A Rarely Seen Fetal Anomaly: Fraser Syndrome

Miğraci TOSUN[1], Özlem ULUSOY[4], Arif KÖKCÜ[1], Mehmet B.ÇETİNKAYA[1], Oğuz AYDIN[2], Gönül OĞUR[3]

Samsun, Turkey

There are about 200 published case reports of patients with Fraser syndrome and several comprehensive reviews have previously been published. Fraser syndrome has a recurrence risk of 25% among siblings, therefore prenatal diagnosis is an important task for the diagnostician counseling affected families. We aimed to report a case of Fraser Syndrome that was diagnosed prenatally at 19 weeks of gestation with multiple ultrasonographic anomalies and terminated at 21 weeks of gestation, to review prenatal diagnostic criteria and possible etiologic factors of Fraser syndrome.

Key Words: Fetal anomaly, Fraser syndrome, Prenatal diagnosis

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Introduction

Zehender in 1872 first described a complex malformation syndrome including bilateral cryptophthalmos, hypertelorism, syndactyly, abnormal genitalia, umbilical hernia, anal stenosis and hoarse voice. In 1962 Fraser published a case of two siblings with cryptophthalmos, syndactyly, ear and nose defects, laryngeal stenosis, and renal and genital malformations.[1] Since then the term Fraser syndrome has been used for similar complex malformation syndromes, including cases without cryptophthalmos. Thomas et al. reviewed 124 cases of cryptophthalmos and associated syndromes and established minimal diagnostic criteria clearly separating Fraser syndrome from isolated cryptophthalmos. There are more than 200 published case reports of patients with CO and FS and several comprehensive reviews have previously been published.[2-4] In the present article, we present a case of Fraser Syndrome which we diagnosed as fetal acites, oligohydramnios, renal agenesis and hyperechogenic lungs at 19 gestational weeks and terminated at 21 gestational weeks and diagnosed as Fraser Syndrome postnatally. Of this syndrome, very rarely seen, we review the possible etiologic factors and prenatal diagnostic criateria.

[1]Department of Obstetrics and Gynecology and [2]Department of Pediatric Genetics and [3]Department of Pathology Faculty of Medicine Ondokuz Mayıs University, Samsun

[4]Department of Obstetrics and Gynecology Sivas State Hospital Sivas

Address of Correspondence: *Miğraci Tosun*
Ondokuz Mayıs University Hospital
Department of Obstetrics & Gynecology
Kurupelit, Samsun
mirtosun@yahoo.com

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Case Report

A 21-year-old woman, gravida 1, para 0, was referred from a local hospital because of an abnormal ultrasound examination at 19 weeks' gestation. The patient and her husband were cousins. At 19 weeks of gestation, fetal ultrasonographic examination revealed multiple abnormal findings with oligohydramnios, fetal ascites, and contrastingly large, hyperechogenic lungs and left renal agenesis. Other abnormal findings included non-visualization of bladder, hepatomegaly and syndactyly of right and left hands and toes. The abdomen was also distended as a result of coexisting ascites. The heart appeared structurally normal at real time scanning and color Doppler flow mapping. Head and long bone biometry was consistent with which was expected for gestational age. Cordocentesis showed 46, XY normal male karyotype. Both parents had normal karyotypes. The parents were informed about these sonographic malformations and they elected to terminate the pregnancy at 21 weeks. After prostaglandin induction, a male fetus with multiple malformations was delivered at 21 gestational weeks. The crown-rump length was 17 cm and the crown-heel length 28.5 cm and weight 630 gram. The umbilical cord had one artery and one vein. In gross pathologic examination, a dysmorphic face with short-neck, hypertelorism, cryptophthalmos, down-turned nasal tip was seen. Rudimentary ear lobes were low-set with stenotic ear canals. There was bilateral cutaneous syndactyly between fingers II, III, IV and between toes II, III, IV. The scrotum was rudimentary developed with a micropenis (Figure 1). Internal examination revealed right renal dysplasia and left renal agenesis with testes in a high abdominal position, open ductus botalli, and open foramen ovale. Both lungs were normally lobulated and histologically patent. No trachea or oesophageal atresia could be found. In the other organs (heart, thymus, spleen, liver, intestine,stomach, duodenum), no histological abnormalities were found. These findings was considered as diagnostic criteria of Fraser Syndrome.

