CASE REPORT

FRASER SYNDROME – A DILEMMA TO PARENTS

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ABSTRACT

In this case report the patient belongs to rural Sindh, with poor prenatal care. She came with her third pregnancy to Ziauddin Hospital referred from interior of Sindh, with the history of previous two premature deliveries due to oligohydramnios.

Fraser syndrome is a rare congenital condition that includes multi-organ abnormalities and usually has a poor prognosis. The most obvious deformities noted are cryptophthalmos, syndactyly, laryngeal stenosis, and bilateral renal agenesis, displacement of umbilicus, undescended testes and clitoromegaly. The transmission of the syndrome is autosomal recessive and is caused by a mutation in the FRAS1, FREM2 or GRIP1 genes. The pathology, however, is unclear, but the mutations are known to alter programmed cell death, causing defects in the metabolism of retinoid.

The details of the case are the patient was of a 20-year-old female presented in her 3rd pregnancy at 34 weeks of gestational amenorrhea which was complicated with severe oligohydramnios. She delivered an underweight baby via cesarean section who had a poor cry and bradycardia at the time of birth. His structural defects included bilateral syndactly, laryngeal stenosis and undescended testes. The patient also had a history of two cesarean sections. Her first child was born with limb defects and anophthalmia and died immediately after birth. Her second child was terminated due to severely reduced amniotic fluid. Patients with a previous history should have genetic counseling beforehand and prenatal ultrasound based diagnosis.

KEYWORDS: Fraser Syndrome, Cryptophthalmos, Syndactyly

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INTRODUCTION

Fraser syndrome is a clinical condition that affects multiple organs. The fetus or newborn has a very poor survival rate. The major malformation includes an eye defect called cryptophthalmos, which is present in 93% of cases. Syndactyly is present in 54% of cases. Other defects include urinary anomalies, laryngeal stenosis or displacement, along with skeletal deformities [1]. The main causes of death are laryngeal atresia and renal agenesis.

The incidence is 0.043 per 10,000 live-born infants and 1.1 in 10,000 stillbirths, making it a rare syndrome [2]. About 15% of cases were born to consanguineous partners, which is a sign that this is an Autosomal recessive condition. At least five mutations were identified in the FRAS1 gene, which encodes a putative extracellular matrix protein [3]. As an autosomal recessive disorder, this condition should only occur when defective genes are inherited from both parents.

CASE REPORT

Our patient was a 20-year-old female, married for four years to her first cousin. Both parents were healthy with no family history of any known abnormalities. She was in her third pregnancy, para 1+1, referred from rural area with 34 weeks of gestational amenorrhea, along with severe oligohydramnios. In her previous pregnancies also, she sought antena-

tal care from a local rural hospital. In first pregnancy, there was oligohydramnios delivered at 30 weeks of gestation, the hospital report indicates limb defects and anophthalmia, child died immediately after birth. In second pregnancy, the parents opted for a termination at 20 weeks due to inadequate amniotic fluid. In the recent pregnancy, they received regular antenatal care at local Hospital, but due to oligohydramnios, she was referred to a tertiary-care hospital. Here at Ziauddin Hospital ultrasound was requested which revealed; a single live fetus corresponding to gestational age of 32±2 weeks breech presentation with an amniotic fluid index (AFI) of 2.3 cm. Umbilical artery Doppler showed normal indices. Previous prenatal ultrasound could not be documented due to unavailability.. In view of her gynecological history a cesarean section was planned. The neonate was a limp male, who did not cry, had no spontaneous breathing and was bradycardic. He was aggressively resuscitated and intubation was attempted, which was unsuccessful due to severe laryngeal stenosis. Ventilator support was provided with the assistance of a neonatal laryngeal mask.

Gross examination revealed a male baby weighing 1.5 kg. Craniofacial examination revealed left cryptophthalmos with an eye ball palpable beneath. His right eye had a narrow palpebral fissure and normal eyeball but a deformed pinna. Besides these findings, he had bilateral syndactyly, laryngeal stenosis, multiple skeletal defects and undescended testes. Thus, the diagnosis of Fraser syndrome was made. Conventional karyo typing done of both parents, and did not show any chromosomal abnormalities.

