Case Report

Fryns Syndrome: Case Report and Review of the Literature

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ABSTRACT: Fryns syndrome (FS) is a rare malformation. We report a case of FS referred to our clinic at 27 weeks' gestation with a diagnosis of congenital diaphragmatic hernia. Sonographic examination of the fetus revealed a left-sided diaphragmatic hernia, pulmonary hypoplasia, and a median orofacial cleft. The diagnosis of FS was made after exclusion of chromosome aberrations and delivery of the fetus. Macroscopic inspection revealed a coarse face (hypertelorism and broad and flat nasal bridge, anteverted nostrils, median cleft lip/palate, poorly shaped auricles with attached earlobes, facial hirsutism), a narrow thorax, nail hypoplasia, and hypoplastic, widely spaced nipples. © 2007 Wiley Periodicals, Inc. *J Clin Ultrasound* **36**:315–317, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jcu.20409

Keywords: Fryns syndrome; congenital diaphragmatic hernia; pulmonary hypoplasia; cleft palate; nail hypoplasia

Fryns syndrome (FS) is an autosomal recessive disorder. More than 70 cases have been reported since the first case described by Fryns and colleagues in 1979.[1] The initial syndrome was diagnosed as a triad including right-sided diaphragmatic hernia, dysmorphic face anomalies, and nail hypoplasia. The phenotypic features were revised by Fryns and colleagues in 1987,[2] and the combination of major features was reported. We report a case of FS and review the published literature on this rare malformation.

CASE REPORT

A 28-year-old woman, gravida 2, para 0, abortus 1, was referred to our perinatology unit following identification of diaphragmatic hernia at 27 weeks' gestation. She had not had any previous prenatal care. Sonographic examination of the fetus revealed a left-sided diaphragmatic hernia with bilateral pulmonary hypoplasia (Figure 1) and median cleft lip and palate (Figure 2). Fetal biometry was normal according to the patient's last menstrual period, and her amniotic fluid volume was normal. No other anomalies were observed. Amniocentesis and umbilical cord blood sampling revealed a normal 46,XY karyotype. A diagnosis of FS was suspected after chromosomal aberrations were eliminated. The parents were informed about the syndrome and the prognosis and chose to continue the pregnancy.

The patient was admitted to our clinic with the diagnosis of rupture of membranes 5 days after ultrasonographic examination. No fetal cardiac activity was detected. After delivery of the fetus, the macroscopic observation revealed hypertelorism and broad and flat nasal bridge, anteverted nostrils, median cleft lip/palate, poorly shaped auricles with attached earlobes, facial hirsutism, narrow thorax, nail hypoplasia, and hypoplastic, widely spaced nipples (Figures 3 and 4). The parents declined an autopsy.

DISCUSSION

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%)[3–5]. Except for nail hypoplasia, most of these anomalies can be detected easily via sonography.[4,6,7]

The optimal management strategies and prognostic indices for neonates have yet to be estab-

