagnosis of fetal bone disorders is the precise analysis of ultrasonographic images. However, when a severe fetal inherited disorder is strongly suspected in late mid-trimester, *CT* may be discussed and usefully contribute to diagnosis and prognosis assessment.

MeSH Keywords: Antley-Bixler Syndrome Phenotype • Bone Diseases, Developmental • Fetal Diseases • Genetic Counseling • Prenatal Diagnosis • Tomography Scanners, X-Ray Computed

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/895526

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Background

The extensive ultrasound workup of fetal skeletal anomalies may be a challenge for prenatal diagnosis, because ultrasound may overlook specific features of constitutional skeletal diseases. Although the first step and most important factor in the proper diagnosis of fetal bone disorders is the precise analysis of detailed ultrasonographic images in order to avoid the mother and the fetus being unnecessarily exposed to radiation, computed tomography (*CT*) may usefully contribute in certain cases to the accurate prenatal diagnosis of severe skeletal dysplasia, when the diagnosis cannot be firmly asserted after acquisition of detailed ultrasound images [1–3].

Case Report

A 28-year-old woman was referred to our prenatal diagnosis center after "malposition of the inferior limbs" was found on first-trimester fetal ultrasound scan. In a first pregnancy with the same healthy, non-consanguineous partner, a termination had been decided on at the end of the first trimester because of "inferior limb anomalies", without any definite diagnosis. Second-trimester fetal ultrasound confirmed severe bilateral femoral bowing, and showed a receding midface. On the other hand, the ribs were of normal size, no visceral anomalies were observed, amniotic fluid amount was normal, and a normal female karyotype was found. 3D ultrasound did not contribute usefully to the diagnosis. Because of severe skeletal anomaly recurrence without any definite diagnosis, *CT* was discussed and performed at 26 gestational weeks. *CT* allowed us to assert severe bilateral femoral bowing with medial concavity (Figure 1), and showed fetal coronal craniosynostosis and radiohumeral synostosis (Figure 2). These anomalies strongly suggested Antley-Bixler syndrome (*ABS*) phenotype, a rare skeletal disease. Indeed, *ABS* phenotype is characterized by craniosynostosis, midface hypoplasia, radio humeral or radio ulnar synostosis, and bowing femora [4]. Severe midface hypoplasia may alter neonatal survival [4–6], and craniosynostosis seriously affects mental prognosis [4, 5]. After comprehensive counseling, the parents elected termination of pregnancy. The fetus weighed 908 g, with trapezoidocephaly caused by the premature closure of the coronal sutures, protruding eyes, severe midface hypoplasia, depressed nasal bridge, short philtrum, hypoplasia of the maxillary and nasal bones, and dysplastic low-set ears. The association of patent ankyloses of both elbows (Figure 3) with bilateral bowing of the femora confirmed prenatal imaging. The autopsy also showed hypoplasia of the labia majora, with small urinary meatus, vaginal hypoplasia, clitoromegaly, and bicornuate uterus. No fluconazole exposure was identified during pregnancy [7], and

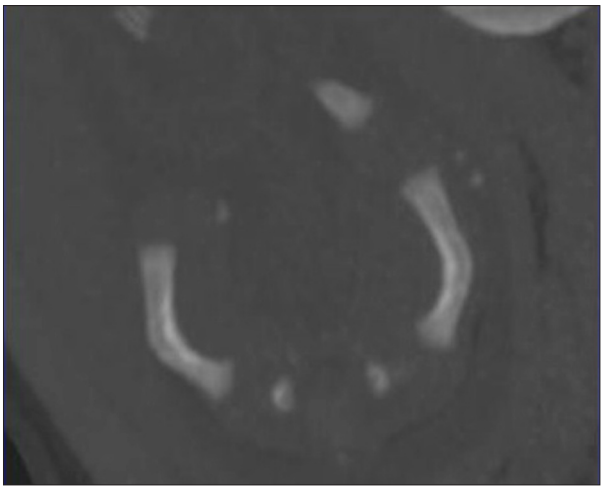

Figure 1. Bowed femora.

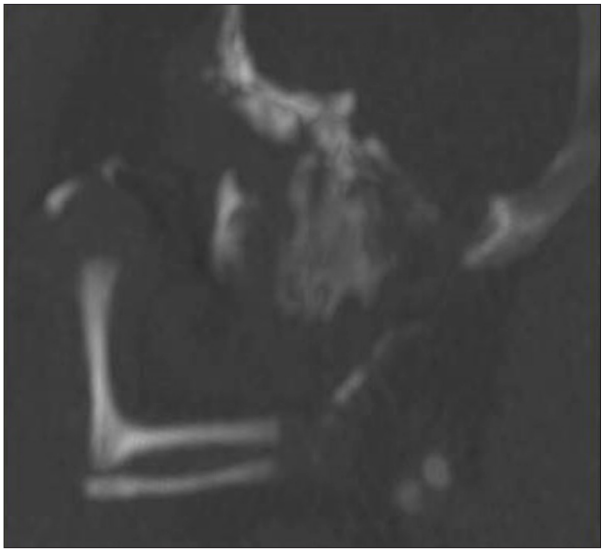

Figure 2. Radiohumeral synostosis.

