Case Report

Cryptophthalmos and Bilateral Renal Agenesis with Cleft Lip and Palate: Fraser Syndrome: Case Report

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Fraser syndrome is a rare autosomal recessive disorder consisting of multiple anomalies including variable expression of cryptophthalmos, syndactyly, abnormal genitalia, malformations of the nose, ear and larynx, renal agenesis, oro-facial clefts, skeletal defects, umbilical hernia and mental retardation. Antenatally detected multiple congenital fetal anomalies during 22nd week of gestation is reported in this paper. Fraser Syndrome was diagnosed according to major and minor criteria. Early antenatal detection is mandatory and clinician should be awere of the high recurrence rates of this syndrome among siblings threatening subsequent pregnancies and should inform affected families.

Key Words: Fraser syndrome, Cryptophthalmos, Syndactyly, Congenital anomaly

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Introduction

Fraser syndrome is a quite rare autosomal recessive disorder with an estimated frequency of 0.46 per 100.000 liveborn.[1] It is characterized by variable expression of cryptophthalmos, syndactyly, abnormal genitalia, malformations of the nose, ear and larynx, renal agenesis, oro-facial clefts, skeletal defects, umbilical hernia and mental retardation.[2] Herein, we report a case with multiple anomalies, which were detected by ultrasonography (US) at 23rd week of gestation.

Case Report

A 22-year-old Caucasian woman gravida 2 and parite 1, was referred to our perinatology department with abnormal US findings at the 23rd week of gestation. Her previous pregnancy and family history was uneventful. There was no history of teratogen exposure during her pregnancy. The patient and her husband denied consanguinity. Laboratory findings including toxoplasma, rubella and cytomegalovirus antibodies (IgM), did not reveal any abnormal results. Nuchal translucency (NT) measurement at 12th week of gestation was 2.1 mm in diameter and subsequent triple screening test at 17th week of gestation was reported as normal. US examination, which was performed at the 22nd week of gestation, revealed single umbilical artery, anhydramnios, and bilateral renal agenesis. Additional findings were as follows; malformed and relatively smaller left bulbus oculi, absence of the left lens, cleft palate and left parieto-occipital calvarial defect causing extracranial herniation of the left cerebral hemisphere (Figure 1). Because of the anhydramnios, fetal extremities could not be visualized sufficiently. Fetal echocardiography did not reveal any cardiac malformations. After getting the informed consent of the family, pregnancy was terminated. A stillborn male fetus was aborted weighing 456 grams, which was concordant with the gestational age. Significant left cryptophthalmos, unilateral (left) cleft lip and palate, bilateral syndactyly and brachydactyly of hands, bilateral renal agenesis, low-set ears, left parieto-occipital calvarial defect of the left cerebral hemisphere and single umbilical artery were reported in autopsy examination (Figure 2). Postmortem chromosome analysis showed normal karyotype (46 XY).

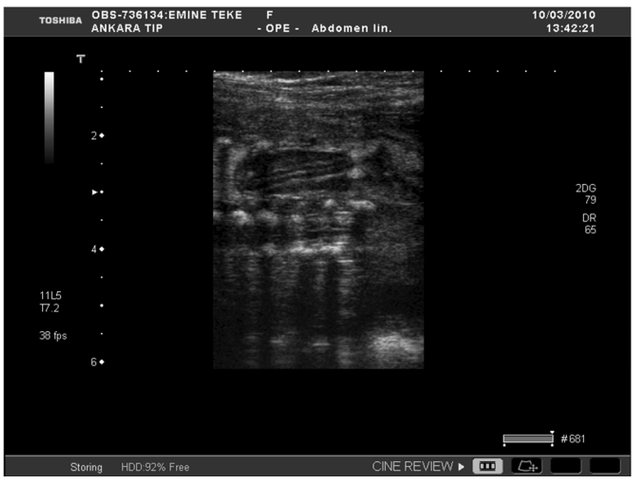

Figure 1a: Sagittal plane US view shows the "lying down" appearance of the adrenal gland, located in the renal fossa, suggesting renal agenesis.

