

Prenatal detection of Fraser syndrome without cryptophthalmos: case report and review of the literature

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KEYWORDS: Cryptophthalmos–syndactyly syndrome, Fraser syndrome, Hydrops fetalis, Laryngeal atresia, Prenatal diagnosis, Renal agenesis, Ultrasound

ABSTRACT

Fraser syndrome (cryptophthalmos–syndactyly syndrome) is an autosomal recessive multiple malformation syndrome whose major manifestations are cryptophthalmos, syndactyly, laryngeal atresia and urogenital defects. Enlarged hyperechogenic lungs contrasted by oligohydramnios, non-visualization of the kidneys and microphthalmia were sonographic markers leading to the prenatal detection of this rare autosomal recessive disorder in earlier reports. We report a case of Fraser syndrome diagnosed at 16 weeks' gestational age in a woman whose previous pregnancy was terminated because of multiple fetal malformations. Abnormal sonographic findings included bilateral agenesis of the kidneys, dilated trachea and main bronchi (suggestive of high airway obstruction), hyperechogenic lungs, syndactyly of the fingers, hepatomegaly, oligohydramnios and hydrops placentae. Face and cerebral structures appeared normal. These findings together with those of the previously affected child led to the diagnosis of Fraser syndrome. The parents elected to terminate the pregnancy. Autopsy results were confirmatory. In conclusion, prenatal diagnosis of Fraser syndrome is possible in the hands of an expert, but due to the great variety of possible malformations the diagnosis will remain doubtful in most cases in which no previous child is affected.

INTRODUCTION

Fraser syndrome (cryptophthalmos–syndactyly syndrome) is a rare autosomal recessive multiple malformation syndrome characterized by variable expression of cryptophthalmos, syndactyly, abnormal genitalia, malformations of the nose, ear and larynx, renal agenesis, clefting, skeletal defects, umbilical hernia, and mental retardation in survivors¹. Other anomalies associated with Fraser syndrome are heart defects, major

vascular anomalies, imperforate anus, intestinal hypoplasia, thymic aplasia, and cerebral malformations^{2,3}. Fraser syndrome has a recurrence risk of 25% among siblings, therefore prenatal diagnosis is an important task for the diagnostician counseling affected families⁴. Prenatal diagnosis of Fraser syndrome has been reported in seven cases^{1,4–10} but the sonographic findings were very inconstant rendering the definition of sonographic markers difficult.

We report a case of cryptophthalmos–syndactyly syndrome detected prenatally at 16 weeks of gestation, in which the most frequent anomalies, the facial defects, were missing. Previous reports on the prenatal diagnosis of this syndrome are reviewed for possible sonographic markers.

CASE REPORT

A 39-year-old woman, gravida 2, para 0, was referred from a local hospital because of an abnormal ultrasound examination at 16 weeks' gestation. The patient and her husband, who fathered both pregnancies, denied consanguinity. The family history was uneventful apart from radius and ulna aplasia in one of the grandmothers. A single prior pregnancy was terminated at 17 weeks' gestation because of multiple fetal malformations detected by ultrasound, including suspected cystic adenomatoid malformation of the lung type III (CCAML III) and renal agenesis leading to severe oligohydramnios. The aborted fetus showed extensive syndactyly of the fingers and toes and imperforate anus at macroscopic examination. Autopsy revealed bilateral renal agenesis as well as absence of ureters and bladder. The fetal lungs were normally lobulated and histologically patent. The combined lung weight was slightly elevated. CCAML III could not be confirmed. A sporadic malformation syndrome was suspected without further diagnosis.

