

A case of Fraser Syndrome Diagnosed by Ultrasound as a Single Modality; Necessity of Genetic Confirmation?

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ABSTRACT

Fraser syndrome is a rare genetic disorder characterized by multiple structural abnormalities, above all of which are cryptophthalmos and syndactyly. According to reviews of reported cases, diagnostic criteria have been established. Here, we report a case of 18 weeks pregnancy diagnosed with Fraser syndrome presenting with cryptophthalmos, syndactyly, kidney agenesis, and hyper-echogenic lungs during an ultrasound examination. The pregnancy was terminated, and diagnostic features of the syndrome were confirmed afterward. Since the imaging characteristics are unique, it is of value that clinicians become familiar with the appearance of the syndrome to provide families with the opportunity to make timely decisions regarding pregnancy termination and use the prenatal diagnostic tools to have healthy children in subsequent pregnancies.

Keywords: cryptophthalmos, Fraser syndrome, syndactyly, ultrasound



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Introduction

Fraser syndrome is a rare genetic disorder, inherited as an autosomal recessive condition, mainly characterized by cryptophthalmos and syndactyly known as major diagnostic criteria (1, 2). For years, most cases were diagnosed postmortem and confirmed by detailed autopsy of the stillborn fetuses (3, 4). Mutations in FRAS1 and FREM2, which fail programmed cell necrosis or defects in epidermal cell adhesion, are the earliest genetic basis understood for the pathogenesis of the disease (5). There are more than 250 cases of Fraser syndrome- cryptophthalmos in the literature, and a few studies reviewing clinical and diagnostic features of this well-known multiple malformation syndrome so that they would represent diagnostic criteria. In 1986, Thomas *et al.* described the diagnostic criteria as cryptophthalmos, syndactyly, abnormal genitalia, and affected sibling as major criteria and malformations of ear, nose, and larynx;

cleft lip/palate; skeletal symptoms; umbilical hernia; renal agenesis and mental retardation as minor criteria, considering the diagnosis confirmed by presenting two major and one minor criterion or one major and four minor ones (6). According to the largest series of newly diagnosed cases, Van Haelst *et al.* (7). Concluded that the major criteria used before should be retained; however, urinary tract and airway anomalies are frequent enough to promote them as major criteria, and they offered a new diagnostic criterion (Table 1).

Since oligohydramnios is a common finding in sonographic evaluation of these fetuses, mainly due to renal agenesis or other abnormalities such as placental insufficiency, prenatal diagnosis of Fraser syndrome during sonographic evaluations is considered difficult and requires superior skills (8, 9).

Table 1. Accepted criteria for diagnosis of Fraser syndrome according to Thomas *et al.* (6) and Van Heelst *et al.* (7) in the review of 124 and 59 cases, respectively.

Thomas criteria		Van Heelst criteria		Our case
Major	minor	major	Minor	Sonographic features
Cryptophthalmos Syndactyly Abnormal genitalia Sib with cryptophthalmos syndrome	Congenital malformation of nose	Syndactyly	Anorectal defects	Unilateral cryptophthalmos Syndactyly Unilateral renal agenesis Congenital malformation of larynx antenatal confirmation of diagnosis according to both criteria
	Congenital malformation of ears	Cryptophthalmos spectrum	Dysplastic ears	
	Congenital malformation of larynx	Urinary tract abnormalities	Skull ossification defects	
	Cleft lip and/or palate	Ambiguous genitalia	Umbilical abnormalities	
	Skeletal defects	Laryngeal and tracheal anomalies	Umbilical hernia, omphalocele, low-set umbilicus)	
	Umbilical hernia	Positive family history	Nasal anomalies	
	Renal agenesis			
	Mental retardation			
Diagnosis confirmed: 2major+1minor or 1major+4minor		Diagnosis confirmed: 3major or 2major+2minor or 1major+3minor		

Here we present a case of 18 weeks gestation fetus diagnosed with cryptophthalmos, syndactyly, high airway obstruction (CHAOS), and renal agenesis during routine sonographic screening for anomalies, whose diagnosis was confirmed after the termination of pregnancy with clinical features of Fraser syndrome according to the diagnostic criteria described above.

Case Presentation

A 26-year-old primigravida at 18^{3/7} weeks gestation, with an ultrasound report indicative of a single umbilical artery, was referred to our hospital for detailed anomaly screening. During ultrasound study, we confirmed the single umbilical cord artery and discovered renal agenesis (found as a lying down the adrenal sign), severe oligohydramnios, bilateral syndactyly, and unilateral microphthalmos along with hyper-echogenic lungs as a result of congenital high airway obstruction syndrome (CHAOS) (Figure 1a-e).

Because of the consanguineous marriage and the typical ultrasound features, the Fraser syndrome was

our top differential diagnosis. Due to the poor prognosis of the pregnancy, detailed consultation with the parents took place, and the pregnancy was terminated as they wished. Abortion was induced using synthetic prostaglandin E1 analogue. Following abortion, the fetus was dead, weighing 160 grams, and underwent complete examination for signs of Fraser syndrome, which revealed bilateral cutaneous syndactyly of the four limbs, unilateral cryptophthalmos, and low-set umbilicus containing a single umbilical artery (Figure 1f-h).