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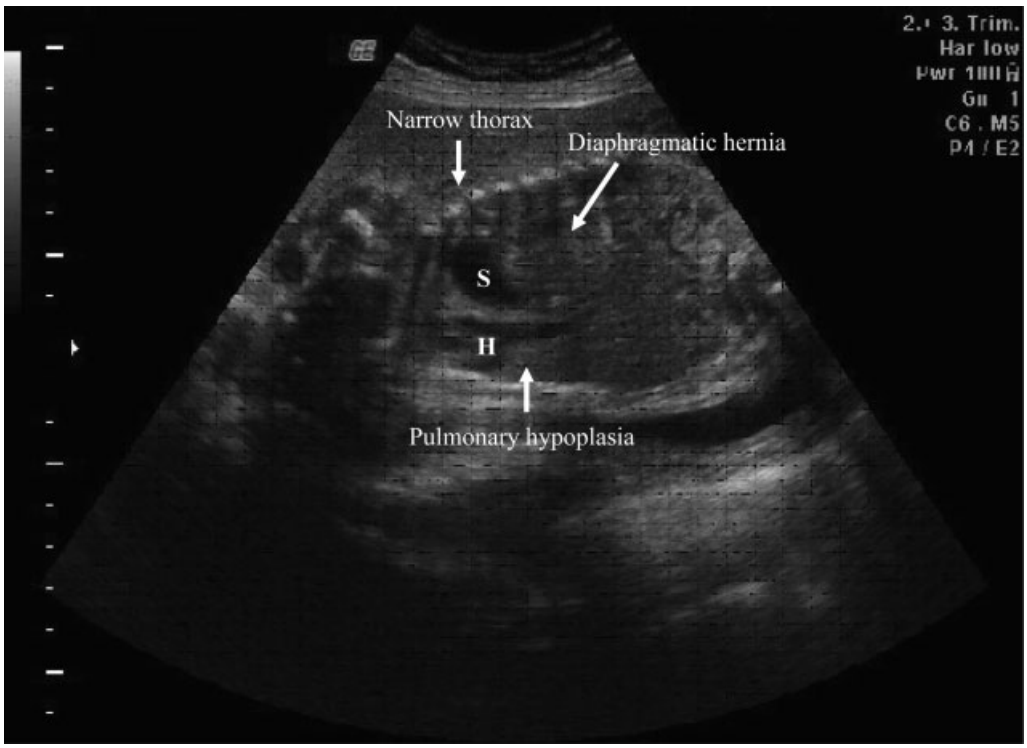

FIGURE 1. Sonogram shows a left-sided diaphragmatic hernia with a narrow thorax and bilateral pulmonary hypoplasia. S, stomach; H, heart.

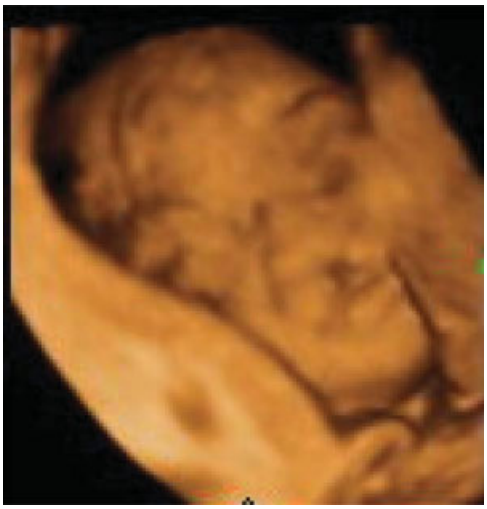

FIGURE 2. Three-dimensional sonogram of the fetal face shows median cleft lip and palate.

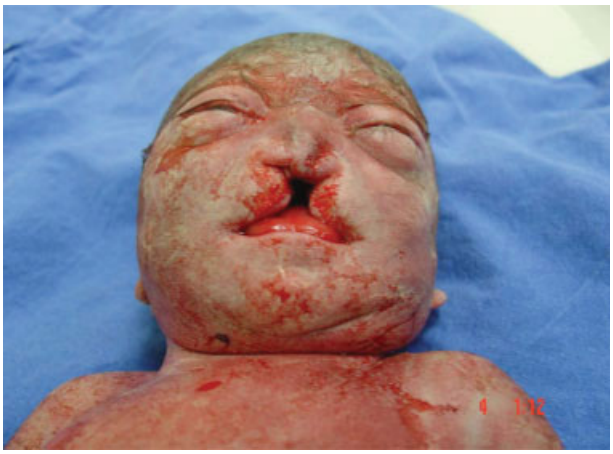

FIGURE 3. Postmortem photograph of the fetus shows face anomalies including median cleft lip and palate.