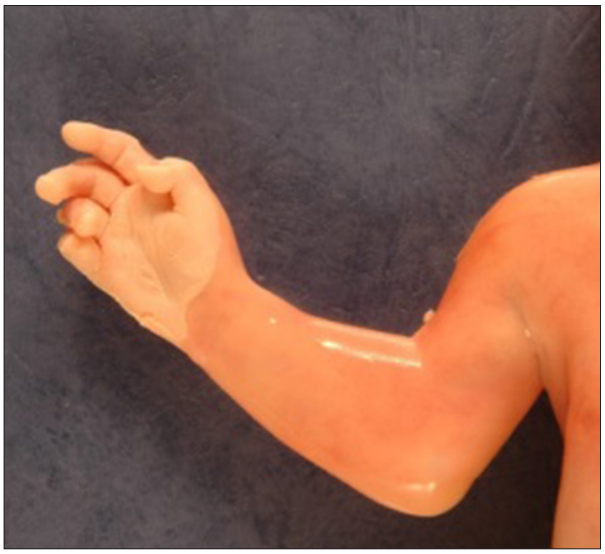

Figure 3. Elbow ankylosis.

the sequencing of the *POR* gene in the fetus and the parents, which revealed compound heterozygous mutations c.859G>C (p.Ala287Pro) in exon 9 and c.732-2A>T in intron 7, inherited from each parent, allowed genetic counseling of the parents regarding future pregnancies.

Discussion

The most suggestive feature of *ABS* is the association of craniosynostosis and midface hypoplasia with femoral bowing and radiohumeral synostosis. However, the prenatal detection of *ABS* ultrasound features may be difficult, even if the occurrence of an index case in a first sibling guides the diagnostic investigation (notably, the evidence of elbow ankyloses needed up to 5 hours of real-time observation in a previous prenatal case report [8]). Though rare, Antley Bixler syndrome should be suspected if ultrasound shows short, curved femurs, especially in patients with a family history of the syndrome, or of unidentified bone anomalies in previous pregnancies. In cases of suspected craniosynostosis, the possibility of other syndromic craniosynostosis must be considered after ruling out karyotype anomalies. Like other reports in the prenatal [9] or even post-natal period [10], we had to discuss the other possible diagnoses of constitutional bone diseases, taking into account the presence of limb abnormalities and the absence of syndactyly. Although fetal *CT* should never be the initial diagnostic imaging modality because of the risk of radiation to the fetus, it may be the only way to depict the fetal skeleton in detail in certain suspected cases in which the osseous abnormalities are particularly severe and the diagnosis cannot be firmly asserted after acquisition of highly detailed ultrasound images [1–3]. After discussion by the multidisciplinary team of maternal-fetal medicine specialists, pediatricians, radiologists, and geneticists in consultation with the parents, fetal *CT* was proposed and performed by our reference pediatric fetal radiologist (CG). The radiation dose was within the diagnostic reference level published in a nationwide radiation dose survey of computed tomography for fetal skeletal dysplasias [3], but still lower radiation dose to the fetus at a minimum may be recommended [2]. In this case, *CT* imaging showed the association of craniosynostosis with femoral bowing (Figure 1) and bilateral radiohumeral synostosis (Figure 2), which together with ultrasonic images strongly evoked Antley-Bixler syndrome (*ABS*), a heterogeneous syndrome characterized by skeletal deformation associated with multiple synostoses. Over 90% of infants with ABS die as neonates because of respiratory failure due to severe midface hypoplasia [5], and craniosynostosis affects mental prognosis [4–6]. Individuals with an *ABS*-like phenotype and normal steroidogenesis tend to have *FGFR* mutations, whereas those with ambiguous genitalia and abnormal steroidogenesis have *POR* deficiency [11–15]. Thus, a definitive diagnosis may be established by the presence of mutation in the *POR* gene in case of urogenital anomalies or in the *FGFR2* gene in absence of these anomalies. In this case with urogenital anomalies, compound heterozygous mutations c.859G>C (p.Ala287Pro) in exon 9 and c.732-2A>T in intron 7, inherited from each parent, were indeed found and allowed an accurate genetic diagnosis and counseling of the parents for future pregnancies.

Conclusions

When a recurrence of severe skeletal disorder is strongly suspected in a fetus during late mid-trimester, and the diagnosis and prognosis are still in question after acquisition of highly detailed ultrasound images, the precise analysis of family history and the combination of computed tomography with detailed assessment of ultrasound images can help in accurate prenatal diagnosis. In this difficult context, appropriate genetic counseling is essential in parental decision-making.

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