Because of the high expenses of the genetic study, the family could not afford the test at that time; however, we advised the parents to be screened for genetic diseases. The mother's whole Exome Sequencing (WES) revealed heterozygous mutations in the FRAS1 gene and some other genes, including NBAS, MYL3, PKD1L1, and NUP160, each one responsible for some kind of autosomal recessive diseases, so her husband was recommended to undergo WES. Screening of hypertrophic cardiomyopathy was recommended due to MYL3 mutation.

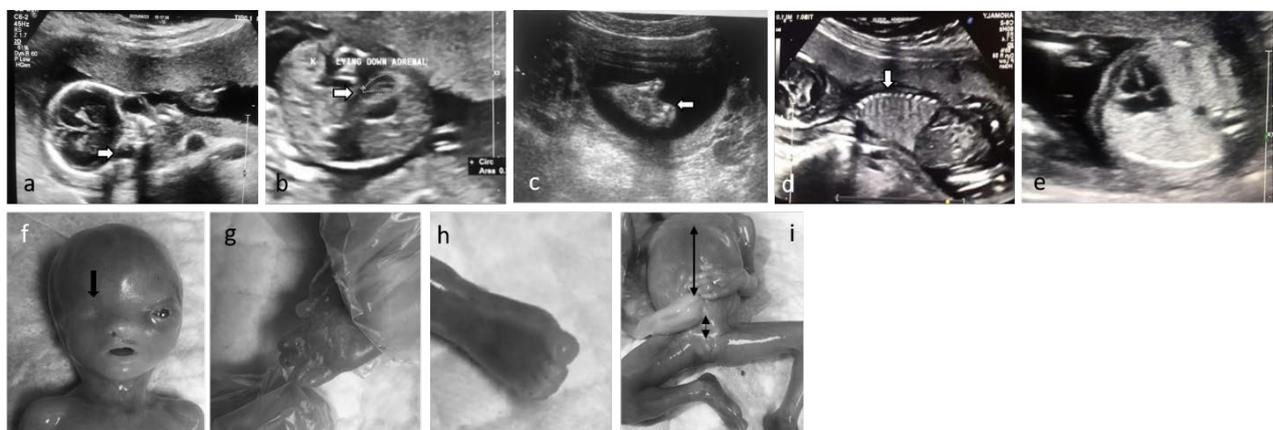


Figure 1. a. microphthalmos (arrow) b. renal agenesis (lying down the adrenal sign) (arrow) c. syndactyly (arrow) d. oligohydramnios, echogenic lung, and high airway obstruction (sagittal view) (arrow). E. echogenic lung (axial view) f. cryptophthalmos (arrow) g. syndactyly (hand). h. syndactyly (foot) I. low-set umbilicus (described as lower than 60% of the way from the inferior border of the xiphoid of the sternum to the superior border of the symphysis pubis).

Discussion

Fraser syndrome is a rare genetic disorder with a poor prognosis, inherited recessively. Based on the review studies, there is a well-defined criteria to confirm the diagnosis, many of which could be diagnosed prenatally during the ultrasound screening (7, 10). Few studies have used genetic mapping and mutation analysis to identify the genetic basis of the disease, and a heterogeneous group of mutations in FRAS1, FREM2, and GRIP1 all of them encoding essential extracellular matrix proteins, has been found to cause Fraser syndrome clinical features (11, 12). Because of the numerous known and unknown genetic mutations and considering the costs of such analyses, it may not always be feasible to detect the defective genes in the first place. However, clinical features present in a wide spectrum, and craniofacial and cryptophthalmos are the most common (13). Accordingly, familiarity with the syndrome's diagnostic features and keeping the criteria in mind could lead to timely diagnosis of this syndrome, providing the families the opportunity to decide whether to terminate the pregnancy or to continue one (14). Should the diagnosis be confirmed with the definite ultrasound criteria, like the one in our case, a genetic study of the fetus may provide us no further information, while genetic evaluation of the parents, especially in consanguine cases, could benefit the parents to take advantage of pre-gestational diagnosis for the future pregnancies. Additionally, genetic evaluation of the parents could determine some other mutations, like the one in our case, leading to recommendations regarding their own health issues. Since there have been reports of confirmed cases of Fraser syndrome with an autopsy after the prenatal

diagnosis (15), We propose that in the cases that all the diagnostic criteria confirm the diagnosis of Fraser syndrome, Whole Exome Sequencing of the consanguine parents be considered. However, large studies are required to make recommendations about the issue.

Conclusion

Since Fraser syndrome is a rare genetic disease of multiple fetal abnormalities and according to our case and several other studies, it would be well diagnosed with ultrasound diagnostic criteria, it is important for physicians who perform anomaly screening ultrasound to be familiar with the criteria to help in timely diagnosis and management. Under such circumstances, genetic studies to confirm the diagnosis could be omitted, while parental whole exome sequencing might reveal precious information regarding their health care and for future pregnancies as well.

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Conflict of Interest

The authors declared no conflict of interest.

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