lished. Generally, one third of these fetuses die in utero, and another one third die in the early neonatal period. Van Hove et al[8] reported that 36.5% of fetuses died before 36 weeks' gestation, and 32.2% were born alive after 36 weeks but died within the first days of life. Both physical and mental developments were reported to be poor in isolated series. A male FS with an IQ of 76 at 24 months of age and a 33-month-old male functioning at a 7-month-old level have been reported previously.[9] The oldest reported patient with FS died in status epilepticus at 15 years age.[10]

Several chromosomal abnormalities show similar manifestations to FS. For this reason, a diagnosis of FS can be made only if the karyotype is tested to be normal. In addition, a congenital diaphragmatic hernia can occur in many different syndromes. The differential diagnosis includes Pallister-Killian syndrome (PKS), trisomy 22, and Cornelia de Lange syndrome. Trisomy 22 can be excluded by karyotype in case of multiple anomalies detected on sonography.[11] Diaphragmatic

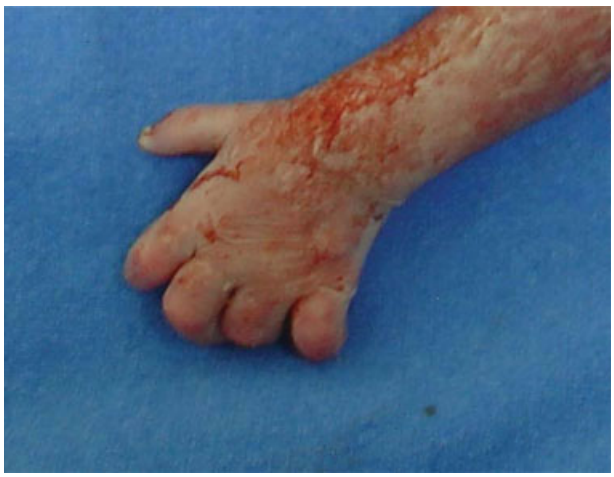

FIGURE 4. Postmortem photograph of the fetus' hand shows thumbnail hypoplasia.

hernia, congenital heart disease, rhizomelic limb shortening, and facial anomalies represent the sonographically detectable anomalies in PKS.[12] A small nose and thin upper lip, which can be considered as constant indicators of PKS, are usually not associated with FS. Whereas the most common dysmorphic facial features in FS are micrognathia and cleft lip/palate, neither of these anomalies are associated with PKS. In rare cases of PKS, only micrognathia can be found occasionally. On the contrary, hypertelorism is rare in FS but is seen frequently in PKS.[3] The final differential diagnosis between the 2 syndromes depends on the demonstration of the 12p isochromosome in fibroblasts by fluorescence in situ hybridization in PKS. For this purpose, both an amniocentesis and a cordocentesis were performed in our case in order to have two fetal tissue tests for the elimination of chromosomal aberrations.

Cornelia de Lange syndrome is another important condition that can present with diaphragmatic hernia.[13] Whereas FS is a prenatal overgrowth syndrome, Cornelia de Lange is characterized by intrauterine growth restriction, distinctive facial features, and variable upper limb malformations. FS is an autosomal recessive disorder with a 25% theoretical risk of recurrence in subsequent pregnancies. For this reason, once the diagnosis of FS is made, genetic counseling should be given to the family if they are contemplating future pregnancies. There is a low risk of recurrence (1%) for trisomy 22, and early prenatal diagnosis is possible.[11] For PKS, there is no risk of recurrence.[14] Cornelia de Lange syndrome is an autosomal dominant genetic disorder; most of the cases are sporadic, and the risk of recurrence is negligible ($<1\%$).[15]

FS is a malformation syndrome characterized by a distinct phenotypic variability. Although congenital diaphragmatic hernia and distal limb hypoplasia are strong indicators of FS, other relevant findings include orofacial clefting, craniofacial dysmorphism, pulmonary hypoplasia, and polyhydramnios. Early genetic counseling should be made to distinguish FS from PKS and Cornelia de Lange syndrome.

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