Prenatal Diagnosis of Fryns Syndrome: A Case Report

Miğraci TOSUN[1], Handan ÇELİK[1], Emre BEŞE[1], Erdal MALATYALIOĞLU[1]
Mehmet B. ÇETİNKAYA[1], Mehmet TÜRE[2], Gönül OĞUR[2]

Samsun, Turkey

Fryns syndrome (FS) is a rare malformation. Major diagnostic criteria include congenital diaphragmatic hernia, distal limb and nail hypoplasia and abnormal facial appearance. We report a case of FS referred to our clinic at 25 weeks' gestation with a diagnosis of congenital diaphragmatic hernia. Sonographic examination of the fetus revealed microretrognathia, a short neck with nuchal folds (17 mm), a left-sided diaphragmatic hernia, bilateral pelviectasis and cutaneous edema. The diagnosis of FS was made after exclusion of chromosome aberrations by amniocentesis and delivery of the fetus. Macroscopic inspection revealed low-set posteriorly rotated ears, microretrognathia, complet mid cleft palate, a broad nasal bridge, low hairline, short neck, distal limb hypoplasia, rocker bottom feet, atypical female dominant genitalia.

Key Words: Fryns syndrome, Congenital diaphragmatic hernia, Ultrasound findings

Gynecol Obstet Reprod Med;15:1 (47 - 49)

Introduction

Fryns syndrome (FS) is an autosomal recessive disorder. It is almost always lethal. More than 70 cases have been reported since the first report in 1979.[1] The major malformations are diaphragmatic defects, distal limb hypoplasia and craniofacial anomalies, including a coarse facies with hypertelorism, a broad nasal bridge, cleft upper lip and/or cleft palate, macrostomia, micrognathia, dysplastic ears and a short, broad neck with nuchal folds.[2] Pregnancy is often complicated by polyhydramnios late in the second trimester and by preterm delivery. We report a case of FS and review the published literature on this rare malformation.

Case Report

A 33 year old pregnant woman, G2 P1 was referred to our clinic with the diagnosis of diaphragmatic hernia and polyhydramnios by sonographically. The parents were non-consanguineous and healthy. There was no family history of congenital malformations. Previously, she had an uncomplicated singleton pregnancy which was delivered by cesarean section under general anesthesia.

Sonographic examination revealed microretrognathia, a short neck with nuchal folds (17 mm), a left-sided diaphragmatic hernia (Figure I), bilateral pelviectasis and cutaneous edema. The last menstrual period of the women was unknown. The sonographic fetal biometry was at a gestational age of 25 weeks. Amniotic fluid volume increased. A cytogenetic study performed on the amniotic fluid cells revealed a karyotype of 46, XX. After the elimination of abnormal karyotyping by amniocentesis, a diagnosis of FS was suspected. The parents were informed about the syndrome and the prognosis. They choose to continue the pregnancy. At 27 weeks of gestation preterm labour started. Because of regular uterine contractions, cesarean section was performed under general anesthesia, delivered a female infant with 38 cm in length and weighing 1540 gr. The Apgar scores were 1, at 1minute and 0, at 5 minute.

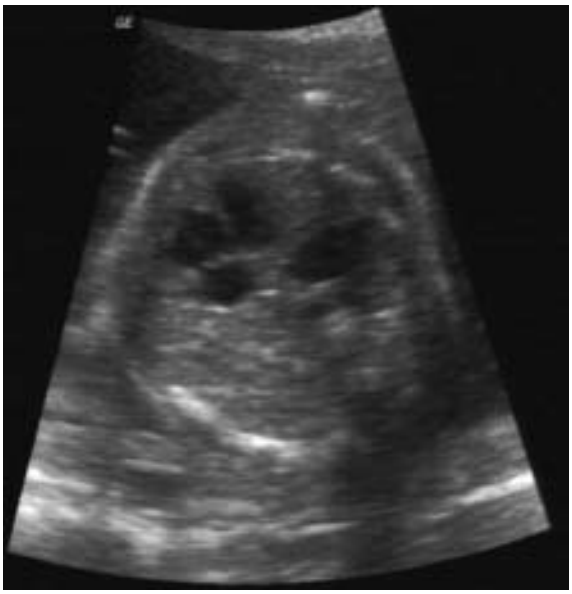

Figure I: Axial view of the thorax demonstrating left diaphragmatic hernia

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

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

Submitted for Publication: *17.09.2008*
Accepted for Publication: *29.09.2008*

After the delivery of fetus, macroscopic observation revealed low-set and posteriorly rotated ears, atypically shaped ear curls, hypoplasic auricles, microretrognathia, a broad nasal bridge, low hairline, short neck (Figure II), complete mid cleft palate, distal phalanx hypoplasia (Figure III), rocker bottom feet, atypical female dominant genitalia. Autopsy was refused by the parents.

