

Antenatal sonographic diagnosis of fryns syndrome: A case report

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Abstract

Fryns et al described a syndrome in the year 1979.¹ Fryns syndrome is characterized by diaphragmatic defects, facial dysmorphism including coarse face, hypertelorism, broad and flat nasal bridge, with thick nasal tip, long philtrum, tented upper lip, wide mouth, micrognathia, low set and poorly formed ears and distal digital hypoplasia, pulmonary hypoplasia and others.² We report a case of fryns syndrome in twenty- nine years old, Chinese, primigravida diagnosed during antenatal ultrasound scan at 26 weeks of gestation. The diagnosis has been confirmed by clinical finding, ultrasound, X-ray chest, CT brain, and ECHO at the postnatal period.

Keywords: Fryns syndrome, Diaphragmatic hernia, Microphthalmia, Lung hypoplasia polyhydramnios.

Introduction

Fryns syndrome is a rare syndrome characterized by a congenital diaphragmatic hernia, facial dysmorphism including coarse face, hypertelorism, broad and flat nasal bridge, with thick nasal tip, long philtrum, tented upper lip, wide mouth, micrognathia, low set and distal digital hypoplasia, pulmonary hypoplasia and others.² The incidence of fryns syndrome is 1/ 12,000 births with an approximate male: female ratio of 1.25:1.³ The incidence of congenital anomalies is 1 in 838 live births in Malaysia.⁴ Fryns syndrome is a rare autosomal recessive disorder with an estimated prevalence of about 0.7 per 10,000 births in France (Ayme et al 1989).⁵ Ayme et al (1989) reported prenatal diagnosis of fryns syndrome by an ultrasound scan, between 24 and 27 weeks of gestation. Manouvrier-Hanu et al. (1996)⁶ detected diaphragmatic hernias and polyhydramnios in the prenatal ultrasound scan of a case of fryns syndrome. We report a case of the fryns syndrome of nonconsanguineous parents with a normal second child.

Case Report

A twenty-nine years old Chinese, primigravida attended the health clinic for antenatal booking at 8⁺⁶ weeks of gestation. Her past menstrual cycle was regular 3-4/38 days. The first ultrasound scan revealed a singleton, live intrauterine fetus of 6⁺⁵ weeks of gestation and expected date of delivery assigned to 09/01/14.

Her marriage was non-consanguineous. Her serological screening for HIV, Australia antigen and syphilis were nonreactive. Her father was diabetic on treatment. There was no family history of congenital anomalies. The patient was referred to us at 23 weeks of gestation for excess weight gain and the uterine height (26cm) was more than a period of gestation. An Antenatal scan revealed fetal biometric data consistent

with a 22 weeks and 2 days singleton gestation. The amount of amniotic fluid was normal. A level one biometry scan was performed. The biparietal diameter, the femur length above the 50th percentile and the abdominal circumference were at the 5th percentile with the fetus small for gestational age. The pregnancy was complicated by gestational diabetes at 23⁺² weeks of gestation. She was on diet control. Her HbA_{1c} was 5.6% and blood sugar profile optimal.

A referral was made to the fetal medicine specialist. A follow-up ultrasound scan was done at 26 weeks of gestation. Multiple fetal anomalies were noted in the fetus. They were a left-sided diaphragmatic hernia, the right hemidiaphragm intact, the right lung normal, the left lung hypoplasia, the stomach was in the thorax (Fig. 1), the liver down in the abdomen, the right eye microphthalmia, unilateral ventriculomegaly, absent cavum septum pellucidum (Fig. 2). The couple was counseled about the prognosis.

A follow-up ultrasound scan was obtained at 30 weeks of gestation for the uterine height was more (34cm) than a period of gestation. There was early onset of polyhydramnios. The amniotic fluid volume was more (AFI 24 cm.). The AC was below the 50th percentile. Fetal growth assessed with biometrics was now consistent with 29+3 weeks of gestation. The placenta was posterior not previa. An umbilical cord showed three vessels.

At 34⁺⁶ week of gestation ultrasound scan revealed the BPD above the 95th percentile, the AC below 50th percentile and the FL at 95TH percentile, unilateral ventriculomegaly, absent cavum septum pellucidum, a left diaphragmatic hernia, the stomach in the thorax, microphthalmia of the right eye, the left lung hypoplasia and the liver in the abdomen.

The patient was under the care of the multidisciplinary team, maternal-fetal medicine consultant, a pediatric surgeon and an obstetrician.

Induction of labor was planned at 38 weeks gestation. She delivered a baby boy on 26/12/2013 at 1.27 pm.