The subsequent pregnancy was complicated by an episode of vaginal bleeding in the first trimester with retroplacental

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Received 1-8-00, Revised 14-11-00, Accepted 4-1-01

hematoma that resolved spontaneously. At 16 weeks' gestation ultrasound examination demonstrated severe oligohydramnios, hyperechogenic lungs and suspected renal dysplasia. The repeat scan in our institution showed severe oligohydramnios, hydrops placentae, and a fetus with ascites. Head and long bone biometry was consistent with that expected for gestational age. The lungs were enlarged and hyperechogenic with fluid bronchogram, prominent hila and downward displacement of the diaphragm (Figure 1). The trachea and bronchi were grossly distended and hypoechogenic, the trachea ending abruptly caudal of the carina (Figure 2). The heart was compressed and centrally located, but appeared structurally normal at real time scanning and color Doppler flow mapping. The abdomen was also distended as a result of coexisting ascites. Other abnormal findings included non-visualization of the kidneys, ureters and bladder, hepatomegaly and syndactyly of one hand. The other hand and the toes could not be visualized satisfactorily. Cerebral scan, profile and portrait with measurement of the interocular, biocular and ocular distances

showed no abnormalities. Blood flow velocity waveforms of the umbilical artery, middle cerebral artery and ductus venosus showed normal indices. These findings, in conjunction with the anomalies in the sibling, were considered diagnostic of Fraser syndrome. The parents elected to terminate the pregnancy at 18 weeks. Placentesis revealed a normal female karyotype (46,XX). Both parents had normal karyotypes. A stillborn fetus was aborted, whose external measurements and weight (190 g) were appropriate for the stated gestational age. Eyes, ears and nose showed no defects. The brain was not remarkable; however, maceration prevented further investigation. Marked soft-tissue syndactyly was present between fingers II, III and IV of the right hand and between fingers III and IV of the left hand and between toes II, III, IV and V on the left side and between toes II and III on the right side. The internal examination revealed markedly enlarged normally lobulated lungs (combined weight 23.3 g; expected 9.1–11 g¹¹) with impressions of the ribs. Examination of the laryngotracheal tube showed marked cross-sectional narrowing of the lumen compatible with atresia. Kidneys, urinary bladder and ureters were absent. An imperforate anus and ambiguous genitals were demonstrated.



Figure 1 Coronal scan of the fetal trunk at 16.0 weeks of gestation. Bilateral enlarged hyperechogenic lungs with fluid bronchogram and downward displacement of the diaphragm are demonstrated.



Figure 2 Coronal scan of fetal lungs, showing a grossly distended trachea, ending abruptly caudal of the carina.

DISCUSSION

Zehender in 1872 first described a complex malformation syndrome including bilateral cryptophthalmos, hypertelorism, syndactyly, abnormal genitalia, umbilical hernia, anal stenosis and hoarse voice¹². Similar cryptophthalmos syndromes were reported in several cases¹. In 1962 Fraser published a case of two siblings with cryptophthalmos, syndactyly, ear and nose defects, laryngeal stenosis, and renal and genital malformations¹³. Since then the term Fraser syndrome has been used for similar complex malformation syndromes, including cases without cryptophthalmos. Thomas *et al.* reviewed 124 cases of cryptophthalmos and associated syndromes and established minimal diagnostic criteria clearly separating Fraser syndrome from isolated cryptophthalmos¹. Cases are diagnosed on the basis of at least two major criteria and one minor criterion or one major criterion and at least four minor criteria (Table 1). In the case of a previously affected sibling, however, the diagnosis is made even without the above criteria being fulfilled.

Table 1 Diagnostic criteria for cryptophthalmos syndrome according to Thomas *et al.* 1986¹

<i>Major criteria</i>
Cryptophthalmos
Syndactyly
Abnormal genitalia
Sibling with Fraser syndrome
<i>Minor criteria</i>
Congenital malformation of the nose
Congenital malformation of the ears
Congenital malformation of the larynx
Cleft lip and/or palate
Skeletal defects
Umbilical hernia
Renal agenesis
Mental retardation

Table 2 Review of the prenatal sonographic findings in 17 fetuses with Fraser syndrome