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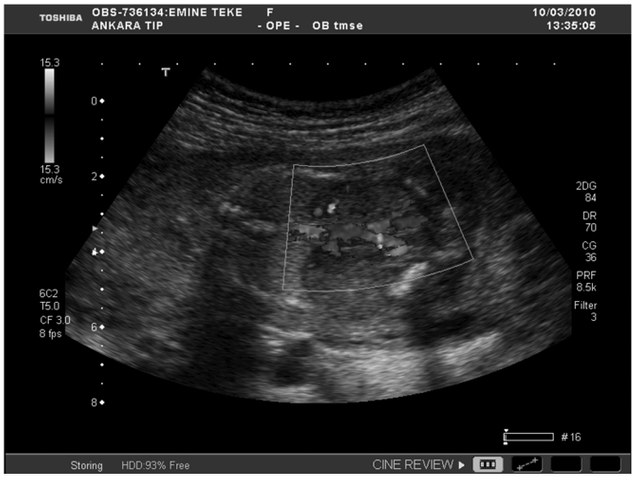


Figure 1b: Sagittal plane color Doppler US view. There are no kidneys, or renal arteries. Adrenal arteries are potential pitfalls which should not be confused with the renal arteries

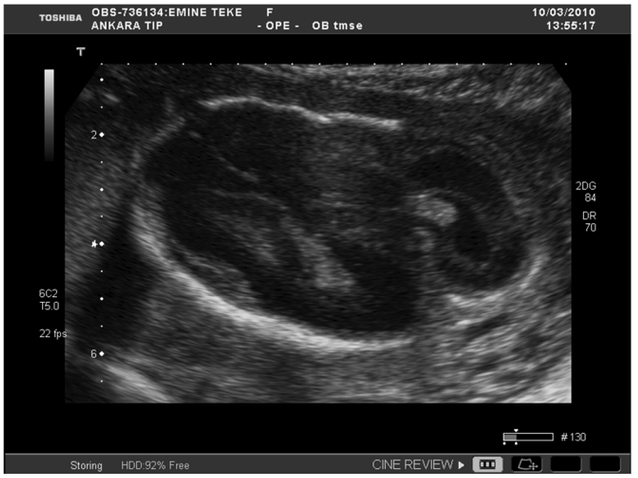
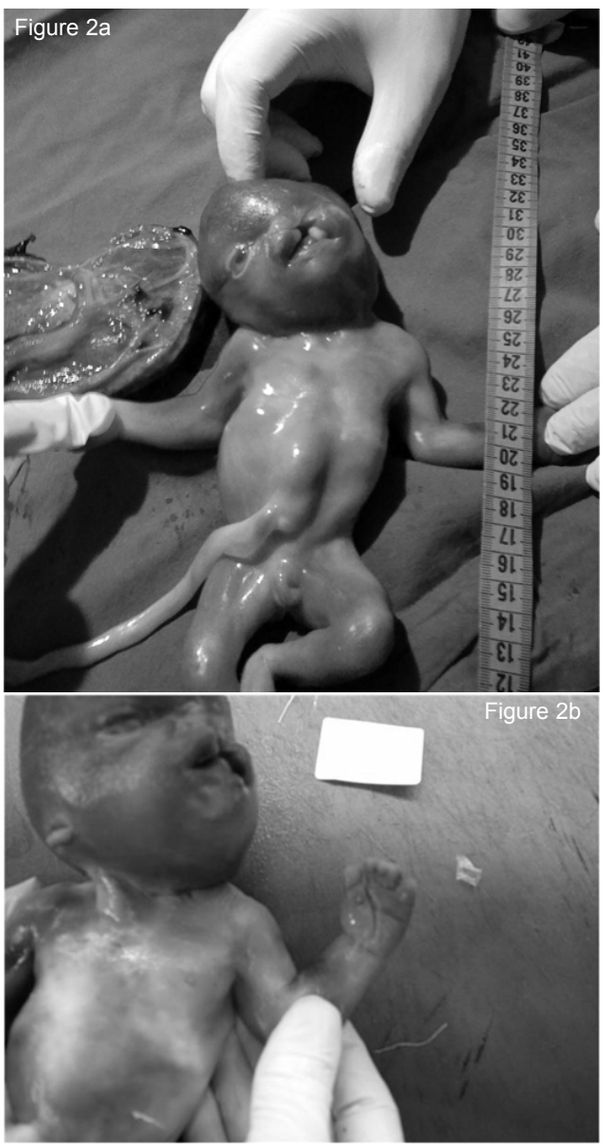
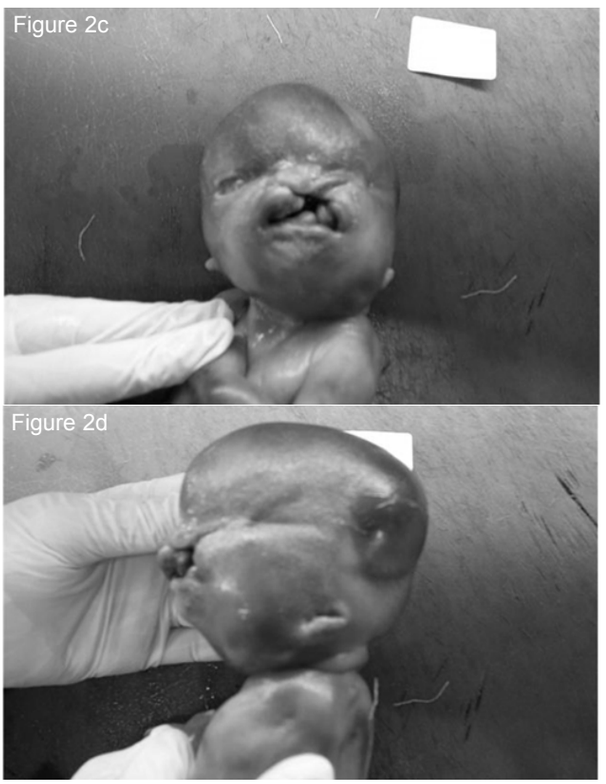