The baby boy was born with Apgar score 9. The baby was intubated immediately after birth. The baby was pink, pulse volume good, Spo₂ 90%, heart rate 124 per minute, blood pressure 60/32 mm of Hg, respiratory rate 60/ minute, capillary refill time <2 seconds. There was no murmur on auscultation of the chest, the heart sound muffled, reduced air entry on the left side and the bowel sounds heard over the left lung. The birth weight was 2.85 kg, the length 47 cm, the head circumference 33.5 cm. On examination, the baby was noted to have multiple dysmorphic features, an anophthalmia of the right eye, the left eye normal, broad nasal bridge, the ears well formed, no cleft lip or palate, the spine normal, scaphoid abdomen, the umbilical cord showed two arteries and one vein, syndactyly of 3rd and 4th fingers of right hand (Fig. 2), syndactyly of first and second toes of the left foot, polydactyly of left foot (6th toe), absent skin crease of the left foot, epispadias and bilateral undescended testis consistent with fryns syndrome.

The baby was transferred to the neonatal intensive care unit for further management. The blood gas analysis report was, pH 7.3, pco₂ 43, Hco₃ 70, BE 5.4. On admission, to the neonatal intensive care unit, urgent bedside X-ray chest, ECHO and USG cranium was done. X-ray chest revealed the left lung hypoplasia, the bowel shadow seen in the left lung, the rib cage abnormally formed, and the heart outline indistinct and shifted to the right and the right hemi diaphragm intact. Diagnosis of the left congenital diaphragmatic hernia was confirmed. Bedside ECHO revealed situs solitus, AV/VA concordance, balanced chambers, IAS/ IVS intact, arch of aorta normal, no pulmonary stenosis and very small patent ductus arteriosus. (Fig. 3) USG cranium revealed left ventriculomegaly, partial agenesis of corpus callosum and periventricular cyst. (Fig. 4) The kidneys were normal on a scan. CT brain revealed the agenesis of corpus callosum, congenital small and atrophic right eye globe (anophthalmia), Dandy-Walker variant. There was communication of cistern magna with 4th ventricle suggesting absent cerebellar vermis.

On Ophthalmologist review of the baby, he had right eye anophthalmos and the left eye was normal, the conjunctiva pink, the cornea clear, the pupil round, 2 mm and the anterior chamber formed.

The parents were counseled about diagnosis and poor prognosis regarding brain malformation, ophthalmic anomaly and lung anomaly. The parents opted for conservative management instead of the surgical treatment of a diaphragmatic hernia, in view of neurological deficit due to congenital brain malformations. They opted for withdrawal of life support. The baby died on 3/1/2014 at 4 pm. The baby lived for 8 days. The parents declined for an autopsy. Her postpartum course was unremarkable and was discharged home on a postpartum day 2.

Her second pregnancy was complicated by gestational diabetes and delivered a baby boy on 3/12/2014. The baby boy had no congenital abnormality and he is healthy until today.



Fig. 1: USG scan at 26 weeks show stomach in the thorax



Fig. 2: USG scan at 31 weeks shows right microphthalmia, absent cavum septum pellucidum and syndactyly 3rd and 4th fingers of right hand



Fig. 3: ECHO show situs solitus, AV/VA concordance, balanced chamber, IAS/IVS intact, arch of aorta normal and very small PDA +



Fig. 4: USG cranium show agenesis of corpus callosum, dandy-walker variant and lateral ventriculomegaly

Discussion

Currently, an ultrasound scan is an important noninvasive diagnostic modality for the prenatal screening of fetuses with congenital anomalies. Fryns syndrome has been diagnosed by two and three-dimensional ultrasonography and fetal magnetic resonance imaging (MRI) (Benacerraf et al 2006).⁷

This case had multiple congenital anomalies detected in the ultrasound scan at 26 weeks of gestation as mentioned earlier. Ayme et al (1989)⁵ reported prenatal diagnosis of fryns syndrome by an ultrasound scan, between 24 and 27 weeks of gestation. Fryn syndrome was diagnosed in the prenatal ultrasound scan by detection of diaphragmatic hernias and polyhydramnios by Manouvrier-Hanu et al. (1996).⁶ Fryns syndrome was diagnosed prenatally as early as 16 weeks by Jeanne S. Sheffield et al.⁸

Peron et al (2014)⁹ had reported polyhydramnios in the second trimester in 56% of cases and a diaphragmatic hernia in more than 80% of the babies with fryns syndrome. Our case had a diaphragmatic hernia one of the key features in the prenatal diagnosis of fryns syndrome. This is due to posterolateral defects in the diaphragm.^{1,10}

In the present case, the fryns syndrome was confirmed postnatally by clinical features, CT scan of the brain, ultrasound cranium, and abdomen, ECHO, and X-ray chest on day one of the life. The CT brain and ultrasound of cranium of the baby revealed congenital anomalies as mentioned earlier.