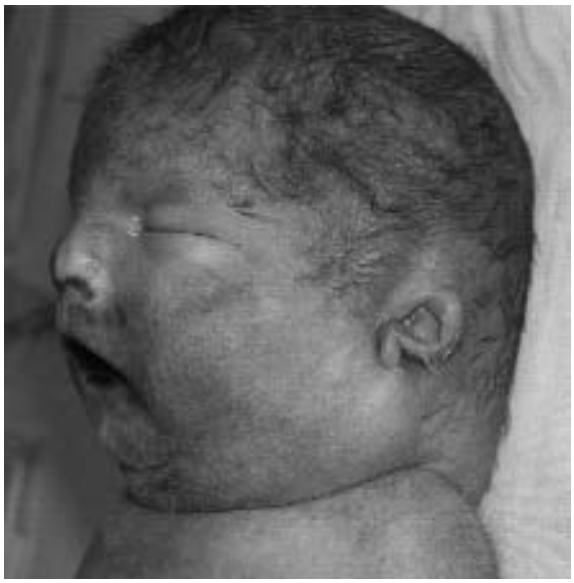

Figure II: X-Ray showing distal phalanx hypoplasia

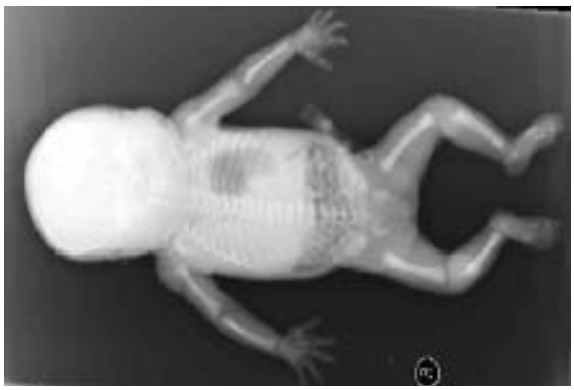

Figure III: Gross appearance of the stillborn neonate. Note that low-set posteriorly rotated ears, atypically shaped ear curls, hypoplasia of auricle, microretrognathia, a broad nasal bridge, low hairline, short ***neck***

Discussion

Fryns syndrome is the most frequent non-chromosomal multiple congenital anomaly syndrome associated with congenital diaphragmatic hernia, accounting for 4-10% of those cases.[3] The incidence may be as high as 1 in 12,000 births with an approximate male:female ratio of 1,25:1.[4] In 1979, Fryns et al. described a variable multiple congenital anomaly (MCA) syndrome consisting of coarse facies, diaphragmatic defects and distal limb hypoplasia.[1] The most common manifestations of FS are diaphragmatic hernia (60-96%), pulmonary hypoplasia (65%), nail hypoplasia (59%), hypoplasia of the distal phalanges (59%), polyhydramnios (56%), craniofacial dysmorphism with cleft palate (50-70%), and ventricular septal defect (40-55%).[5] Similarly, we demonstrated microretrognathia, a short neck with nuchal folds (17 mm), a left-sided diaphragmatic hernia, bilateral pelviectasis, cutaneus oedema, a broad nasal bridge, low hairline, distal limb hypoplasia and polyhydramnios in our case.

A review of the literature relating to Fryns syndrome suggests that the neural crest cell developmental field, midline structures and the skeletal system are disturbed in most cases.[6] Survival appears to be related both to the degree of diaphragmatic and lung hypoplasia and the presence of cardiac defects. Diaphragmatic hernia, which is frequently secondary to a postero-lateral diaphragmatic defect, and lung hypoplasia have been recorded in 80% of affected patients, but the exact pathogenesis is controversial.[7] Although diaphragmatic hernia is one of the major diagnostic criteria for Fryns syndrome, it is not invariable and 14 cases have now been reported with no diaphragmatic defect.[8] Prenatal overgrowth and polyhydramnios are often present, while cystic hygroma has been implicated in several instances.[7]

A diagnosis of Fryns syndrome should not be made until it is known that the karyotype is normal. As a number of aneuploidies exist with similar manifestations. It has been suggested that the relatively constant anomalies were probably due to a single mutant gene; however, the variety of different genetic defects recently reported that give rise to a phenotype similar to Fryns syndrome make this less likely. Two cases of trisomy 22 and a third case of partial trisomy 22 were recently reported to cause a phenotype similar to Fryns syndrome.[9] A number of chromosome abnormalities show similar manifestations to Fryns syndrome. These include Pallister-Killian syndrome (mosaicism for isochromosome 12p), isochromosome 6q, duplication of 1q22-32 and a ring chromosome 15.[1] One common chromosome example is trisomy 18 (Edwards syndrome) with its characteristic findings of craniofacial anomalies, camptodactyly, polyhydramnios, and multiple visceral anomalies including diaphragmatic hernia.[7] Fryns Syndrome should be suspected in differential diagnosis in patient with normal or large for gestational age fetus with polyhydramnios.[10]