Figure 1c: Axial US view showing a calvarial bone defect at the left parietooccipital region





2a,b,c,d: Postmortem analysis of the fetus

Discussion

Zehender et. al[1] described cryptophthalmos in association with multiple malformations and later, Fraser et al.[2] published a report of two siblings with cryptophthalmos, syndactyly, ear and nose defects, laryngeal stenosis and genitourinary malformations. Later,, Thomas et al. reviewed 124 cryptophthalmos cases with associated syndromes and finally established the diagnostic criteria that distinguish the Fraser syndrome from

isolated cryptophthalmos cases.[3] Additional reviews concerning phenotypic features of Fraser syndrome were also reported by Slavotinek[4] and Gatusso et al.[5] and all were compatible with earlier published data.

The syndrome can be diagnosed either in the fetal life,[6] newborn period,[7] childhood[8] or elder. Interestingly, 96-year old female was reported as the oldest case with Fraser syndrome recently.[9] The inheritance pattern is autosomal recessive on the basis of parental consanguinity and FRAS1/FREM2 gene mutations, which are located at 4q21, and 13q13.3 respectively, are both responsible.[10,11] Interfamilial heterogeneity is common, ranging from lethal phenotypes to children with normal intelligence and minor malformations.

Fraser syndrome can be diagnosed on the basis of at least two major criteria with one minor criterion or one major criterion with at least four minor criteria (Table 1).[3] In the present case, after the prenatal detection of several congenital malformations pointing at a possible syndrome, genetic counseling was achieved and possible syndromes with differential diagnosis were discussed. According to their properties and inheritance patterns, branchiooculofacial syndrome, hemifacial microsomia, syndromic microphthalmia and Fryns microphthalmia syndrome standed in the forefront of suggested syndromes. However, after reviewing the diagnostic criteria of Fraser syndrome, the diagnosis was much clear. Additionally, postmortem investigation revealed multiple defects concerning head, face and extremities and finally, Fraser syndrome was diagnosed on the basis of diagnostic criteria that Thomas et al.[3] previously defined, even though there was no affected sibling (Table 2).