	Gestational age	Lungs	Amniotic fluid	Abdomen	Kidneys	Head and face	Heart	Biometry	History	Diagnosis
Feldman 1985 ⁵	18 +	nm	nm	nm	nm	Microphthalmia, hydrocephalus	nm	nm	Consanguineous sib with FS	FS
Thomas 1986 ¹	20 +	nm	Oligohydramnios	Ascites	Bilateral renal agenesis	Hydrocephalus	Small	nm	Sib with FS	FS
Boyd 1988 ⁶	24 +	nm	nm	nm	Obstructive uropathy	nm	nm	nm	Uneventful	Obstructive uropathy
	36 +	nm	nm	nm	Hydronephrosis	Hydrocephalus	nm	nm	Uneventful	Hydronephrosis, hydrocephalus
Serville 1989 ¹⁵	18 +	nm	Oligohydramnios	nm	nm	nm	Normal	IUGR	Uneventful	Bladder enlargement, IUGR
Francannet 1990 ¹⁶	24 +	nm	Oligohydramnios	Ascites	Bilateral renal and urinary tract agenesis	Hydrops	nm	nm	Consanguineous sib with FS	Bilateral urinary tract agenesis
Woodhead 1990 ¹⁷	32 +	nm	nm	nm	nm	nm	nm	nm	Sib with hexadactyly	None
Ramsing 1990 ⁴	23 +	nm	Normal	nm	nm	Cleft lip/palate	nm	nm	Sib with FS	FS
	37 +	nm	Oligohydramnios	nm	Renal dysplasia	nm	nm	IUGR	Uneventful	Renal dysplasia, IUGR
Schauer 1990 ⁷	17 +	Bilateral hyperechoic	Oligohydramnios	Ascites	Bilateral renal agenesis	Microphthalmia, hydrocephalus	Compressed, bradycardia	nm	Sib with FS	FS
Labbe 1992 ⁸	24 +	Bilateral hyperechoic	Oligohydramnios	Ascites	Bilateral renal and urinary tract agenesis	nm	nm	nm	Consanguineous sib with FS	Agensis urinary apparatus
Stevens 1994 ⁹	17 +	Bilateral hyperechoic	Oligohydramnios	Ascites	Normal	Hydrops	Elstein's anomaly	nm	Sib with anencephaly	Multiple malformations
	16 +	Bilateral hyperechoic	Oligohydramnios	Ascites	Hydronephrosis, dilated bladder	Hydrops	nm	nm	Sib with FS	FS
Fryns 1997 ¹⁰	23 +	Bilateral hyperechoic	Oligohydramnios	Ascites	nm	nm	nm	nm	Sib with FS	FS
	18 +	Bilateral hyperechoic	Oligohydramnios	Ascites	Left absent, right multicystic kidney	Nuchal edema	nm	nm	Sib with FS	FS
Balci 1999 ²⁹	25 +	Bilateral hyperechoic	Oligohydramnios	Ascites	nm	nm	nm	nm	Consanguineous sib with FS	CCAML III
Present case	16 + 0	Bilateral hyperechoic	Oligohydramnios	Ascites	Bilateral renal and urinary tract agenesis	Normal	Compressed	Normal	Sib with multiple malformations	FS

nm, no special abnormality mentioned; IUGR, intrauterine growth restriction; sib, sibling; FS, Fraser syndrome; CCAML, cystic adenomatoid malformation of the lung.

Feldman *et al.* reported the first prenatal detection of Fraser syndrome in 1985. Their diagnosis was based on microphthalmia and hydrocephalus being present in a fetus at 18 weeks' gestation with a previously affected sibling⁵. In a review of the literature we found 16 cases of Fraser syndrome that underwent sonographic examination prior to delivery or termination of pregnancy. The sonographic findings are summarized in Table 2. In seven of these cases the prenatal diagnosis of Fraser syndrome was made; all of them were preceded by at least one affected sibling, prompting a detailed scan as in our own case. In the remainder, multiple malformations were diagnosed; however, the definitive diagnosis of Fraser syndrome was missed. This is probably due to the variability of expression of the possible malformations found in this entity.