Neurological outcome appears to be the most important long-term issue for survivors, and mental retardation varies from mild to severe. A great variety of neuroanatomical abnormalities have been reported including hydrocephalus, ventrigulomegaly, agenesis of the corpus callosum, Dandy Walker anomaly, cerebellar heterotopia and hypoplasia, persistent cavum septum pellucidum, cerebral cortical atrophy and arhi-

nencephaly.[11] The oldest known patient with Fryns syndrome, who was severely mentally handicapped, died in status epilepticus at 15 years of age.[12]

Prenatal diagnosis of Fryns syndrome should be possible in many cases with the routine use of ultrasound scans. This has important implications considering the high mortality among affected individuals and the almost universal developmental delay noted in reported survivors. When counselling families, it is important to bear in mind the 25% theoretical risk of recurrence in subsequent pregnancies.

Prenatal Tespit Edilen Fryns Syndrome: Olgu Sunumu

Fryns sendromu (FS) nadir görülen bir malformasyondur. En önemli tanı kriterleri konjenital diafragmatik herni, distal ekstremite ve tırnak hipoplazisi ve anormal yüzdür. Bu çalışmamızda, 25. gebelik haftasında konjenital diafragmatik herni tespit edilmesi üzerine kliniğimize gönderilen FS olgusu sunulmaya çalışıldı. Ultrasonografik incelemede mikroretrogınati, kısa boyun ve artmış ense kalınlığı (17 mm), sol yerleşimli diafragmatik herni, bilateral pelviektazi ve cilt ödemi tespit edildi. Kromozomal anomalilerin amniosentezle ekarte edilmesi ve fetusun doğumuyla Fryns Sendromu tanısı konuldu. Makroskopik incelemede aşağı yerleşimli arkaya dönük kulaklar, mikroretrogınati, komplet orta damak yarığı, geniş burun kökü, saç çizgisinde düşüklük, kısa boyun, distal ekstremitelerde hipoplazi, beşik ayak (rocker bottom feet), atipik görünümde dişi belirgin genital yapı izlendi.

Anahtar Kelimeler: Fryns sendromu, Konjenital diafragmatik herni, Ultrasonografi

References

1. Vasudevan P.C, Stewart H. A case of Fryns syndrome without diaphragmatic hernia and review of the literature. Clin Dysmorphol 2004;13(3):179-82.
2. Fryns JP, Moerman F, Goddeeris P. A new lethal syndrome with cloudy cornea, diaphragmatic defects, and distal limb deformities. Hum Genet 1979;50:65.
3. Pierson D.M, Subtil A, Taboada E, Butler M.G. Newborn with anophthalmia and features of Fryns syndrome. Pediatr Dev Pathol 2002;5(6):592-6.
4. Pinar H, Carpenter M.W, Abuelo D, Singer D.B. Fryns syndrome: a new definition. Pediatr Pathol 1994;14(3): 467-78.
5. Lin AE, Pober BR, Mullen MP. Cardiovascular malformations in Fryns syndrome: is there a pathologic role for neural crest cell? Am J Med Genet 2005;139:86.
6. Ramsing M, Gillessen-Kaesbach G, Holzgreve W, Fritz B, Rehder H. Variability in the phenotypic expression of Fryns syndrome: A report of two sibships. Am J Med Genet A 2000;95:415-24.
7. Sheffield JS, Twickler DM, Timmons C, Land K, Harrod M, Ramus RM. Fryns syndrome: prenatal diagnosis and pathologic correlation. J Ultrasound Med 998;17:585-9.
8. Willems PJ. Fryns syndrome without diaphragmatic hernia? Am. J. Med. Genet 1991; 41:255-7.
9. Ladonne JM, Gaillard D, Carre-Pigeon F, Gabriel R. Fryns phenotype and trisomy 22. Am. J. Med. Genet 1996; 61:68-70.
10. Fryns J.P. Fryns syndrome: a variable MCA syndrome with diaphragmatic defects, coarse face, and distal limb hypoplasia. J Med Genet 1987;24(5):271-4.
11. Davis C, Samarakkody U. Fryns syndrome: a surviving case with associated Hirschsprung's disease and hemidiaphragmatic agenesis. J Paediatr Child Health 2002;38 (3):318-20.
12. Dingens M, Fryns JP. Hematometra and sudden death after status epilepticus in the adolescent female with Fryns syndrome. Genet Couns 1999;10:329-30.