Table 1: Diagnostic criteria of Fraser syndrome[3]

Major criteria	Minor criteria
Cryptophthalmos*	Congenital malformation of nose
Syndactyly*	Congenital malformation of ears*
Abnormal genitalia	Congenital malformation of larynx
Affected sibling	Cleft lip/palate *
	Skeletal defects*
	Umbilical hernia
	Renal agenesis*

** Diagnostic criteria, that are present in this case*

In the literature, the exact time of prenatal diagnosis range between 18th weeks of gestation[6] to term.[7] Antenatal renal agenesis, orbital abnormalities, increased thoracic volume, hyperechogenic lungs accompanying oligohydramnios or anhydramnios are all reported as characteristic manifestations of this syndrome and should seriously raise suspicion for Fraser syndrome.[12,13] Oligohydramnios or anhydramnios is the most frequent finding during pregnancy with an incidence of 17%, while fetal ascites, fetal hydrops, nuchal edema, in-utero growth retardation, single umbilical artery are other findings with slightly lower incidence.[4] In the present case, anhydramnios, bilateral renal agenesis and oral-facial-cranial deformations were the leading US findings that highlight the possible syndrome and there was no significant malformation detected within fetal lungs.

A careful scan of the fetal kidneys is important for the antenatal diagnosis of Fraser syndrome, because in up to 80% of cases, uni- or bilateral renal agenesis can be detected.[14] Early detection of anhydramnios with bilateral renal agenesis is an important task to preclude possible complications of late pregnancy termination procedure. Antenatal detection of syndactyly and cryptophthalmos can often be impaired by the associated oligo- or anhydramnios. Also the diagnosis can be much more challenging especially in cases that the previous siblings are not affected, as in our case. Intraamniotic saline infusion may be helpful in visualizing the fetus better with US, in the presence of severe oligo-or anhydramnios.

Consequently, Fraser syndrome should be taken into account as a possible diagnosis in fetus when bilateral renal agenesis accompanies oro-facial and/or extremity anomalies. Clinician should be awere of the inheritance pattern of this rare syndrome and its high recurrence rates among siblings that threatening subsequent pregnancies and should inform parents about the nature of this syndrome.

Kriptoftalmus Bilateral Renal Agenezi ve Yarık Damak Dudaklı Bir Olgu: Fraser Sendromu Vaka Sunumu

Fraser Sendromu, kriptoftalmusun çeşitli varyasyonları, sindaktili, anormal genitalya, burun-kulak-larinks anomalileri, re-

Table 2: Frequencies of clinical features in Fraser syndrome.

%	Thomas 3 (n=124) %	Slavotinek 4 (n=117) %	Gattuso 5 (n=68) %	Van Haelst 14 (n=59) %	Present case
Cryptophthalmos	85	88	93	85	+
Cutaneous syndactyly	79	62	54	95	+
Ambiguous genitalia	60	40	30	66	-
Urinary tract abnormalities	80	49	37	80	+
Larynx atresia	83	31	21	49	_

nal agenezi, yarık damak ve dudak, iskelet deformiteleri, umbilikal herni ve mental retardasyon ile karakterize, otozomal resesif kalıtım özelliği gösteren oldukça nadir bir sendromdur. Bu yazıda, 22. gebelik haftasında çoklu fetal anomali olarak değerlendirilen ve tanı kriterleri doğrultusunda Fraser Sendromu olarak değerlendirilmiş bir olgu ele alınmıştır. Antenatal dönemde tanı, bu olgular için oldukça önemlidir. Kalıtım paterni nedeni ile sonraki gebelikleri de tehdit eden bu sendrom için etkilenmiş ailelerin bilgilendirilmesi akılda tutulmalıdır.

Anahtar Kelimeler: Fraser sendromu, Kriptoftalmus, Sindaktili, Konjenital anomali

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