DISCUSSION

Fraser syndrome was previously known as cryptophthalmos syndrome. Later, it was revised and noted that cryptophthalmos may not be a compulsory feature. It can be caused by a homozygous or compound heterozygous mutation in the FRAS1 gene (607830) on chromosome 4q21, the FREM2 gene (608945) on chromosome 13q13, or the GRIP1 gene (604597) on chromosome 12q14. Therefore, Fraser syndrome is an optimal term. It is a rare autosomal recessive disorder with variable expressivity [4]. In 1986, Thomas et al established major and minor criteria to diagnose Fraser syndrome. It was modified by Van Haelstetal.[5] in 2007 as; Major criteria were Syndactyly, Cryptophthalmos spectrum, Urinary tract abnormalities, Ambiguous genitalia, Laryngeal and tracheal anomalies, Positive family history. The minor criteria were Anorectal defects, Dysplastic ears, Skull ossification defects, Umbilical abnormalities, Nasal anomalies.

Diagnosis of Fraser syndrome is based on either 3 major criteria, 2 major and 2 minor criteria, or 1 major and 3 minor criteria.

According to the revised Fraser syndrome criteria, our findings in this case, and based on previous pregnancy outcomes our patient fulfills the criteria of Fraser syndrome.

There is no difference in incidence of Fraser syndrome in female and male children. Some racial predisposition has been observed, as it seems to be more common in gypsy families as well as in families with history of the same malformation [6]. The exact etiology is unknown, and it is believed that most of the anomalies are due to defects in programmed cell death and apoptosis as well as in metabolism of retinoid [7]. The manifestation of autosomal recessive disorders occurs when the affected child receives the abnormal genes for the same trait from both parents. If the individual receives one normal and one defective gene, the neonate will only be a carrier and will not show any symptoms. Therefore, the risk of a diseased child is 25% when both parents carry defective genes, 50% of their offspring will be carriers, and 25% will have normal genes. Hence, in consanguineous marriages, there is more risk of the same defective genes and the subsequent transfer to their children.

In our case, the patient has suffered from the same disorder thrice. The literature reviews suggest that consanguinity is in 15–24% of cases and the recurrence rate among siblings is 25% [8].

Fraser syndrome can be diagnosed by ultrasound during pregnancy, which may show hyper echoic lungs, oligohydramnios and microphthalmia. It can also be detected based on the previous pregnancy losses owing to still birth, oligohydramnios, and renal agenesis. In our case, the patient received suboptimal antenatal care and had no ultrasound report showing any abnormality. Also, her previous history of fetal loss was not considered as a high risk for any genetic disorder. Each time she underwent a cesarean section and hysterectomy, it affected her potential chances of conceiving. When the patient was received, her ultrasound scans identified an AFI of about 2 cm, because of which it was not possible to identify any anomaly. With the intention to save the fetus, a delivery was planned immediately; the born child had multiple anomalies including syndactyly, cryptophthalmos and laryngeal atresia. Even after resuscitation efforts, it was not possible to save the child. A subsequent diagnosis of Fraser syndrome was made. It is imperative that the mother receives adequate antenatal care, including an ultrasound scan in early pregnancy [9]. Other symptoms like syndactyly, ear and facial abnormalities can also be found on an ultrasound. Therefore, in the case of oligohydramnios, fluid instillation in amniotic cavity can be considered to improve the visualization of the kidney, face, ears, and limbs [10].

In conclusion, Fraser syndrome is a lethal genetic disorder with a poor prognosis. Currently, there are

no specific methods to prevent this condition, but genetic testing may help to identify families at risk.

Couple, who have diagnosis of Fraser syndrome at first pregnancy, should have genetic counseling. Mother with Fraser syndrome neonatal history should be kept on critical prenatal ultrasound checking that may be helpful for diagnosis during early pregnancy. Further research should be conducted to help provide treatment to such parents.

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Figure 1 & 2: show multiple gross malformations. Including anopthalmia, dysmorphic face and limb defects. (Parents of the newborn had given written consent to take the pictures shown above)

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