According to our own review of the literature cryptophthalmos occurs in 88% of the cases. Prenatal diagnosis of cryptophthalmos might be possible by sonographic assessment of the fetal palpebral fissure slant¹⁴; however, in fetuses with Fraser syndrome this might often be impaired by concomitant oligohydramnios. Other less frequent ophthalmologic abnormalities that could be detected by ultrasound include microphthalmia, anophthalmia, hypertelorism and defects of the anterior segment of the eye³. Hypertelorism and microphthalmia were demonstrated by ultrasound in previous cases of Fraser syndrome^{5,7}. Abnormalities of the ears and the nose occur with a frequency of approximately 85%¹ and are further possible targets detectable by sonography, together with the rare cases of hydrocephalus and cleft that had led to the diagnosis in earlier reports^{1,4-6}. In our case, however, there were no detectable cranial, facial or cerebral defects. We are not aware of any other report on Fraser syndrome with absence of any defects of the face and head. In a review of the literature we identified 15 cases of missing cryptophthalmos out of 130 cases of Fraser syndrome evaluable for ocular defects. All of these fetuses, however, had associated other defects of the cranium, face or cerebrum^{2,4,6,18-28}. This emphasizes, that none of the malformations associated with Fraser syndrome is an obligatory feature.

Syndactyly as detected by sonography in our case occurs in 79% of fetuses with Fraser syndrome¹; however, the prenatal diagnosis is often impaired by the associated oligohydramnios. This might explain why sonography did not detect any abnormality of the digits in the previously published 16 cases. Syndactyly was present in 15 of them, 11 of which had severe oligohydramnios.

Table 3 Proposed sonographic markers for the prenatal diagnosis of Fraser syndrome

Hyperechogenic lungs
Laryngeal stenosis/atresia
Oligohydramnios
Ascites
Renal agenesis/dysplasia
Microphthalmia/hypertelorism
Hydrocephalus
Syndactyly
Ear defects
Ambiguous genitals

Therefore, in cases of oligohydramnios, instillation of fluid in the amniotic cavity should be considered, in order to improve the visualization of face, ears, kidneys and digits, important structures for the diagnosis of Fraser syndrome.

Previous reports suggested that the contrasting association of oligohydramnios indicating renal agenesis and bilateral hyperechogenic lungs, as were present in our case, might be a sonographic marker of Fraser syndrome^{10,29}. Indeed seven of the 16 reviewed cases had this sequence. Laryngeal stenosis or atresia is known to be associated with bilateral hyperechogenic and enlarged lungs in fetuses with isolated laryngotracheal obstruction^{30,31}. However, in fetuses with Fraser syndrome it does not necessarily lead to pulmonary hyperplasia as postulated by Stevens *et al.*⁹, but can also be associated with pulmonary hypoplasia as shown in one case by Ramsing *et al.*⁴, one case by Thomas *et al.*¹ and four cases by Boyd *et al.*⁶. Bilateral hyperechogenic lungs can also be caused by CCAML III³². It has been suggested that a clear differentiation between CCAML III and upper airway obstruction can only be made if the obstruction is evident on the scan³³. A clearly dilated airway imaged below the level of obstruction, as seen in our case, can accurately establish the diagnosis; however, according to a review of 12 cases of isolated laryngeal obstruction these findings can only be diagnosed in the minority of cases^{31,34}. This may be due to the fact that normative data for the fetal upper airways have only recently been established³⁵. In previous reports the tracheal diameter was probably assessed subjectively and the diagnosis of a mild dilated trachea could have simply been missed. Color flow Doppler might further enhance the diagnosis and may allow an exact location of the lesion³⁴.

Another pitfall in the prenatal detection of Fraser syndrome seems to be the kidney scan. Two previous reports described normal kidneys at scan; however, in both cases bilateral renal agenesis was demonstrated at autopsy^{4,9}. Bilateral enlarged adrenal glands were the possible explanation for the misdiagnosis at scan⁴. Proposed sonographic markers for the prenatal diagnosis of Fraser syndrome according to our review of the recent literature are summarized in Table 3.

In conclusion, the prenatal diagnosis of Fraser syndrome is possible in the hands of an expert at ultrasound, but due to the great variety of possible malformations the diagnosis will remain in doubt in most cases in which no previous child is affected.

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