The baby had an anophthalmos of the right eye. CT brain done on day one of life revealed congenital small and atrophic right eye globe. The left eye was normal. The abnormal eye findings had been identified in 12 out of 77 patients with fryns syndrome by Pierson et al (2004)¹¹ They also described unilateral microphthalmia and cloudy cornea in one case. Cursiefen et al (2000)¹² reported central/ paracentral corneal clouding that may result from abnormal corneal endothelium, microphthalmia, irregularities of Bowman's layer, thickened posterior lens capsule, and retinal dysplasia.

Slavotinek (2004)² reevaluated the diagnostic guideline of the fryns syndrome. Along with congenital diaphragmatic hernia, distal limb hypoplasia, polyhydramnios and pulmonary hypoplasia, they also

included ventricular dilatation or hydrocephalus, agenesis of the corpus callosum, abnormalities of the aorta, dilatation of the ureters, proximal thumbs and broad clavicles. There are six diagnostic criteria of the fryns syndrome proposed by Lin et al (2005)² based on clinical features. These are diaphragmatic defect, characteristic facial appearance, distal digital hypoplasia, pulmonary hypoplasia, characteristically associated anomalies like polyhydramnios, brain malformations, renal dysplasia, gastrointestinal system malformation and genital malformations and parental consanguinity.

At least three findings should be present for the diagnosis of fryns syndrome. This case fulfilled five criteria out of six. The ears, the kidneys, the heart, the lip and the palate were normal in this case. Angela Peron et al (2015)⁹ reported five of five cases of fryns syndrome with no orofacial clefting. Slavotinek (2004)² has reported the presence of cleft palate in 50% and cleft lip in 25% of cases of fryns syndrome. There was no history of parental consanguinity in our case.

The parents of an affected child are heterozygotes and each carries one mutated allele. Heterozygote's (carriers) are asymptomatic. There is 25% chance of being neither affected nor a carrier. Each sibling of an affected individual has a 25% chance of being affected and 50% chance of being an asymptomatic carrier. Prenatal molecular genetic testing is not possible because the gene(s) in which pathogenic variants occur have not been identified. The second child is normal and healthy in the present case.

Differential Diagnosis: Trisomy 18 also present with a diaphragmatic hernia, cardiac and cranial anomalies, and polyhydramnios. However, the fetuses with this syndrome often are growth restricted, unlike the fetuses with fryns syndrome and diagnosed by karyotyping. In case of Pallister-Killian syndrome (mosaic tetrasomy 12 p) the fetus has similar facial features to those of fryns syndrome, diaphragmatic hernia, distal digital hypoplasia and cardiac anomalies and diagnosed by chromosome microarray analysis.

In case of Mathew- Wood syndrome, there is severe pulmonary and ocular malformation. However, there is an absence of digital defects as seen in fryns Syndrome. It is an autosomal recessive disorder.

Pathogenic variants in STRA6 have been described in patients with Mathew – Wood syndrome (Pasutto et al 2007).¹⁴ Molecular genetic testing for STRA6 confirms a diagnosis of Mathew –Wood syndrome.

Management: In this case in view of neurological deficit due to congenital brain malformations, the parents opted for conservative management instead of the surgical treatment of a diaphragmatic hernia. The medical therapy is used to stabilize the infant prior to surgical repair. ECMO has achieved recent popularity in the treatment of CDH (Fallon et al 2013).¹⁵

In severe cases of CDH, FETO is used as a prenatal interventional strategy with an increase in survival. (Cundy et al 2014).¹⁶ This technique has been most frequently used for isolated CDH.

Prognosis: Majority of babies born with Fryns syndrome usually die soon after birth, however, Van Hove et al (1995) reported survival up to 3 years of age in a boy with Fryns syndrome.¹⁷

Conclusion

We report a case of Fryns syndrome of nonconsanguineous parents with a normal second child. Fryns syndrome has a high rate of stillbirth and early neonatal mortality. Ultrasound scan done in early weeks of pregnancy is a useful prenatal diagnostic tool for identifying this lethal syndrome. In view of 25% risk of recurrence in next pregnancy, we recommend early prenatal screening and counseling of the parents.

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