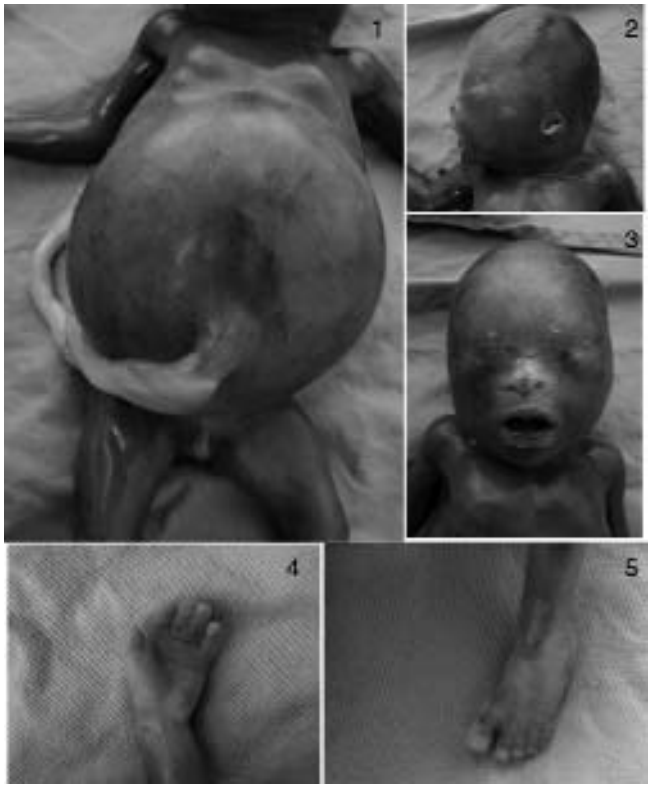

Figure 1: Postpartum photographs of a 21 weeks' fetus with Fraser Syndrome (1.Abdomen distended as a result of ascites, abnormal genitalia with scrotal hypoplasia and micropenis; 2. Low-set malformed ears; 3. Cryptophthalmos, hypertelorism, and a broad nose with low nasal bridge; 4. Soft-tissue syndactyly between fingers II, III and IV; 5. Soft-tissue syndactyly between toes II, III and IV).

Discussion

Fraser syndrome is characterised by cryptophthalmos (90%), cutaneous syndactyly(62%), ear and nose abnormalities (85%), renal agenesis (45%), congenital heart defects (12%), malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies. Other anomalies associated with Fraser syndrome are major vascular anomalies, imperforate anus, intestinal hypoplasia, thymic aplasia, abnormal genitalia with scrotal hypoplasia, a micropenis, cryptorchidism in males and large labia majora, vaginal atresia and rudimentary uterus in females. In 45% of cases, affected individuals are stillborn or die in the first year; surviving infants are often developmentally delayed. Death is usually associated with renal agenesis and laryngeal stenosis. The inheritance is autosomal recessive. No diagnostic cytogenetic abnormalities have been documented in affected patients, and no molecular genetic studies have been reported.[1-5] The case presented here didn't have any cytogenetic abnormality and its karyotype was 46XY.

Several of the abnormalities in Fraser syndrome are found in areas temporarily fused during embryogenesis, suggesting that failure to remodel these regions is secondary to an abnormality of apoptosis. Cell adhesion to extracellular matrix (ECM) proteins is crucial for the structural integrity of tissues and epithelialmesenchymal interactions mediating organ morphogenesis. It has been suggested that Fraser syndrome is a mid-gestational developmental defect due to a defective ECM. The sites of malformation in Fraser syndrome and histology of diseased kidneys suggests a defect in apoptosis secondary to the molecular mutation. A relationship between the insoluble matrix and soluble factors during limb patterning has been shown in mice with knockouts of both Fbn2 (encoding fibrillin 2) and Bmp7, which develop syndactyly and have reduced apoptosis. Moreover, it has been shown that glutamate receptor interacting protein 1 (GRIP1) is required for normal cell-matrix interactions during early embryonic development and that inactivation of Grip1 causes Fraser syndrome–like defects in mice.[5-7]

Feldman et al.[8] reported the first prenatal detection of Fraser syndrome in 1985. Their diagnosis was based on microphthalmia and hydrocephalus being present in a fetus at 18 weeks' gestation with a previously affected sibling. In a review of the literature, that 16 cases of Fraser syndrome underwent sonographic examination prior to delivery or termination of pregnancy has been found. Fraser syndrome has a recurrence risk of 25% among siblings, therefore prenatal diagnosis is an important task for the diagnostician counseling affected families.[5] Fraser Syndrome can be antenatally diagnosed by sonography according to the diagnostic criteria proposed by Thomas et al.[2] (1986). The authors defined (1) cryptophthalmos, (2) syndactyly, (3) abnormal genitalia and (4) sibling with cryptophthalmos as the four major criteria. Congenital malformations of the nose, ears, and larynx; cleft lip/cleft palate; skeletal defects; umbilical hernia; renal agenesis; and mental retardation in survivors are considered minor criteria for diagnosis. Cases are diagnosed on the basis of at least two major criteria and one minor criterion, or on the basis of one major criterion and at least four minor criteria.[2-4]

Prenatal diagnosis of cryptophthalmos might be possible by sonographic assessment of the fetal palpebral fissure slant; however, in fetuses with Fraser syndrome this might often be impaired by concomitant oligohydramnios. Other less frequent ophthalmologic abnormalities that could be detected by ultrasound include microphthalmia, anophthalmia, hypertelorism and defects of the anterior segment of the eye. Abnormalities of the ears and the nose occur with a frequency of approximately 85%. It has been reported that the prenatal diagnosis of syndactyly is often impaired by the associated oligohydramnios. Therefore, in cases of oligohydramnios, instillation of fluid in the amniotic cavity should be considered, in order to improve the visualization of face, ears, kidneys and digits, im-

portant structures for the diagnosis of Fraser syndrome.[2-5] Previous reports suggested that the contrasting association of oligohydramnios indicating renal agenesis and bilateral hyperechogenic lungs, as were present in our case, might be a sonographic marker of Fraser syndrome. In our case, however, the abnormalities in the fetal face, ears and digits couldn't be detected by sonography. Not being able to detect these abnormalities may be due to the existence of oligohydramnios in the case. We were not aware of the fact that oligohydramnios, renal agenesis and hyperechogenic lungs could be sonographic markers of Fraser syndrome. Since we decided to terminate the pregnancy due to the major malformations we detected antenatally, we didn't think of instillation of fluid in the amniotic cavity. It has been reported that so far 16 cases of Fraser syndrome were able to diagnose by sonographic examination prior to delivery or termination of pregnancy.[1]

In conclusion, the prenatal diagnosis of Fraser syndrome is possible in the hands of an expert at ultrasound, but due to the great variety of possible malformations the diagnosis will remain in doubt in most cases in which no previous child is affected.

Nadir Görülen Bir Fetal Anomali: Fraser Sendromu

Fraser Sendrom'u tespit edilen yayınlanmış yaklaşık 200 vaka sunumu ve birkaç kapsamlı inceleme vardır. Fraser Sendromu' nun kardeşler arasında %25 tekrarlama riski olduğundan etkilenmiş ailelere tanısal danışmanlık verilmesi önemlidir. Bu vaka taktiminde 19. gebelik haftasında birçok ultrasonografik anomali ile prenatal tanısı konulan ve 21 gebelik haftasında sonlandırılan Fraser Sendromu'nu sunmayı ve ancak postnatal 21. haftada tanı konulan Fraser Sendrom'unu sunmayı, prenatal tanı kriterlerini ve muhtemel etyolojik faktörleri gözden geçirmeyi amaçladık.

Anahtar Kelimeler: Fetal anomali, Fraser sendromu, Prenatal tanı

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